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Development of a high ratio isotope dilution mass spectrometry calibration technique for chemical metrology

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IDMS with calibration by “exact” or “approximate signal matching” methods offers a number of advantages for chemical metrology applications where measurements of low uncertainty are required for analytes at low concentrations in complex matrices. These methods have been applied extensively but are unsuitable for some important applications because in many cases, the concentration of the spike isotope in each measured blend of a sample or standard should be as close as possible to the concentration of the natural analyte isotope. In this paper we discuss recent work investigating the extent to which it is possible to move away from this ideal 1 : 1 blend isotope ratio whilst retaining the key benefits of the approximate matching technique. This has been used for the first time for applications where the sample has a very high analyte concentration, which would require unacceptably high amounts of spike with the existing method. The methodology has been validated for sulfur using a well-characterised candidate matrix reference material – NIST SRM1624d. This is a diesel fuel sample that contains approximately 4000 μg g^{-1} sulfur. Results were obtained using a ratio for ^{32}S/^{34}S of 14, achieving accuracy and uncertainty comparable with the original method using a blend isotope ratio of 1.

Introduction

The technique of isotope dilution mass spectrometry (IDMS) was initially developed for elemental analysis during the 1950s[1] using thermal ionisation mass spectrometry (TIMS).[2] More recently, inductively coupled plasma mass spectrometry (ICP-MS) has facilitated the use of IDMS for elemental analysis because it requires much less sample preparation. Elemental IDMS uses an enriched isotope of the target analyte as the optimal form of internal standard, the isotopic “spike” being added at the earliest possible stage of the measurement procedure. In principle, an isotopically enriched spike of known concentration can be used directly as the calibration standard. However, the so-called double IDMS method[3] avoids the need for an accurately characterised spike by incorporating a parallel IDMS measurement involving the enriched material and a natural standard of the analyte. IDMS is classified as a definitive method[4] with definable uncertainty values because as a ratio technique it can be described completely in terms of a measurement equation. This is reflected in the widespread adoption of the technique by national measurement institutes for the preparation of certified reference materials (CRMs) and provision of traceable reference values.[5–8]

For routine, single collector ICP-MS instruments the uncertainty budget for IDMS is governed primarily by the ability to measure precise isotope ratios with additional contributions from the sample preparation, the primary standard concentration and other minor components.[9] The latest multi-collector ICP-MS instruments enable isotope ratio measurements with extremely high precision (typically 0.05% or better),[10] opening the way for analysis of complex matrix samples by IDMS with uncertainties achievable by few other techniques.

The approaches to IDMS calibration which are described in this paper are based on the so-called “exact signal matching” method.[3,4] It involves an iterative adjustment procedure requiring isotope ratio measurements for many gravimetrically prepared “blends” containing the enriched (spike) isotope and either the unknown sample or a natural calibration standard. The terms adopted in this paper for the various mixtures and ratios are described in Table 1. This process culminates with calibration and sample blends that are exactly matched *i.e.* they have exactly the same concentration of analyte isotope in the spiked sample and the spiked calibration standard. Ideally, the ratio of the analyte isotope to the spike isotope in each sample or standard blend should be equal to 1.[11] This can result in very low uncertainties, as systematic errors in the determination of the isotopic ratios are cancelled out under exact matching conditions. However, this approach is relatively laborious as several iterations may be required and it is not always feasible to achieve a blend isotope ratio of 1. The “approximate signal matching” technique[4,12] provides a less onerous alternative to “exact signal matching” whilst retaining many of its advantages. This is essentially the same except that fewer iterations are carried out. The two approximately matched solutions are then run alternately to provide a series of replicate measurements which can be averaged as with the “exact matching” technique. The method has been used extensively at LGC,[8,13,14] for certification of reference materials or provision of accurate reference values and has been extensively proven in a series of international comparisons involving analysis of unknown samples.[15]

Regardless of the specific calibration procedure used, there are number of parameters which influence the optimum spiking ratio necessary to minimise error and maximise precision for each IDMS application. These include the so-called error propagation factor and the characteristics of the mass spectrometer (precision, ion counting uncertainty, background signal, linear dynamic range and detector dead time). The error propagation factor is a theoretical optimum for spiking samples to achieve the best precision for the ratio measurements.[2,16] It can be calculated from the isotopic abundances in the natural sample and the isotopically enriched spike and is dependent on the isotope system being measured. The exact theoretical optimum, EPF$_{opt}$ (expressed as spike isotope over analyte isotope), is eqn. (1), where h = isotopic abundance, S = spike isotope, A = analyte isotope, sp = enriched solution and

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Table 1 Standardised terms used in the text to describe IDMS measurement procedures

Spiking	Addition of an isotopically enriched material to a natural calibration standard or a sample.
Blend	A mixture obtained by spiking a natural calibration standard or sample with the isotopically enriched material.
Spike isotope ratio	The ratio of the amounts of the natural and enriched isotopes in the material used for spiking.
Natural isotope ratio	The ratio of the amounts of the natural and enriched isotopes in either a natural calibration standard or a sample.
Blend isotope ratio	The ratio of the amounts of the natural and enriched isotopes in a blend.

sa = sample. The calculated optimum ratio for the sulfur materials used in this study is 0.88.

$$\mathrm{EPF_{opt}} = \sqrt{\frac{h^S_{sp}}{h^A_{sp}}\frac{h^S_{sa}}{h^A_{sa}}} \qquad (1)$$

The rate at which the error propagated by this factor alters (as one moves away from the theoretical optimum) varies significantly for each specific combination of natural (analyte) and enriched (spike) isotope abundances for the element of interest. The error propagation factor as a function of the blend isotope ratio for the sulfur materials used in this study is shown in Fig. 1. This has been calculated using the equation described by Ohata *et al.*[17] The chart shows that a deviation in blend isotope ratio beyond the range 0.2–5 (^{34}S/^{32}S) leads to a dramatic increase in error factor. This range is consistent with general recommendations in the literature that the spiking ratio should lie between 0.25 and 4.[6] The optimum blend ratio based on error propagation factors alone does not always fall within this range. In practice, the optimum blend ratio is a compromise between EPF and the instrument performance (deadtime, linearity, *etc*). Whatever blend isotope ratio within this range is selected, guidance for the approximate matching technique is that the standard blend isotope ratio should be the same as the sample blend isotope ratio within 5%.[4]

As discussed above, the optimum blend isotope ratio is as close to 1 as possible but achieving this is often a practical problem, for example:

(1) samples with high analyte concentration (*e.g.* major components of metal alloys, purity assay of single substances) require very large amounts of spike which is expensive and may be impracticable (because the spike is available only as a relatively dilute solution leading to excess dilution of the sample).

(2) The uncertainty at very low analyte concentrations is poor because both isotopic signals are close to detection limit, leading to an imprecise ratio measurement.[18]

(3) For some analytes, the only practicable spike is radioactive (*e.g.* ^{236}U or ^{229}Th) making it desirable to use very low spike concentrations.

In this paper we discuss recent work investigating the extent to which it is possible to move away from the ideal 1 : 1 isotopic ratio for the first of the applications listed above, whilst retaining the key benefits of the approximate matching technique. Initial experiments looked at the applicability of a high-ratio IDMS method for the quantification of sulfur. The applicability of the high-ratio IDMS concept has been proven by using a diesel fuel sample with high sulfur content (approximately 4000 μg g^{-1}). The sample has been well characterised as part of a comparison between several national metrology laboratories which are expert in this type of analysis.[19]

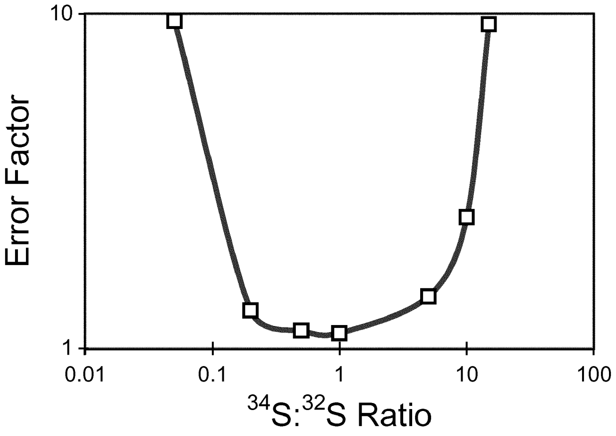

Fig. 1 The error propagation factor for sulfur as a function of blend isotope ratio (^{34}S/^{32}S).

Experimental

Samples and reagents

High-purity nitric acid (Romil, Cambridge, UK) and 18 ΩM deionised water (Elga, Marlow, UK) were used throughout the measurements and sample preparation procedures described below.

NIST SRM3154 (a sulfur standard solution certified at 10.3 ± 0.03 mg g^{-1}) was used for calibration purposes. A stock solution of isotopically enriched spike was prepared from a pure sulfur material (ORNL, Oak Ridge, Tennessee, USA) enriched in ^{34}S at 94.27% abundance. The spike isotope ratio (^{32}S/^{34}S) was 0.060 ± 0.001. The sulfur was fully oxidised to H_2SO_4 in concentrated HNO_3 using a closed vessel microwave technique outlined elsewhere[8] and diluted to the working spike solution ^{34}S concentration as required. A second, independent standard solution was prepared from high-purity sulfur (99.999 95%, Alfa Aesar, Karlsruhe, Germany) using the same microwave digestion technique.

NIST SRM8553 was used in the measurement of the samples and standards to determine the natural isotope ratios of sulfur. This reference material is pure elemental sulfur certified for sulfur isotope ratios. It was prepared by microwave digestion as above.

The fuel sample used to validate the high-ratio IDMS method was a NIST candidate reference material, SRM1624d. This is a diesel sample with a high concentration of sulfur that has been analysed[19] by four national metrology institutes as part of an international comparison study. LGC originally participated in this study using its normal approximate matching method with a blend isotope ratio of 1 and a single-collector magnetic sector ICP-MS.

Instrumentation

Measurements for the high-ratio experiments were made using a multi-collector ICP mass spectrometer (Neptune MC-ICPMS, Thermo Finnigan, Bremen, Germany). The instrument has a detector array that comprises nine faraday detectors. It is also equipped with a high resolving function which allows resolution of ^{32}S and ^{34}S from the interfering ions of $^{16}O_2$ and $^{16}O^{18}O$, respectively. Standard operating conditions used in this investigation are detailed in Table 2. The multi-collector instrument was chosen because of the superior isotope ratio precision. This provided additional confidence in measurements made with high spiking ratios and also allows precise measurement of the natural sulfur isotope ratios in the samples (see below).

A single collector magnetic sector ICP-MS (Element 1, Thermo Finnigan, Bremen, Germany) was used for analysis

Table 2 Standard operating conditions for measurement of $^{32}S/^{34}S$ on the multi-collector ICP-MS

Forward power	1175 W
Ar cool gas flow rate	13.5 L min^{-1}
Ar auxiliary gas flow rate	1.0 L min^{-1}
Ar nebuliser gas flow rate	0.9 L min^{-1}
Nebuliser	ESI PFA nebuliser
Nebuliser uptake rate	0.05 ml min^{-1}
Spray chamber	SIS
Slit width	32 µm
Number of cycles	5
Number of cycles	5

of the fuel sample using a blend isotope ratio of 1, which provided a benchmark for comparison of the IDMS methods.

Acid digestion of samples was performed using a Multiwave 2000 closed-vessel microwave system (Anton Paar, Austria) with quartz vessels.

Measurement of the isotopic composition of the samples and standard solutions

The natural isotope ratios of sulfur vary in nature and as such their IUPAC values[20] have very high uncertainties. Hence, measuring the sulfur natural isotope ratios directly for samples and natural calibration standards using the multi-collector instrument reduces the overall measurement uncertainty. This reduction is significant given the small uncertainties that are achievable when using high-accuracy IDMS methods.

The isotopic composition of NIST SRM 3154 was determined by analysis of the $^{32}S/^{34}S$ ratio with instrumental mass discrimination determined relative to NIST SRM 8553. The absolute $^{34}S/^{32}S$ isotope ratio of NIST SRM 8553 was calculated based upon values published by Ding[21] and adopting the certified $\delta^{34}S$ of 16 ‰ to give a $^{32}S/^{34}S$ ratio of 22.29. Drift in mass discrimination was corrected by monitoring $^{28}Si/^{30}Si$ added to the sulfur standards and samples as described by Evans *et al.*[22]

SRM 3154 and the secondary standard solution (prepared from high-purity sulfur) were determined to have an indistinguishable $^{32}S/^{34}S$ ratio of 22.44 ± 0.009. This is in keeping with published compilations of $\delta^{34}S$ which indicate only small isotopic differences in sulfuric acids.[23] The results were also in good agreement with previously determined $^{32}S/^{34}S$ ratio by sector ICPMS for SRM 3154.[22]

The fuel sample was prepared by closed-vessel microwave digestion and was found to have a $^{32}S/^{34}S$ ratio of 22.41 ± 0.02. The difference between fuel and standards is at the limits of differentiation for the technique.

Comparison of standard solutions at varying blend isotope ratios

As a preliminary experiment, two aqueous standard solutions of sulfur from different sources were prepared for comparison by IDMS. The standard solution prepared from pure sulfur was treated as the unknown sample and spiked with appropriate isotopically enriched solutions to yield blend isotope ratios of 1, 10, 15 and 20. The other standard (NIST SRM3154) was used to prepare calibration solutions with the same blend isotope ratios.

The measurement sequencing method employed was that of bracketing in which a calibration standard blend is measured immediately before and after each sample blend. The average measured isotope ratio of the two calibration standard blends is used in the IDMS calculation. Each sample blend was measured only against the calibration standard blend with the same blend isotope ratio.

Analysis of fuel sample SRM1624d

The fuel sample was analysed using the original IDMS technique (blend isotope ratio = 1) as well as using the high-ratio technique (blend isotope ratio = 14). In both cases, sample and standard blends were prepared by the addition of appropriate quantities of spike material followed by microwave acid digestion with nitric acid (5 ml) as described elsewhere.[8] Standard blends were prepared from a dilution of SRM3154 with the same spike solutions such that standard blend isotope ratio equalled that in the sample blends. After digestion, the solutions were diluted with deionised water to yield appropriate concentrations of sulfur. Measurements were performed using the same bracketing technique as described above.

Initial analyses were performed on three replicates of the fuel sample using LGC's original matching IDMS method (*i.e.* blend isotope ratio $^{32}S/^{34}S$ of 1) with the single collector magnetic sector ICP-MS. The measurement solutions contained approximately 400 ng g^{-1} sulfur. The instrument signals were approximately 1 million counts per second for each isotope.

Four other replicate sample blends were prepared such that the blend isotope ratio $^{32}S/^{34}S$ was 14 and measured using the multi-collector ICP-MS. The measurement solutions contained approximately 7.5 µg g^{-1} ^{32}S and 0.5 µg g^{-1} ^{34}S. The instrument signals were approximately 7.5 volts for ^{32}S and 0.5 volts for ^{34}S.

IDMS calculations and uncertainty budget

The symbols used for each of the components in the double IDMS equation are detailed in Table 3. Two equations have been applied in this study. The derivation of these equations is

Table 3 Description of symbols used in the IDMS equations

Symbol	Description
C_X	Mass concentration of S in sample X
C_Z	Mass concentration of S in calibration standard Z
M_Y	Mass of spike Y added to the sample X to prepare the blend B (= $X + Y$)
M_X	Mass of sample X added to the spike Y to prepare the blend B (= $X + Y$)
M_{Zc}	Mass of calibration standard solution Z added to the spike Y to make calibration blend Bc (= $Y + Z$)
M_{Yc}	Mass of spike Y added to the spike Y primary standard solution Z to make calibration blend Bc (= $Y + Z$)
R'_B	Measured isotope amount ratio of sample blend ($X + Y$) (*e.g.* $^{32}S/^{34}S$)
R'_{Bc}	Measured isotope amount ratio of calibration blend ($Bc = Z + Y$) (*e.g.* $^{32}S/^{34}S$)
R_X	Natural isotope amount ratio of sample X (*e.g.* $^{32}S/^{34}S$)
R_Y	Natural isotope amount ratio of spike Y (*e.g.* $^{32}S/^{34}S$)
R_Z	Natural isotope amount ratio of calibration standard Z (*e.g.* $^{32}S/^{34}S$)
$\sum R_{iX}$	Sum of all isotope amount ratios of sample X relative to the spike isotope (*e.g.* ^{34}S)
$\sum R_{iZ}$	Sum of all isotope amount ratios of primary standard Z relative to the spike isotope (*e.g.* ^{34}S)
R_{Bc}	Gravimetric value of the isotope amount ratio of calibration blend ($Bc = Z + Y$) (*e.g.* $^{32}S/^{34}S$)

detailed elsewhere.[9] Eqn. (2) is the full IDMS equation which contains expressions for the natural isotope abundances in the sample (R_X) and calibration standard (R_Z) as well as the sum of all natural isotope ratios in the standard and samples relative to the spike isotope (in this case ^{34}S). Eqn. (3) is a simplified IDMS equation, in which R_X is assumed to be equal to R_Z. In this case, the sum expressions cancel out and are therefore not required in the equation. All of the ratio expressions in eqns. (2) and (3) refer to the analyte isotope over the spike isotope *i.e.* ^{32}S/^{34}S.

$$c_X = c_Z \frac{m_Y}{m_X} \frac{m_{Zc}}{m_{Yc}} \frac{R_Y - R'_B \frac{R_{Bc}}{R'_{Bc}}}{R'_B \frac{R_{Bc}}{R'_{Bc}} - R_X} \frac{R_{Bc} - R_Z}{R_Y - R_{Bc}} \frac{\sum R_{iX}}{\sum R_{iZ}} \qquad (2)$$

$$C_X = C_Z \frac{m_Y}{m_X} \frac{m_{Zc}}{m_{Yc}} \frac{R_Y - R'_B \frac{R_{Bc}}{R'_{Bc}}}{R'_B \frac{R_{Bc}}{R'_{Bc}} - R_X} \frac{R_{Bc} - R_Z}{R_Y - R_{Bc}} \qquad (3)$$

All uncertainty components were estimated and combined according to the *ISO Guide to Measurement Uncertainty (GUM)*[24] and the *EURACHEM Uncertainty Guide*.[25] Sensitivity coefficients were calculated using partial derivatives and multiplied by each parameter's standard uncertainty to obtain the combined standard uncertainty associated with the mass fraction of sulfur in the sample.

Results

Comparison of standard solutions at varying blend isotope ratios

The results for the standard solutions calculated using eqn. (2) (see Fig. 2) are in agreement (within their measurement uncertainties) with the ideal blend isotope ratio of 1, although, the blend isotope ratio of 20 may indicate a deterioration both in terms of accuracy and uncertainty.

Analysis of fuel sample SRM1624d

The recoveries for the replicates of the fuel sample using a blend isotope ratio of 1.0 are given in Table 4. For each sample blend, the table also shows the extent to which its blend isotope ratio was matched to the standard blend isotope ratio (R'_B/R'_{Bc}, expressed as a percentage) together with the average match for each standard blend. The results demonstrate that even when these differed by as much as 8%, the recovery obtained for the reference material was not significantly affected.

The results for the quantification of SRM1624d at a blend isotope ratio of 14 are shown in Fig. 3. These results were obtained using the full IDMS eqn. (2) with the measured values for R_X and R_Z. The four sample blends were each measured against two separate standard blends as illustrated. There is a significant difference between the results from each standard blend, with only one standard blend resulting in acceptable recoveries. Table 5 shows the relationship between the recovery and the extent of matching (R'_B/R'_{Bc}, expressed as a percentage). Only the standard blend 2, which was matched to the sample blend within ±0.5%, gave acceptable recoveries. Standard blend 1, which was matched to the sample blend within only >1%, gave recoveries outside of the expected range. This shows that when high blend isotope ratios are used, the matching is much more critical than when using a conventional blend isotope ratio of 1.

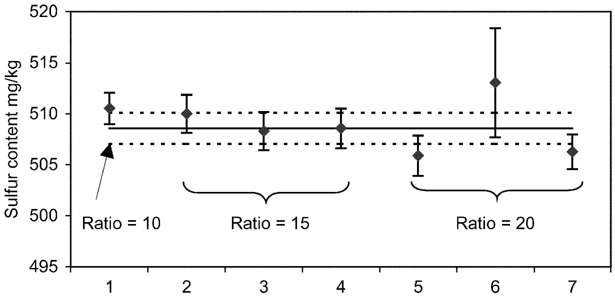

Fig. 2 Analysis of a solution of a pure sulfur standard at blend isotope ratios (^{32}S/^{34}S) varying from 10 to 20. The horizontal lines represent the mean and uncertainty obtained using a blend isotope ratio of 1.

Table 4 Relationship between recovery of the expected value for SRM1624d and the match between sample blend isotope ratio and standard isotope blend ratio (R'_B/R'_{Bc} expressed as a percentage) when the ratio is 1. Results show that a recovery >99% can be achieved when the match between the two solutions differs significantly from the ideal

Standard	Replicate	R'_B/R'_{Bc} Match (%)	Recovery (%)
1	1	97.7	100.1
	2	101.6	100.8
	3	102.4	99.4
Mean ± standard deviation		100.5 ± 2.5	100.1 ± 0.7
2	1	91.9	101.9
	2	92.7	99.1
	3	94.8	99.5
Mean ± standard deviation		93.1 ± 1.5	100.2 ± 1.5

The results for the fuel sample were also calculated using the full eqn. (2) and the simplified eqn. (3), both where R_X and R_Z are taken from IUPAC.[20] These results, given in Table 6, show that the simplified equation with IUPAC natural isotope ratios is sufficient since the concentrations and their uncertainties are in good agreement with those obtained using the full equation with measured R_X and R_Z natural isotope ratios. However, it is clear that use of the full equation with IUPAC values for R_X and R_Z gives a highly elevated and unrepresentative uncertainty estimate.

This observation can be explained by examining the partial derivatives of the natural isotope ratios, R_X and R_Z. The partial derivatives in the full IDMS eqn. (2), involve the multiplication of the uncertainties of these ratios by the parameter R_{Bc} (the expected standard blend ratio) such that the sensitivity coefficients for R_X and R_Z increase as the value of the blend ratio increases. Therefore, when using the full equation with IUPAC values for R_X and R_Z, the overall uncertainty is unacceptably high if the blend ratios are high. In contrast, when the blend isotope ratio is 1, the uncertainties for R_X and R_Z form an insignificant part of the total uncertainty budget regardless of whether measured or IUPAC values are used.

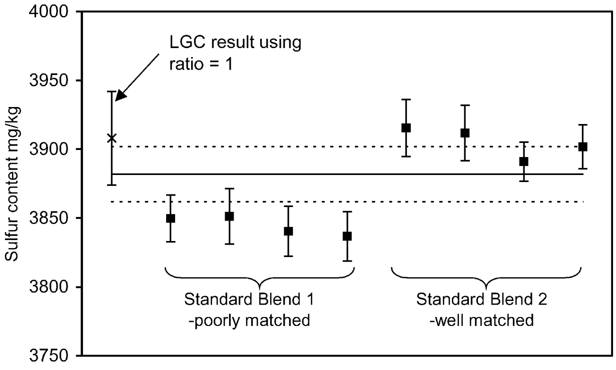

Fig. 3 Analysis of a diesel fuel candidate reference material (NIST SRM1624d) at a high blend isotope ratio (^{32}S/^{34}S) of 14 (■). The horizontal lines represent the mean and uncertainty of the NIST value[19] for the candidate reference material.

Table 5 Relationship between recovery of the expected value for SRM1624d and the match between sample blend isotope ratio and standard blend isotope ratio (R'_B/R'_{Bc} expressed as a percentage) when the blend isotope ratios are 14. Results show that a recovery >99% can only be achieved when the match between the two solutions differs by <1% from the ideal

Standard	Replicate	R'_B/R'_{Bc} Match (%)	Recovery (%)
1	1	98.7	98.9
	2	98.1	98.9
	3	98.5	98.6
	4	98.5	98.5
Mean ± standard deviation		98.5 ± 0.3	98.7 ± 0.2
2	1	100.3	100.6
	2	99.6	100.5
	3	99.9	100.0
	4	100.1	100.2
Mean ± standard deviation		100.0 ± 0.3	100.3 ± 0.3

Table 6 Comparison of results obtained for SRM1624d at a blend ratio of 14 when using different equations and IUPAC or measured values for R_X and R_Z

IDMS equation	Values for R_X and R_Z	Concentration/ µg g^{-1}	Uncertainty % ($k = 1$)
Full eqn. (2)	Measured	3875	0.47
Simplified eqn. (3)	IUPAC	3864	0.50
Full eqn. (2)	IUPAC	3864	9.7

Discussion

Previous work in our laboratory has shown that, for inorganic IDMS, modifying the "exact matching" procedure of Henrion[3] to an "approximate matching" procedure (usually having the standard and sample blend isotope ratios matched within 5%) retains the benefit of high-accuracy IDMS measurements whilst considerably reducing the time and effort required. It was, however, assumed that the need remained for an optimum blend isotope ratio of 1. The current work has demonstrated that the accuracy of this IDMS technique for high analyte concentrations can be maintained even at high blend isotope ratios. However, in this case, extra care must be taken to match the blend isotope ratios of the sample and standard blends as closely as possible.

The work presented here also shows the possibility to use a high-ratio IDMS technique without the necessity to perform high-accuracy determination of the natural isotope ratios in the sample and standard materials.

The efficacy of the modified technique has been demonstrated through the quantification of sulfur in a candidate diesel fuel reference material. Use of this technique makes it practicable to apply high-accuracy IDMS to difficult application areas where the concentration of the analyte is so high that use of a blend isotope ratio of 1 would require the addition of a prohibitively large amount of spike material. Typical certification applications, other than that described here, include major elements in matrix reference materials (*e.g.* sulfur in pharmaceutical compounds) or high-purity compounds used for preparation of calibration standards (*e.g.* sulfur in dibutyl sulfide).

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