The principle of pooled calibrations and outlier retainment elucidates optimum performance of ion chromatography

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ABSTRACT

A principle with quality assurance of ion chromatography (IC) is presented. Since the majority of scientists and costumers are interested in the determination of the true amount of analyte in real samples, the focus of attention should be directed towards the concept of accuracy rather than focussing on precision. By exploiting the principle of pooled calibrations and retainment of all outliers it was possible to obtain full correspondence between calibration uncertainty and repetition uncertainty, which for the first time evidences statistical control in experiments with ion chromatography. Anions of bromide were analysed and the results were subjected to quality assurance (QA). It was found that the limit of quantification (LOQ) was significantly underestimated by up to a factor of 30 with respect to the determination of concentration of unknowns. The concept of lower-limit of analysis (LLA) and upper-limit of analysis (ULA) were found to provide more acceptable limits with respect to reliable analysis with a limited number of repetitions. An excellent correspondence was found between calibration uncertainty and repetition uncertainty. These findings comply with earlier investigations of method validations where it was found that the principle of pooled calibrations provides a more realistic picture of the analytical performance with the drawback, however, that generally higher levels of uncertainties should be accepted, as compared to contemporary literature values. The implications to the science analytical chemistry in general and to method validations in particular are discussed.

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1. Introduction

Determination of stoichiometric ratios relies on analytical chemistry (AC) and results of IC provide such information with limits of detections (LODs) frequently reported in the range of micrograms or sub-micrograms per liter. IC is applied to analysis of industrial streams [1], quality control of potable water [2–5], analysis of food and beverages [6–9], medicine [10], determination of components in aerosols [11] and analysis of epoxy-curing agents [12]. New developments of IC imply that it is suitable to construction of devices such as on-chip manifolds of micron-scale dimensions, which exhibit a sustainable functionality with minimum expenditures of consumables [13,14]. Garcia-Fernandez et al. [15] showed that it was possible to couple IC with ICP-MS for analysis of anions in water and Haddad et al. [16] demonstrated that anions may also be determined by coupling IC with capillary electrophoresis.

Owing to the importance of IC for pharmaceutical analyses, it is the aim of the present investigation to establish the correct picture of method performance in terms of quality assurance. IC is an established technology for analysis of cations and anions in aqueous solution [13] and, owing to the general interest of quality assurance, several publications are devoted to method validation [3,4,10,11]. Considerations of the ordinary figures of merits, such as limit of quantification (LOQ) and regression coefficients [17] are not adequate for ensuring high quality of measurements in normal AC, as realized by Joint Committee for Guides on Metrology (JCGM) who published the Guide to the expression of uncertainty in measurement (GUM) [18]. In order to ensure reproducibility of the method it is validated with analysing certified reference materials and reporting results in association with an expanded uncertainty. This approach provides results of a high degree of reliability and analysts in other laboratories will be able to obtain the same results within the limits of uncertainty. The International Standardisation Organisation (ISO) [19] provides several procedures for detection of outliers and ISO recommends rejection of outliers, which is confusing to some scientists who erroneously believe that outliers may be removed from data sets by means of statistical methods. Neither GUM nor the Eurachem/CITAC guide (QUAM) [20] addresses the problem of outlier rejection.

In the present investigations, bromide ions [20] were considered for application as an internal standard for measurements with

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IC. A careful analysis of the performance of the method should be performed before the correct level of uncertainty could be established. It is the aim to perform the method validation observing three important conditions: 1. No outliers were rejected during the analysis. 2. The uncertainty of calibration (u_c) must correspond to the uncertainty of repetitions (u_r). 3. All results must be determined at concentrations above the lower-limit of analysis (LLA) and below the upper-limit of analysis (ULA). Uncertainties are evaluated in terms of pooled calibrations and expanded uncertainties [20,22–24].

2. Experimental

2.1. Chemicals

Potassium bromide (*KBr*, CAS 7758 – 02-3, Fluka), potassium tartrate ($K_2C_4H_4O_6$, CAS 921-53-9, Fluka), sodium lactate (CAS 50-21-5, Aldrich), sodium acetate (CAS 127-09-3, Fluka), sodium propionate (CAS 79-09-4, Fluka), potassium formate (CAS 590-29-4, Fluka), methanesulphonate (CAS 75-75-2, Alltech), potassium chloride (CAS 7447-40-7, Fluka), sodium trifluoroacetate (CAS 2923-18-4, Fluka), potassium bromide (7758 – 02-3, Fluka), nitric acid standard for IC (CAS 7697-37-2, Fluka), glutaric acid (CAS 110-94-1, Sigma Aldrich), succinic acid, disodium salt (CAS 150-90-3, Sigma Aldrich), maleic acid (CAS 110-16-7, Sigma Aldrich), sulphuric acid standard for IC (CAS 7664-93-9, Fluka), oxalate standard IC (CAS 144-62-7, Fluka), Phosphoric acid standard for IC (CAS 7664-38-2), Fluka), citric acid standard for IC (CAS 77-92-9, Fluka) were used to prepare the standards. A sample containing 22.1% of hydrogen bromide (21.9% bromide) (*HBr*, CAS 10035-10-6, Fluka) was applied as the sample of unknown concentration, and henceforth denoted as the unknown. All standards and samples were prepared by dilution with Millipore water (18.2 MΩ cm). Standards were prepared at concentrations within the range from the LOD of the manufacturer and concentrations where the significant deviations from linearity were observed in the curve of responses depicted as a function of concentration (working curve). The performance of the IC apparatus with respect to resolution was checked by analysis of a certified reference containing chloride, bromide, fluoride, nitrite, nitrate, phosphate and sulphate (MultiAnion calibration standard, IC-FAS-1A, CAS 7732-18-5, Inorganic Ventures). *KOH* was used as eluent and it was supplied to the system by an internal *KOH* generator.

2.2. Apparatus

The IC apparatus utilized conductivity detection with suppressor (Reagent-free-ion chromatography; RFIC, Anion SRS 300 (4 mm): 200 μeq/min) (ICS-2000, Dionex). The eluent and solutions were propelled by an electronically controlled dual-piston pump that provided a stable baseline. Standards and samples were introduced to the system by autosampler (Dionex AS40) and an injection valve with a loop volume of 10 μL. The chromatographic column was an IonPac AS11 – HC (4 mm × 250 mm) with anion-exchange layer prepared with ammonium groups (particles structure composed of a highly crosslinked core and a MicroBead®, 9-μm diameter macroporous resin bead) and the guard column was an IonPac NG 1 (4 mm × 35 mm). The flow rate of the eluents was 1.5 mL min^{-1} and the temperature was set at 30 °C.

3. Results and discussion

Method validations rely on a reliable estimate of the terms included in an uncertainty budget and this is obtained by including a series of measurements with a high number of repetitions of each term. Such work is tedious and time consuming but sometimes necessary when new methods of AC are evaluated. In the present work is performed method validation without construction of an uncertainty budget [13,20]. It is the idea to perform a series of calibrations and from the pooled data of all calibrations combined; it is the aim to predict the level of relative uncertainties as a function of concentration [22–24]. Finally are compared the predicted uncertainties with the uncertainties of repetitions, that is, the uncertainties obtained by calculating concentration upon the basis of a series of determinations of unknowns [22].

3.1. Precision and repeatability

Experiments of IC are published with attractive figures of merits that allow determinations in the range of concentrations well below 1 mg L^{-1} [4], as evidenced by the numbers reproduced in Table 1. The initial results of the present work were obtained by using a single calibration line and a single set of blanks, which thus provide figures of merits that relate to the apparatus' precision and not to the accuracy. Under these conditions were the results thus found complying with literature values (Table 1). Since the determination of the LOQ differs by up to two orders of magnitude (Table 1), it is worthwhile to investigate the origin of this discrepancy in further detail. When the determination of LOQ is based upon measurements of blanks, it might be expected that the LOQ values would be almost identical when they were determined by the same type of technology. However since there are several fundamentally different procedures for the determination of the limit of detection (LOD) [25] and LOQ, may be anticipated some degree of discrepancy. In brief, determination of the LOQ relies on the STDEV of either 10 blanks or the STDEV of 10 samples of very low concentration, which may introduce considerable differences when analysing different types of samples because uncertainty of measurement depends on the concentration also at low concentrations. LOQ may be considered as a limit beyond, which analysis becomes unreliable when a low number of repetitions are performed. In testing of apparatus performance, 17 anions were analysed, as shown in Fig. 1. The LOQ was determined as 0.04–0.5 mg L^{-1} where the LOQ of chloride ions showed the lower value while formate ions showed the higher value. In order to perform an initial test of accuracy were all ions determined by six repetitions at the concentration that corresponded to the LOQ of each ion. The corresponding relative standard deviations of this series of experiments yielded RSDs of peak areas ranging between 5% for formate ions, 11% for bromide and 92% for sulphate ions. This large span of RSDs may be expected at very low concentrations close to the LOQ but it would be favorable to know more about the RSD at the concentration of LOQ taking into account to large spread of LOQ values found in literature (Table 1). RSD of bromide at the LOQ concentration was higher than the values that are presented in Table 1, which is also expected because the RSDs for samples were determined at concentrations much above the LOQ.

By considering a single experiment comprising calibration of 11 standards and determination of a single unknown, it was found that the expected concentration of 21.9% bromide in the sample

Table 1
Figures of merits reproduced from determination of bromide by IC.

Linear range (mg L^{-1})	LOQ (mg L^{-1})	RSD of peak area (%)	Reference
0.03–100	0.06	<6	[8]
2–1000	0.5	<4	[10]
0.002–2	0.005	0.8–2.8	[5]
2.5–50	0.003	0.76	[28]
3.1–1080	0.1	1.1[a]	This work

[a] Average of six repetitions (50 mg L^{-1}) obtained in four independent measurements.

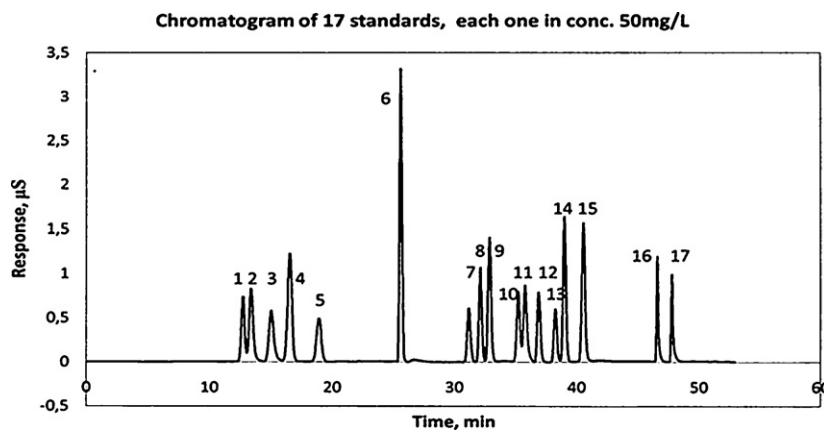**Chromatogram of 17 standards, each one in conc. 50mg/L**

Fig. 1. Ion chromatogram of 17-standards mixture. (1) Lactate; (2) acetate; (3) propionate; (4) formate; (5) methansulphonate; (6) chloride; (7) trifluoroacetate; (8) bromide; (9) nitrate; (10) glutarate; (11) succinate; (12) tartrate; (13) maleic; (14) sulphate; (15) oxalate; (16) phosphate; and (17) citrate.

was determined as $21.0 \pm 2.6\%$, which is an excellent correspondence. However, since the STDEV of the sample was determined by a single measurement of the unknown, the magnitude of the STDEV is associated with a low degree of reliability, which may indicate that the result is not completely true. A series of experiments was thus undertaken with more series with measurements, in order to obtain a more correct picture of the genuine level of uncertainty.

3.2. Accuracy and reproducibility

In order to secure universal reproducibility of the present results there is a need to transform STDEV into an expanded uncertainty, which expresses that anyone else in another laboratory using the same type of procedure also is able to reproduce results within a 95% confidence range [18,20]. In the present investigation, the expanded uncertainty is calculated as the STDEV multiplied by a factor of two, where the STDEV is found by multiple determinations of the unknown. As opposed to the standard uncertainty from the uncertainty-budget built into the 'new' STDEV the long-term variations (day-to-day variations), which then is supposed to include all possible variations that could be imposed measurements with the apparatus. Accordingly, the standard uncertainty is set to compare with the STDEV of measurement. This approach requires that the STDEV of calibration equals the STDEV of multiple repetitions of the unknown, which only can be verified experimentally by performing several large series of measurements and repetitions during the method validation. Upon proper construction of the uncertainty-budget must the standard uncertainty correspond to both the STDEV of calibration and to the STDEV of repetition. When the two STDEVs are comparable then are all contributions to the uncertainty understood in detail and the system is said to be in statistical control.

The STDEV of repetition is calculated by utilizing the simple formula $(STDEV^2 = \sum (x_i - \bar{x})^2 / (N - 1))$ while calculation of STDEV of calibration is more subtle. There are two distinctly different methods available to calculate the STDEV of calibration, which also have been published by ISO/IUPAC [18,19,26] and by Eurachem/CITAC [20]. Both methods refer to single calibration lines and a few repetitions of the unknown. The IUPAC method is based upon the concept measurement 'error' that is associated with a regression line whereas the Eurachem/CITAC method applies the concept of uncertainty that relates to the standard uncertainty and the corresponding expanded uncertainty. These are two fundamentally different concepts where the former relates to confidence ranges whilst the latter relates to expanded uncertainty.

Recent results indicate that the concentration range with calibrations may be estimated by using the principle about

pooled calibrations [22–24]. In that scenario, the concentration of unknowns may be determined in series of experiments with calibrations and multiple determinations of unknowns. Before any comparisons are made, is the uncertainty on calibrations as a function of concentration determined upon the basis of all pooled calibration lines but the regression line of pooled calibrations cannot be applied to determine concentrations of unknowns. Pooled calibrations are applied exclusively to the determination of uncertainties. The final concentration of the unknown is then determined as the average value of every single determination of independent series of measurements and the corresponding uncertainty is calculated by application of pooled calibrations. The results of Fig. 2 shows the pooled calibrations of bromide determination by IC where the expected increase in STDEV depicted as a function of concentration gives a characteristic 'funnel-shaped' appearance, where absolute STDEVs increase as a function of concentration. The regression line of Fig. 2 should not be applied to calculate the concentrations of unknowns but the uncertainties of slope and intercept are used to calculate the STDEV of calibration. The concentrations of unknowns are calculated by utilizing single regression lines of each individual experiment of separate days or separate independent measurements. In Fig. 3 is shown the STDEV (s_y) as a function of concentration as deduced from the results of Fig. 2. The point at $[Br^-] = 400\,mg\,L^{-1}$ (Fig. 3) falls below the general linear dependence because only a few measurements were performed at this point, which renders the STDEV unreliable and it falls low by shear accident. However, determination of the STDEV of
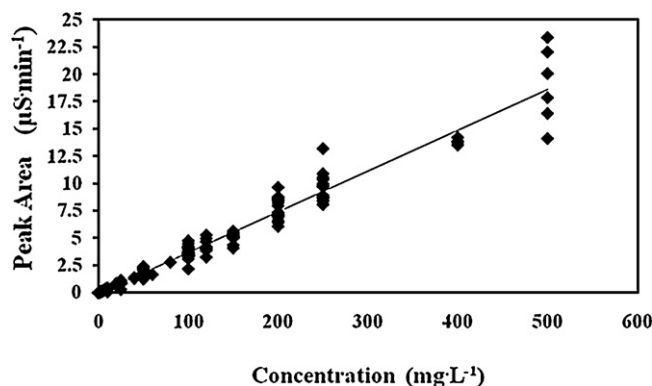

Fig. 2. Regression line of pooled data of multiple and independent calibrations. The regression line is used for calculating the STDEV of unknown as if it were a standard. The regression line of pooled calibrations cannot be used to calculate concentrations of unknowns; they are determined independently in association with every single calibration line.
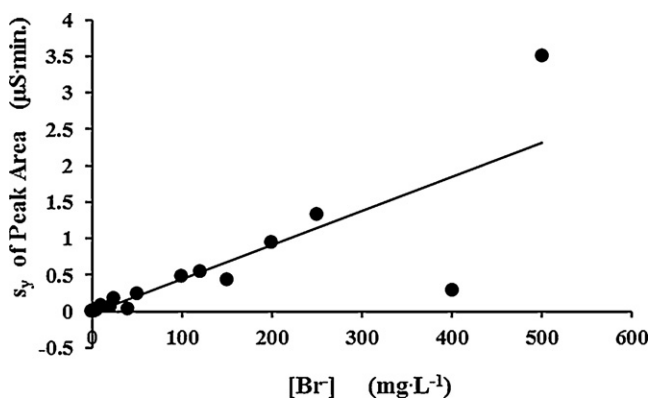
Fig. 3. Absolute standard deviations depicted as a function of concentration. The empirical formula is a straight line with intersection at the origo. Slope and intercept of the regression line are $0.0047\,\mu S\,min\,L\,mg^{-1}$ and $-0.031\,mg\,L^{-1}$, respectively.

calibration is not very sensitive to the magnitude of s_y and the regression line of Fig. 3 provides a reasonable value of s_y related to unknowns, which enters the equation applied to determine STDEV of calibration. The STDEV of calibration covering the full range of calibration was constructed by the formula derived by the law-of-propagation of uncertainties and then converted to relative standard deviations (RSDs) as shown in Fig. 4 where the RSD is depicted as a function of concentrations. At high concentrations the RSD rises slightly but it is approximately constant within the range 20–$500\,mg\,L^{-1}$ approaching a value of 8%. The corresponding lower-limit of analysis (LLA) was determined as $3.1\,mg\,L^{-1}$ and the upper-limit of analysis (ULA) was determined as $1080\,mg\,L^{-1}$ (by the aid of peak heights). The LLA thus determined was approx. 30 times higher than the corresponding LOQ (Table 1), which indicates that results determined in the concentration range between LOQ and LLA are associated with an RSD in excess of 50%. Samples may thus not be analysed at concentrations between 0.1 and $3.1\,mg\,L^{-1}$, unless an inconveniently high number of repetitions is performed. Thus, the concentration range stretching from $3.1\,mg\,L^{-1}$ to $1080\,mg\,L^{-1}$ represents a useful working range, and the LLA corresponds to the concentration where the RSD is 50%. The linear range differs very much from the findings of Kumar et al. [7], Miskaki et al. [4] and Okamoto et al. [27] but it compares well
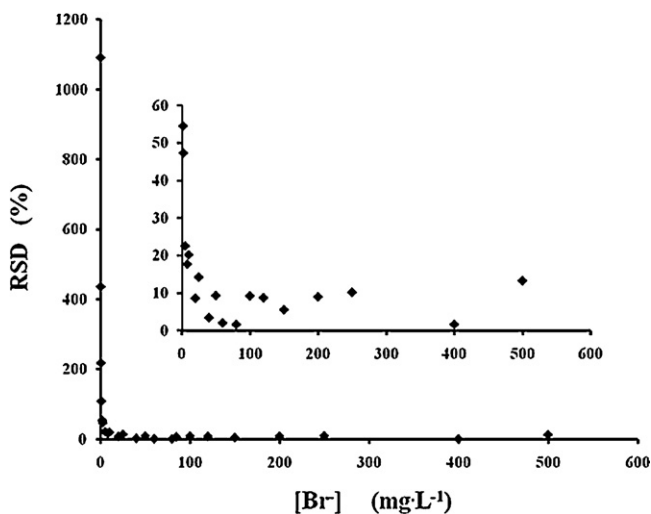
with the results of Ding et al. [9] (Table 1). At higher concentrations, the RSD increased slightly up to approx. 9% (at $[Br^-] = 500\,mg\,L^{-1}$), which corresponds to RSDs of peak areas reported earlier [7,9]. The RSD of 3–5% also corresponds to the RSD found by determination of inorganic bromide by means of ICP-MS [28]. Table 1 provides linear range of calibrations where the method used to assess the upper limit was not reported, however.

By preconcentrating by an order of magnitude, Böhme et al. reported a limit of determination of $1.8\,\mu g\,L^{-1}$ and a value of $2.2\,\mu g\,L^{-1}$ for determination of bromate by IC [21]. These values are thus more than three orders of magnitude higher (1500 times higher) than the LLA of the present work without preconcentration. The corresponding sensitivity of determination of bromate was 7 times lower than that of bromide, however [21]. By introducing post-column reaction Delcomyn at al. [29] achieved a practical detection limit of staggering $0.05\,\mu g\,L^{-1}$ for determination of bromate. In this context it is very surprising indeed that Okamoto et al. [27] were able to obtain a bromide-LOQ of only $3\,\mu g\,L^{-1}$ using a column of graphitized carbon without a step of preconcentration.

Bromate is of concern in drinking water owing to its possible carcinogenic effects on humans and because it can be generated when bromide is oxidized by ozone in water-treatment plants. With a provisional-guideline value of merely $10\,\mu g\,L^{-1}$ [30] of bromate in drinking water it is important to secure accuracy of analysis rather than precision of analysis. In view of the present findings, it is important to further improve accuracy of IC in order to achieve performance that provides an LLA lower than $10\,\mu g\,L^{-1}$. Otherwise, capital errors may be encountered with respect to investments in cleansing procedures and health issues related to bromate. Therefore, validation of IC is particularly important to clinical chemistry as shown by Röhker et al. [10] and Waterworth [3]. However, Röhker et al. [10] validated the IC method with respect to accuracy whereas Waterworth validated with respect to precision [3].

Relative-confidence limits were calculated, in order to illustrate the difference between relative-confidence limits [26] and relative-expanded uncertainties. At relatively low concentrations ($[Br^-] < 100\,mg\,L^{-1}$) the RSD of the Danzer and Currie formula [26] (not shown) was found to exceed the RSD of Fig. 4 by up to a factor of three. A high concentrations, however, the RSD of Danzer and Currie approaches zero, reaching 2% at $[Br^-] = 500\,mg\,L^{-1}$ while the RSD of pooled calibrations approached a constant value of 9% (see above) at this concentration and at higher concentrations. Most concentrations of unknowns were determined at values of approx. $36\,mg\,L^{-1}$, which provides an RSD of approximately 8% according to the RSD-curve of Fig. 4 and in excess of 25% for the Danzer and Currie data.

The average percentage of bromide in the sample was determined as $20.6 \pm 2.4\%$ that was obtained by multiple repetitions, which corresponds to an RSD of 12% and a relative-expanded uncertainty of 24%. The corresponding uncertainty determined by the formula of propagation of uncertainties (Eurachem/CITAC) [20] and the regression line of Fig. 4 provided an RSD of approx. 8% within the linear-calibration range. The uncertainty of measurement should be reported as the double value of the RSD or 16% equal to the RSD of calibrations multiplied by a factor of two, which in the present context corresponds to the relative-expanded uncertainty [18,20]. Accordingly, the uncertainty of calibration was found to be in excellent agreement with the uncertainty of repetition. In addition, the relative-expanded uncertainty may be compared to the uncertainty predicted by the Horwitz formula [31] that also provides a value of 9% in good agreement with the present results (~24% of repetition and ~16% of calibration).

It was found in some instances that the slope of the individual calibration lines (not shown) did not correlate perfectly well with the amount of bromide determined in the CRM. A high value could be obtained with a low value of slope and vice versa within certain
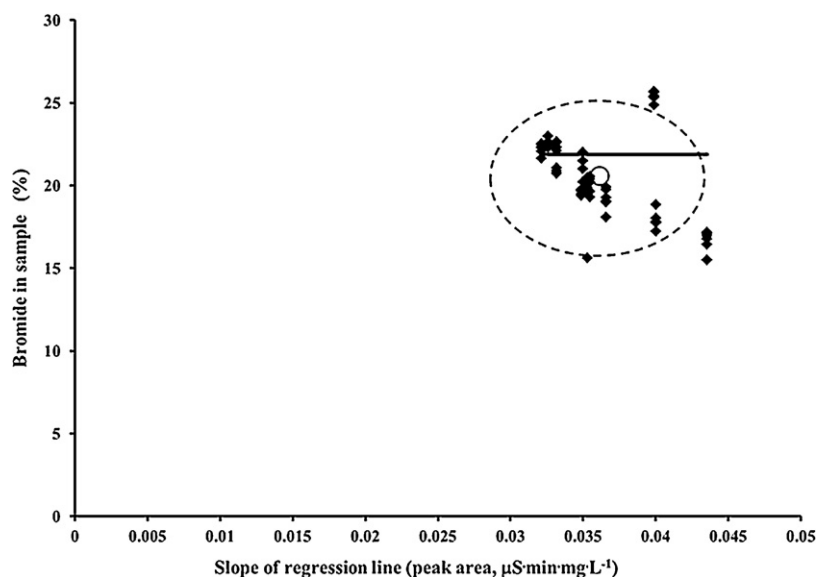

Fig. 4. The RSD of calibrations depicted as a function of concentration with inset showing details of low-concentration range. The LLA value corresponds to the concentration where the RSD equals 50%. At higher concentrations $c > 20\,mg\,L^{-1}$, the RSD levels at an approximately constant value of 8%.

Fig. 5. The bromide concentration of each sample (♦), which was determined by independent series of measurements, shown as a function of corresponding slope of regression line. The spread of data indicates that the calibration procedure does not fully correct for long-term variations of the system. A slight bias of the average value (○) in relation to the expected value (---) was identified by conventional methods of *t*-testing. However, the bias was not real according to the present method of comparing results. The ellipse (—) is defined by the expanded uncertainty associated with values of the two axes. Approx. 84% (56 out of 67 measurements) of the measurements were found within the limits of the ellipse, which is in acceptable proximity of the expected 95% when taking into account the limited extension of the data set.

limits. In order to investigate this correspondence in more detail the content of bromide in the CRM was depicted as a function of slope of regression line by which the content was determined (Fig. 5). The average value of all slopes and content of bromide is represented by an open circle and the certified value is indicated by a horizontal-full line (Fig. 5). An ellipse is introduced to encircle the area where 95% of the measurements are expected to be found. The horizontal axis of the ellipse has a radius that corresponds to the expanded uncertainty of slope and the vertical axis of the ellipse has a radius that corresponds to the expanded uncertainty of certified-bromide contents. It was found that 56 out of 67 measurements or approx. 84% were captured within the limits of the ellipse (Fig. 5). Although this percentage seems much less than 95% the difference may be ascribed to accidental variations associated with the finite number (N = 67) of bromide determinations. The ellipse with axis of expanded uncertainties [18,20] is thus considered to be a useful tool to provide an overview of the general performance of the method.

4. Conclusion

A major difference was identified between the LLA and LOQ. It was suggested that the LOQ merely provides information about precision of the method whilst the LLA provides information related to universal accuracy for IC. Statistical control may be obtained by changing method validation according to the following points:

1. It was possible to estimate accuracy and trueness of IC without constructing an uncertainty budget. The initial series of experiments showed a perfect correspondence between measured values and expected values whereas more detailed investigations showed that a slight bias might be associated with determination of bromide by IC.
2. Absence or presence of bias depended on type of testing. According to conventional *t*-testing was there a bias while bias was absent according to the Eurachem/CITAC testing with limits given by expanded uncertainty.
3. Uncertainties derived from pooled calibrations corresponded well to uncertainties of multiple repetitions. The regression line

of pooled calibrations can be used for uncertainty estimates but it cannot be used for calculation of concentrations of unknowns.
4. Interferences were most likely not present during analysis. Tentative interferences should impose an influence on the determination of bromide that provides a systematic-relative difference of more than approx. 16% as compared with to the certified value.
5. Application of bromide as an internal standard would contribute a universal-relative-expanded uncertainty of approx. 16% to the results of analysis of other anions.
6. It is suggested that IC cannot be used to quantify bromide at any degree of reliability at concentrations below the LLA of 3.1 mg L^{-1} unless an inconveniently high number of repetitions is performed. The results strongly indicate that a peak, which is easily identified in the chromatogram, may not necessarily be used for quantitation; it is important that the corresponding concentration resides above the LLA value.

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