Blank correction in isotope dilution

Pagliano, Enea; Mester, Zoltan; Meija, Juris

Publisher's version / Version de l'éditeur:
https://doi.org/10.1021/acs.analchem.5b02924
Analytical Chemistry, 2015-10-08

Blank correction in isotope dilution

Enea Pagliano, * Zoltán Mester, and Juris Meija

National Research Council of Canada, 1200 Montreal Road, Ottawa, ON K1A 0R6, Canada

E-mail: enea.pagliano@nrc-cnrc.gc.ca

Phone: +1(613)993-2527. Fax: +1(613)993-2451

Abstract

A novel method for compensation of the procedural blank in isotope dilution is presented. This method - entitled "blank-matching" - copes with the blank through experimental design. Both sample and calibration solutions are exposed to the same amount of isotopic standard and same procedural blank. The identical treatment of sample and calibrators eliminates the need for subtracting the procedural blank from the result obtained by isotope dilution. A further advantage of the method is that quantitation of the analyte in the procedural blank is not required. Blank-matching is simple and fast to implement and it permits direct determination of results without further corrections. This aspect has an important metrological outcome: blank-matching isotope dilution can be considered a primary method of analysis that does not involve the procedural blank as a potential source of bias.

Introduction

Procedural blank correction is a topic of importance in trace analysis.[1] Sample preparation can be responsible for the introduction of contaminants that can lead to the overestimation of the analytical result.[2] In most methods, correction for procedural blank is achieved by direct subtraction of the blank contribution (n_{blank}) from the gross amount of analyte detected ($n_{\text{A-gross}}$):[3,4]

$$n_{\text{A}} = n_{\text{A-gross}} - n_{\text{blank}} \tag{1}$$

where n_{A} is the the unbiased amount of analyte in the sample. In practice, the procedural blank is evaluated by performing a separate determination under the same conditions of sample analysis, but without the sample.[3]

In isotope dilution mass spectrometry (IDMS)[5–8] blank correction is a topic of interest;[9] a systematic study of the blank in IDMS was presented by Lamberty and Pauwels in 1991[4] and procedures recommended in Roth's IUPAC technical report in 1997.[7] These authors discussed procedural blank correction for a classic experiment of single isotope dilution (ID^{1}MS). Over the years, ID^{1}MS has undergone many developments, resulting in the formulation of various higher-order models.[10] Up to date IDMS equations have been proposed for double[11–13] triple[14–17] and quadruple[10,18] isotope dilution. Moreover, isotopic internal standards have been intensively employed in organic LC/MS and GC/MS for the preparation of calibration functions[19] (isotope ratio *vs* analyte concentration). Whereas ID^{1}MS is uniquely based on the measurement of the sample, all other isotope dilution methods require measurement of additional blends (A*B) prepared from a primary standard of natural isotopic composition (A*) and from an isotopic standard (B). In such cases, procedural blank correction becomes less intuitive. In 2005, Yang and Sturgeon[1] studied the situation for double isotope dilution, concluding that *"when a blank contributes to both isotope dilution and reverse isotope dilution processes, only a fraction of this blank concentration is subtracted from the gross analyte concentration"*. In practice, the blank that contributes to both direct (sample blend AB)

and reverse (calibration blend A*B) isotope dilution does not need to be accounted for: only that portion of the blank that contribute uniquely to the sample blend AB is subtracted. This conclusion can be extended to all isotope dilution models that require measurement of one or more A*B calibrators. Yang and Sturgeon′s method for blank correction requires direct measurement of the blank followed by its partial subtraction from the gross analyte concentration. Blank determination, however, can be challenging, depending on the analyte levels. In this study we propose an alternative approach for blank compensation in isotope dilution that does not require the determination of the analyte in the blank. When the experiment is designed such that both isotopic standard and procedural blank contribute equally to sample and calibrators, no blank correction is needed. The identical treatment of sample and reference standards eliminates systematic errors due to procedural blank in an isotope dilution experiment. This technique of blank-matching aligns with the principle of identical treatment[20] and can be applied in conjunction with the method of exact-matching IDMS[13,21] where measured isotope ratios are matched to minimize the measurement biases.

Theory

Isotope dilution mass spectrometry is recognized as one of the most accurate methods in instrumental analytical chemistry. When a contaminant is introduced into the sample through common preparation procedure, overestimated results can be observed and corrective actions are required to avoid biases. The classical method for procedural blank compensation entails direct subtraction of the blank according to Eq. 1.[4] The major practical disadvantage of this approach is the need for a dedicated experiment for quantitation of the analyte in the blank. Furthermore, Eq. 1 is fundamentally an indirect measurement wherein estimation of the analyte is obtained by subtraction of two measured values. For better control of uncertainty propagation, and for a shorter traceability chain, direct measurement of the analytical property value is preferred. With isotope dilution, this condition can be achieved

applying the proposed blank-matching procedure. The novel method copes with the procedural blank through experimental design. All sample and calibration solutions that define the IDMS experiment are treated with the same amount of isotopic internal standard (B) and are exposed to the same amount of potential contaminants. This design is illustrated in Fig. 1. If the procedural blank and the isotopic internal standard are considered a single entity, then the blank-matching experiment is nothing other than *blank-free* isotope dilution that uses as isotopic standard a B* solution comprising the formal summation of B and procedural blank. *In other words, in such experiment, the procedural blank can be perceived as an apparent decrease of the isotopic enrichment of the internal standard*. The idea for this method stemmed from the general equation for isotope dilution. No matter which IDMS model (single, double, triple, quadruple dilution or calibration function) [10–19] is chosen for quantitation, the potential overlap between the isotopes of natural and enriched material needs to be accounted for. Indeed, in all isotope dilution models the isotopic composition of natural (R_A) and isotopic (R_B) standards are the variables that allow deconvoluting such overlap. In principle this *overlap* is a *blank* problem; the blank-matching method takes full advantage of this aspect by transfering the effect of the procedural blank into R_B (Fig. 1). This *"internalization"* of the procedural blank makes blank-matching isotope dilution a primary method that does not require any further corrections to account for the blank.

Experimental

The blank-matching method was demonstrated experimentally. A quadruple isotope dilution model [10] was implemented for the determination of bromide in a synthetic water sample by gas chromatography mass spectrometry (GC/MS) after aqueous derivatization of bromide with triethyloxonium. [22] Bromide was converted to bromoethane and detected by MS in EI positive mode on mass 110 Da ($C_2H_5{}^{81}Br^+$) and 108 Da ($C_2H_5{}^{79}Br^+$). The isotope ratio $R_{AB} = n(C_2H_5{}^{81}Br^+)/n(C_2H_5{}^{79}Br^+)$ was utilized for quantitation purposes. Sample A of

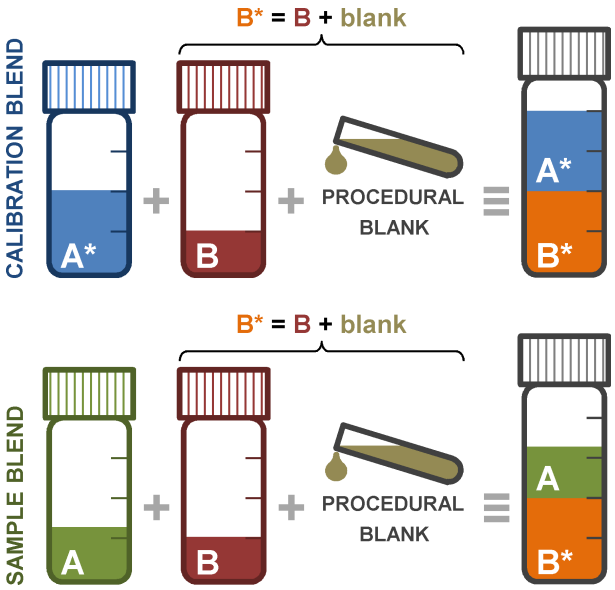

Figure 1: Blank-matching method. When identical amounts of isotopic internal standard (B) and reagents (considered procedural blank arising from sample preparation) are introduced in all calibration/sample blends, no blank subtraction is required. The blank-matching experiment becomes equivalent to a *blank-free* isotope dilution that uses an isotopic internal standard B* equivalent to the formal summation of B and procedural blank.

natural isotopic composition bromide ($w(\mathrm{Br}^-) = 0.10004 \pm 0.00010$ μg/g) was prepared by gravimetric dilution of NIST Standard Reference Material 3184 Bromide Anion (Br^-) Standard Solution. The same source of bromide was used to prepare the primary standard A* and to model the artificial procedural blank. The isotopic internal standard B was a ^{79}Br enriched bromide ($x(^{79}\mathrm{Br}) = 0.94$ mol/mol) sourced from Trace Science International. The bromide content in sample A was measured after pretreatment with a clean reagent (no detectable blank) and with a contaminated one. In the latter experiment a procedural blank corresponding to 20% of the sample analytical signal was detected. For correcting this blank, the traditional subtraction approach (Eq. 1) was compared with the proposed blank-matching. Each experiment was repeated five times and uncertainty evaluation was carried out according to the JCGM guideline.[23] Reported uncertainties are based on a coverage factor $k = 1$.

Results and discussion

As a requirement for accurate trace analysis, the procedural blank contribution should be the same for every single solution in a sequence. If this condition is not satisfied - i.e., the blank levels are not reproducible - both classic blank subtraction (Eq. 1) and blank-matching will produce poor results, depending on the variation of the blank. The situation modeled in this study is one of reproducible procedural blank. For example, the blank associated with a reagent can be considered reproducible if the reagent is homogeneous and manipulated in a contamination-free manner. When the blank levels are not reproducible, there is no strategy that can efficiently handle the problem. In this situation, the only remedy can be sought in a better control of the working conditions.

Use of a contaminated reagent

In an ideal scenario an analysis is executed in a *blank-free* environment. This situation is a theoretical limit that in practice could be approached when the instrument does not show a signal corresponding to the blank. This favorable condition was achieved for the determination of bromide by GC/MS. The bromide content in sample A could be measured with a signal-to-noise ratio of 1000, without detecting a procedural blank. Five replicate measurements of bromide in sample A resulted in an average of $w(\mathrm{Br}^-) = 0.1011 \pm 0.0010$ μg/g (Table 1). This measurement is in agreement with gravimetric data within 1%. At this point, the determination of bromide in sample A was performed using a contaminated reagent for the sample pretreatment step. Without any corrections - as expected - the latter measurement produced a biased result (20%): $w(\mathrm{Br}^-) = 0.1212 \pm 0.0012$ μg/g. In order to give significance to this second measurement, a correction is required.

Table 1: Comparing the gross analytical results of Br^- in sample A ($w(Br^-)_{gravimetric} = 0.10004$ $\mu g/g$) using a clean and a contaminated reagent for the sample preparation

Clean reagent[a]	Contaminated reagent[b]
$w(Br^-)$ $\mu g/g$	$w(Br^-)$ $\mu g/g$
0.1002 ± 0.0023	0.1190 ± 0.0027
0.1029 ± 0.0023	0.1248 ± 0.0027
0.0998 ± 0.0022	0.1208 ± 0.0027
0.1012 ± 0.0023	0.1194 ± 0.0027
0.1014 ± 0.0023	0.1218 ± 0.0027

Result $\pm$ standard uncertainty ($k = 1$)
[a] No blank was detected
[b] A blank corresponding to 20% of the sample analytical signal was detected

Blank subtraction *vs* matching

The classic approach for blank correction is based on Eq. 1: subtraction of the excess. For each of the five measurements reported in Table 1, a dedicated experiment was performed to obtain the bromide content in the contaminated procedural blank (Table 2).

Table 2: Classic approach for procedural blank subtraction

m_{sample} g	$m_{reagent}$ g	$w(Br^-)_{gross}$ $\mu g/g$	$w(Br^-)_{reagent}$ $\mu g/g$	$w(Br^-)$ $\mu g/g$
2.00198	0.39637	0.1190 ± 0.0027	0.0965 ± 0.0047	0.0999 ± 0.0029
1.99915	0.39679	0.1248 ± 0.0027	0.1055 ± 0.0047	0.1039 ± 0.0029
1.99921	0.39757	0.1208 ± 0.0027	0.1047 ± 0.0047	0.1000 ± 0.0028
1.99949	0.39752	0.1194 ± 0.0027	0.1043 ± 0.0052	0.0986 ± 0.0029
1.99679	0.39534	0.1218 ± 0.0027	0.1014 ± 0.0047	0.1017 ± 0.0029

Result $\pm$ standard uncertainty ($k = 1$)

Determination of the analyte in the blank was difficult due to the low analyte level: the combined uncertainty for quantitation of the blank was two fold that of the sample (Table 2). Data reported in Table 2 were blank corrected by applying the following equation:

$$w(\mathrm{Br}^-) = w(\mathrm{Br}^-)_{\mathrm{gross}} - \frac{m_{\mathrm{reagent}}}{m_{\mathrm{sample}}} \cdot w(\mathrm{Br}^-)_{\mathrm{reagent}} \tag{2}$$

whereas the error on $w(\mathrm{Br}^-)$ was calculated according to JCGM guideline:[23]

$$u^2\left[w(\mathrm{Br}^-)\right] = u^2\left[w(\mathrm{Br}^-)_{\mathrm{gross}}\right] + \left(\frac{m_{\mathrm{reagent}}}{m_{\mathrm{sample}}}\right)^2 \cdot u^2\left[w(\mathrm{Br}^-)_{\mathrm{reagent}}\right] \tag{3}$$

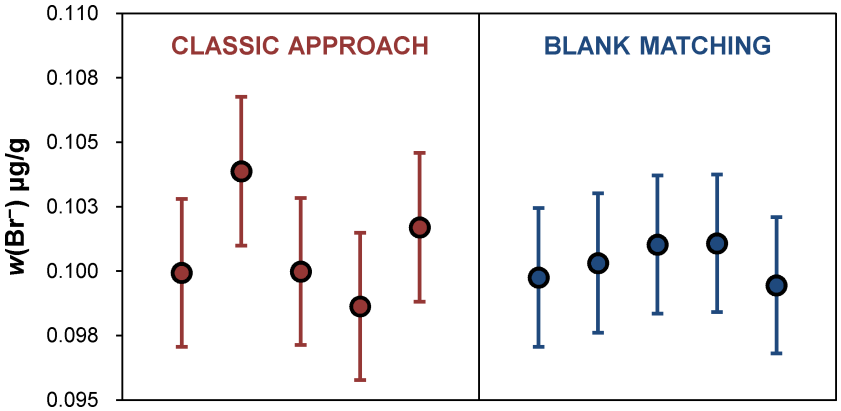

Figure 2: Determination of Br^- in sample A: classic approach *vs* blank-matching. Error bars represent the standard uncertainty ($k = 1$)

Uncertainty on mass measurement was considered negligible. The classical method for blank correction requires considerable experimental effort for quantitation of the analyte in the blank; moreover it implies a certain mathematical complexity for the calculation of the result (Eq. 2) and uncertainty (Eq. 3). The novel blank-matching method avoids these shortcomings. As noted in the theory section, when the experiment is prepared according to Fig. 1, no blank subtraction is needed to achieve the correct isotope dilution result. The blank-matching technique was applied to quantify the bromide content in sample A when a contaminated reagent was used for sample preparation (Table 3). In this case, classic correction and blank-matching produce comparable results: both methods provide the expected mass fraction of bromide with similar uncertainty (Fig. 2). The blank-matching, however, is superior from a practical point of view because it does not require a dedicated experiment to determine the blank. The blank-matching design allows a direct response to

the question *"what is the bromide mass fraction in sample A?"* while the classic method is more complex in providing the same analytical information.

Table 3: Determination of Br^- in sample A: dealing with a procedural blank

Classic approach[a]	Blank-matching[b]
$w(Br^-)$ $\mu g/g$	$w(Br^-)$ $\mu g/g$
0.0999 ± 0.0029	0.0998 ± 0.0027
0.1039 ± 0.0029	0.1003 ± 0.0027
0.1000 ± 0.0028	0.1010 ± 0.0027
0.0986 ± 0.0029	0.1011 ± 0.0027
0.1017 ± 0.0029	0.0994 ± 0.0026

Result $\pm$ standard uncertainty ($k = 1$)
[a] Blank subtraction (Eq. 2, Table 2)
[b] Direct measurement (Fig. 1)

Isotopic composition of the blank

For the majority of practical cases, the isotopic composition of the blank is natural and can be assumed to be equal to that of the primary standard used for quantitation. For some elements like lithium or lead, this assumption might not be acceptable for high-precision measurement.[10] In such cases, for a classic subtraction of the blank contribution, the analyst should account for the difference between the isotopic composition of the blank and primary standard;[4] this task, however, could be challenging from a practical point-of-view. In a blank-matching experiment, the blank can be seen as part of the *effective* internal standard B* used for quantitation (Fig. 1). The internalization of the blank into the model of isotope dilution eliminates the need for any assumption on the isotopic composition of the blank. As a result, the blank-matching design also copes with any potential difference between the isotopic composition of the blank and primary standard without the need of further investigation.

Conclusion

A novel approach for the correction of procedural blank has been described for isotope dilution quantitation. When sample and calibration solutions of the sequence are subjected to the same amount of blank (from reagents and manipulations) and isotopic internal standard, no blank subtraction is required. Blank-matching copes with the blank through experimental design: the sample preparation is simply executed in a way that eventual contamination arising from reagents does not affect the accuracy of the results. Direct determinations of blank concentration and of its isotopic signature are therefore not needed. In this vein, blank-matching is an easy and fast approach to compensate for a predictable blank in isotope dilution quantitation.

Acknowledgement

The authors thank Ralph Sturgeon, Beatrice Campanella, and Lucia D′Ulivo for inspiring conversations on this subject.

References

(1) Yang, L.; Sturgeon, R. E. *J. Anal. At. Spectrom.* **2005**, *20*, 724–729.

(2) Sturgeon, R. E.; Berman, S. S.; Desaulniers, J. A. H.; Mykytiuk, A. P.; McLaren, J. W.; Russell, D. S. *Anal. Chem.* **1980**, *52*, 1585–1588.

(3) Vogel, A. I. *A text-book of quantitative inorganic analysis including elementary instrumental analysis*, 3rd ed.; Longman: London, 1961.

(4) Lamberty, A.; Pauwels, J. *Int. J. Mass Spectr. Ion Processes* **1991**, *104*, 45–48.

(5) De Bièvre, P. *Fresenius J. Anal. Chem.* **1990**, *337*, 766–771.

(6) De Bièvre, P. *Anal. Proc.* **1993**, *30*, 328–333.

(7) Roth, E. *Pure Appl. Chem.* **1997**, *69*, 1753–1828.

(8) Meija, J.; Mester, Z. *Anal. Chim. Acta* **2008**, *607*, 115–125.

(9) Meija, J. *Anal. Bioanal. Chem.* **2014**, *406*, 2739–2740.

(10) Pagliano, E.; Mester, Z.; Meija, J. *Anal. Bioanal. Chem.* **2013**, *405*, 2879–2887.

(11) Bloch, K.; Anker, H. S. *Science* **1948**, *107*, 228.

(12) Rosenblum, C. *Anal. Chem.* **1957**, *29*, 1740–1744.

(13) Henrion, A. *Fresenius J. Anal. Chem.* **1994**, *350*, 657–658.

(14) Milton, M. J.; Wang, J. *Int. J. Mass Spectr.* **2002**, *218*, 63 – 73.

(15) Milton, M. J. T.; Wang, J. *Rapid Commun Mass Spectr.* **2003**, *17*, 2621–2625.

(16) Vogl, J. *Rapid Commun. Mass Spectr.* **2012**, *26*, 275–281.

(17) Frank, C.; Rienitz, O.; Swart, C.; Schiel, D. *Anal. Bioanal. Chem.* **2013**, *405*, 1913–1919.

(18) Pagliano, E.; Meija, J.; Mester, Z. *Anal. Chim. Acta* **2014**, *824*, 36–41.

(19) Pickup, J. F.; McPherson, K. *Anal. Chem.* **1976**, *48*, 1885–1890.

(20) Werner, R. A.; Brand, W. A. *Rapid Commun. Mass Spectr.* **2001**, *15*, 501–519.

(21) Mackay, L.; Taylor, C.; Myors, R.; Hearn, R.; King, B. *Accred. Qual. Assur.* **2003**, *8*, 191–194.

(22) D'Ulivo, A.; Pagliano, E.; Onor, M.; Pitzalis, E.; Zamboni, R. *Anal. Chem.* **2009**, *81*, 6399–6406.

(23) Evaluation of measurement data - Guide to the expression of uncertainty in measurement. JCGM 100, 2008.

Graphical TOC Entry