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Detection Limit of Isotope Dilution Mass Spectrometry

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The detection limit is an important figure of merit for evaluating instrumentation and analytical methods. While the detection limit for techniques using linear calibration functions has been studied extensively, this fundamental metric has rarely been discussed for mass spectrometry that bases the calibration on the principle of isotope dilution. We have developed a formulation for the detection limit for isotope dilution mass spectrometry (IDMS) after a thorough analysis of the uncertainty of IDMS measurements. The new formulation describes the IDMS detection limit as a function of the enrichment of the isotopic spike and the linear calibration detection limits measured at the masses for the isotope ratio measurement.

The detection limit is an important figure of merit in analytical chemistry. It is defined as the minimum concentration or weight of analyte that can be detected at a known confidence level.[1] The subject of detection limit commands a great deal of interest among analytical chemists, because it is not only of academic curiosity but also of practical significance: detection limit is a widely used criterion to evaluate analytical methods and the quality of analytical instrumentation.

Linear calibration functions are widely used in analytical measurements. Detection limits for techniques using a linear calibration function have been extensively studied, and the formulation for this type of calibration function has been elegantly described.[2]

Elements with two or more stable isotopes may be quantified by an alternative mode of calibration called isotope dilution, which uses an artificially enriched isotope (called a "spike") as an internal standard.[3] Isotope dilution by plasma source mass spectrometry is one of the most accurate methods for elemental analysis.[3] With the expanding installed base of the plasma source mass spectrometers, isotope dilution methods are gaining popularity, especially at national metrology laboratories. Due to the fact that the isotope ratio, the measurand, is not a linear function of the analyte concentration, the detection limit formulation for the linear calibration functions does not apply to isotope dilution mass spectrometry (IDMS). Being a critical specification of analytical techniques, the detection limits for IDMS are frequently found in the literature despite a lack of fundamental development on the subject. These literature values are estimated empirically to be three times the standard uncertainty of the concentration of a blank measured at the mass of the reference isotope using a linear calibration function.[4]

We have developed a novel formulation for the determination of IDMS detection limit and have assessed the robustness of the new formulation relative to the empirical one used in the literature. We show that the empirical formulation does not produce the correct detection limit, and only the new formulation is able to serve as the benchmark for comparing the detection capabilities of various instruments and techniques.

IDMS Detection Limit. The detection limit is the threshold uncertainty of the measurement that separates the determinable quantities from the undeterminable quantities, and it is expressed as the standard uncertainty for measuring a blank multiplied by a factor (typically 3) to achieve a desired confidence level.[5] Since the detection limit is a function of the measurement uncertainty at the limit of zero analyte concentration in the sample, a logical starting point to assess the IDMS detection limit is to develop a general expression for the uncertainty of IDMS measurements. The uncertainty expression can then be evaluated at the limit of zero concentration to derive the expression for IDMS detection limit. We begin assessing the uncertainty of the measurement by analyzing the IDMS equation. Although we treat the detection limit of the analyte in terms of concentration, the discussion also applies to absolute amount. The frequently used symbols are listed in Table 1, and additional symbols will be defined as they appear in the text.

In the following, it is assumed that corrections for instrumental mass bias, fractionation, and detector dead time have been made. The concentration of the analyte, C_x, in a sample is then given by the IDMS formula:[3]

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Table 1. List of Symbols

symbols	definition
subscripts p, x, and m	denotes the isotopic spike, the sample, and the spiked sample, respectively
A and B	isotopes A and B of the analyte
I_a and I_b	intensities of isotopes A and B, respectively
A_p, B_p, A_x, and B_x	atom fraction of isotopes A and B in the spike and isotopes A and B in the sample, respectively
C_a, C_b, C_p, and C_x	in the spiked sample, the concentration (mol/kg solution) of isotopes A and B, that of the analyte of the spike, and that of the analyte of the sample, respectively
R_m, R_x, and R_p	ratio of isotopes A to B for the spiked sample, the unspiked sample, and the spike, respectively
u_a, u_b, and u_x	standard uncertainties of C_a, C_b, and C_x, respectively

$$C_x = C_p \frac{R_m B_p - A_p}{A_x - R_m B_x} \quad (1)$$

The standard uncertainty for measuring C_x near the detection limit is described by the following:[6]

$$u_x = \frac{\sqrt{u_a^2 + R_m^2 u_b^2 - 2R_m u_a u_b \rho_{a,b}}}{|A_x - R_m B_x|} \quad (2)$$

where $\rho_{a,b}$ is the correlation coefficient for intensities of isotopes A and B (derivation in Appendix).

We evaluate the measurement uncertainty as the analyte concentration approaches zero, since the detection limit is typically described as a multiple of the standard uncertainty of the blank. For ultratrace analysis by IDMS, the optimum spike-to-sample analyte ratio that results in the minimum measurement uncertainty is determined by the isotopic compositions of the sample and the spike.[7,8] This optimum ratio is independent of the amount of the analyte from the sample for a given sample and a given isotopic spike.[7,8] As the analyte concentration in the sample decreases, the amount of the isotopic spike added to the sample must also decrease proportionally to maintain the optimum spike-to-sample analyte ratio to keep the measurement uncertainty u_x at a minimum. Consequently, the concentrations of isotopes A and B in the spiked sample, C_a and C_b approach zero as the concentration of the analyte from the sample approaches zero. The intensity at masses A and B approaches the shot noise of the detector, provided that the baseline intensity of the spectrometer is limited by the dark noise of the detector. The correlation coefficient approaches zero, and eq 2 is reduced to the following:

$$u_x = \frac{\sqrt{u_a^2 + R_m^2 u_b^2}}{|A_x - R_m B_x|} \quad (3)$$

There are three variables, u_a, u_b, and R_m, in eq 3, and these variables are evaluated at the limit of zero concentration of the analyte from the sample. Provided that the linear calibration detection limit of isotopes A and B equals three times the standard uncertainty for measuring the isotopes in the blank, the uncertainty terms u_a and u_b can, in turn, be expressed as one-third of the linear calibration detection limit of isotopes A and B, respectively. The isotopic ratio of the spiked blank equals that of the spike, R_p, since a finite amount of the isotopic spike must be present (and just as importantly, u_x reaches a minimum as R_m approaches R_p). In accordance with the detection limit criterion being three times the standard uncertainty of the concentration of a blank, both sides of eq 3 are multiplied by a factor of 3, and the uncertainty expression of eq 3 is transformed to describe the IDMS detection limit L_D:

$$L_D = \frac{\sqrt{L_{Da}^2 + R_p^2 L_{Db}^2}}{|A_x - R_p B_x|} \quad (4)$$

where L_{Da} and L_{Db} are the linear calibration detection limits for isotopes A and B, respectively.

To complete the discussion on the correlation coefficient in eq 2, we consider the case that the intensities of isotopes A and B do not approach zero for a blank solution. Previous arguments being used to evaluate u_a, u_b, and R_m in deriving eq 4 are applicable here, and eq 2 is transformed to formulate the IDMS detection limit:

$$L_D = \frac{\sqrt{L_{Da}^2 + R_p^2 L_{Db}^2 - 2R_p L_{Da} L_{Db} \rho_{a,b}}}{|A_x - R_p B_x|} \quad (5)$$

The most common occurrences of nonzero intensity at mass of isotopes A and B for a blank are when the instrument is contaminated with the analyte. This is true for isotope dilution measurements of most elements by ICPMS. In the extreme, when the instrument is heavily contaminated and the intensity at the mass of isotopes A and B is perfectly correlated, $\rho_{a,b}$ approaches 1 and eq 5 reduces to the following:

$$L_D = \left|\frac{L_{Da} - R_p L_{Db}}{A_x - R_p B_x}\right| \quad (6)$$

Equations 6 and 4 are the minimum and the maximum estimates, respectively, of the IDMS detection limits that correspond to $\rho_{a,b}$ being 1 and 0 for eq 5. The actual detection limit in this case is less than what is calculated from eq 4 when $\rho_{a,b} \neq 0$; therefore, eq 4 gives a conservative estimate of the IDMS detection limit when the correlation coefficient $\rho_{a,b}$ is neglected.

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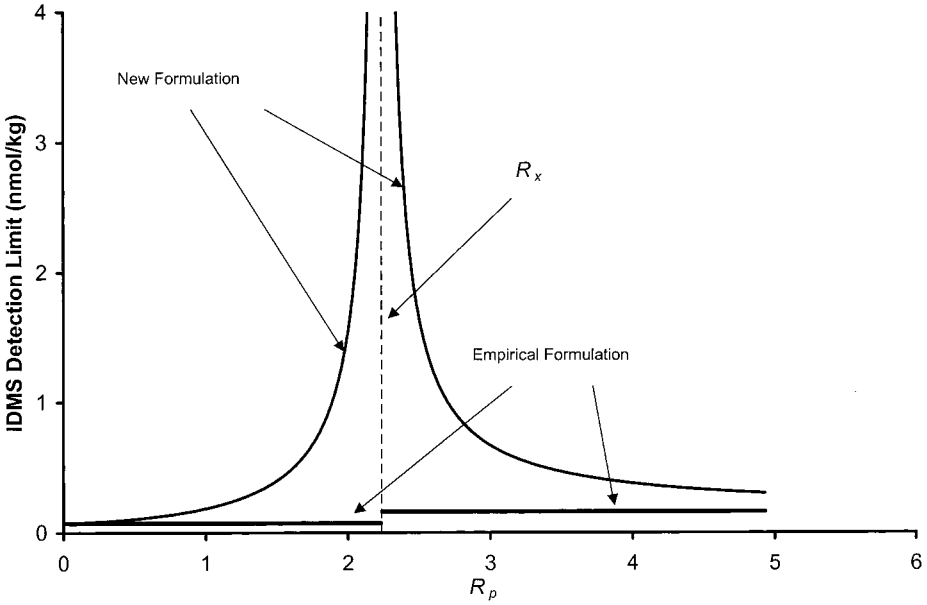

Figure 1. IDMS detection limit of Cu as a function of the $^{63}Cu/^{65}Cu$ ratio of the spike material. The linear calibration detection limits of ^{63}Cu and ^{65}Cu are 0.05 and 0.05 nmol/kg, respectively. The vertical line at 2.235 denotes the natural isotopic ratio of Cu. The two horizontal lines at 0.07 and 0.16 nmol/kg are the IDMS detection limits calculated by the empirical formulation.

DISCUSSION

Characteristics of the Formulation. An inspection of eq 4 reveals that R_p is the only variable since the linear calibration detection limits, L_{Da} and L_{Db}, are constants for a given experimental condition. Therefore, we evaluate the IDMS detection limit with respect to R_p. Considerations are given to R_p in three regions: R_x, from R_x to *0*, and from R_x to ∞.

At $R_p = R_x$, the isotopic spike is not enriched with either isotope A or isotope B. Substituting R_p in eq 4 with the natural isotopic ratio yields the relation

$$L_D \rightarrow \infty \tag{7}$$

The formulation indicates that when the spike is not isotopically enriched, the detection limit is infinite and the analyte in the sample cannot be determined by the method of IDMS.

The second region for R_p, from R_x to 0, is characterized by isotope B being the enriched isotope relative to isotope A. As R_p decreases, the denominator on the right-hand side of eq 4 increases and the numerator decreases. Accordingly, the detection limit decreases monotonically until a minimum is reached at $R_p = 0$. At this point, eq 4 is reduced to the following:

$$L_D = L_{Da}/A_x \tag{8}$$

Note that the right-hand side of eq 8 is the linear calibration detection limit measured at the unspiked or the reference isotope. The implication is that when the isotopic spike contains no isotope A, the determination of isotope A, and hence the analyte of the sample, is not affected by the spike. The IDMS measurement uncertainty depends only on how well isotope A can be measured, and hence, the IDMS detection limit is determined only by how low isotope A can be measured.

The third region for R_p, from R_x to ∞, is characterized by isotope A being the enriched isotope relative to isotope B. Note that the formulation for the IDMS detection limit, eq 4, is symmetric with respect to isotopes A and B. By transposing isotopes A and B, the discussion for the second region applies here. As R_p increases (corresponding to a decrease of R_p in the second region), the detection limit decreases, and the detection limit approaches a minimum as R_p approaches infinity:

$$L_D = L_{Db}/B_x \tag{9}$$

Similarly, the right-hand side of eq 9 is the linear calibration detection limit measured at the unspiked or the reference isotope.

Figure 1 gives an example of IDMS detection limit of Cu as a function of R_p ($^{63}Cu/^{65}Cu$), assuming the linear calibration detection limits for ^{63}Cu and ^{65}Cu to be 0.05 and 0.05 nmol/kg, respectively. It shows that the IDMS detection limit increases monotonically until R_p reaches R_x, which is denoted by a vertical dashed line. Then, the IDMS detection limit decreases monotonically as R_p increases beyond R_x.

New Formulation versus Empirical Formulation. The empirical formulation is widely used in the literature. This formulation is apparently borrowed from that for the linear calibration methods; however, its relevance to the IDMS detection limit is never substantiated. This formulation lacks the statistical rigor required of a formulation for the IDMS detection limit and, therefore, is fundamentally weak. The flaw of the empirical formulation is manifested in that it fails to account for the enrichment of the spike and that it fails to account for the uncertainties in the measurement of the spiked isotope.

According to the empirical formulation, the IDMS detection limit is a constant being the linear calibration detection limit of the reference isotope (Figure 1). This detection limit is independent of the enrichment of the spike material. The previous discussion and common sense suggest that an IDMS measure-

ment becomes more and more difficult as the spiking material becomes less and less enriched. At the extreme, the detection limit becomes infinite and IDMS measurement becomes impossible when the spiking material is not enriched. This fact contradicts the implication of the empirical formulation.

The empirical formulation also implies that IDMS detection limits are independent of the intensities at the spiked isotope. However, it is common sense that an IDMS measurement is dependent on the successful measurement of the intensity at the spiked isotope. The precision and the accuracy of the IDMS measurements suffer if, for example, interferences are present at the mass of the spiked isotope, and the measurements become impossible if the interferences are severe enough. This fact is also contradicted by the implication of the empirical formulation.

In contrast, the formulation developed in this work correctly predicts that the IDMS detection limit is a function of how well both isotopes can be measured. It also predicts that an IDMS measurement is impossible when the spike is not enriched with either isotope. As previous discussions have shown, the empirical formulation is just a special case of the new formulation, and it is true only when the spike material contains only one of the isotopes. For all other enrichment of the spike material, the empirical formulation underestimates the IDMS detection limit. The magnitude of the underestimation, in the Cu example, is the vertical distance between the curve of the new formulation and the horizontal line of the empirical formulation in Figure 1, and the underestimation is smaller at higher enrichment of the isotopic spike.

The usefulness of a formulation is measured not only by how well it predicts the outcome but also by how easily it is applied in practice. The determination of IDMS detection limit involves experimental measurements and calculations. The material requirement in the measurement is the same using both the new and the empirical approach. Isotopically enriched spike material is not needed in either approach; therefore, the extra cost to the new approach is the doubling of the measurement time since two isotopes are measured relative to the single reference isotope with the empirical approach. The calculation is trivial for both formulations within the spreadsheets with which all experimental data are processed in our laboratories.

CONCLUSION

The detection limit is a critical attribute of techniques for trace element analysis and, thereby, the most frequently published and quoted figure in the literature. Despite its renowned accuracy and precision, IDMS is less frequently applied to trace element analysis relative to the linear calibration techniques, partly because the detection capability of the technique cannot be appropriately evaluated. We have developed a robust formulation for IDMS detection limit. The new formulation affords a unique insight into the IDMS detection capability relative to the enrichment of the isotopic spike. Most importantly, it enables the evaluation of IDMS relative to the other techniques in terms of the detection capabilities and, thus, eliminates a handicap to the wide adoption of this accurate and precise technique.

APPENDIX

The isotope A to isotope B ratio of the spiked sample must satisfy the following relation:

$$R_m = \frac{I_a}{I_b} = \frac{C_a}{C_b} = \frac{C_{ax} + C_{ap}}{C_{bx} + C_{bp}} \tag{A1}$$

where C_{ax}, C_{ap}, C_{bx}, and C_{bp} are the concentrations of isotope A from the sample, isotope A from the spike, isotope B from the sample, and isotope B from the spike, respectively. Substituting R_m in eq 1 with eq A1 yields the following relation:

$$C_x = C_p \frac{C_a B_p - C_b A_p}{C_b A_x - C_a B_x} \tag{A2}$$

Assuming that the variance of the isotopic abundance of the sample and the spike do not contribute significantly,[7,8] the variance for the analyte concentration C_x is given by the following:[5]

$$u_x^2 = \left(\frac{\partial C_x}{\partial C_p}\right)^2 u_p^2 + \left(\frac{\partial C_x}{\partial C_a}\right)^2 u_a^2 + \left(\frac{\partial C_x}{\partial C_b}\right)^2 u_b^2 + 2\frac{\partial C_x}{\partial C_a}\frac{\partial C_x}{\partial C_b} u_a u_b \rho_{a,b} \tag{A3}$$

where $\rho_{a,b}$ is the correlation coefficient for C_a and C_b. The covariance term for C_p and C_a and the covariance term for C_p and C_b are not needed since C_a and C_b are independent of the determination of C_p. The quantity C_p can be accurately and precisely measured, and the relative uncertainty of C_p is generally better than 0.3%.[7] Provided that the detection limit is three times the standard uncertainty of the noise, the relative uncertainty of C_x at concentrations near the detection limit, a region of interest to this work, is estimated:

$$u_x / C_x \approx u_x / 3u_x \approx 30\% \tag{A4}$$

The variance from the first term in eq A3 is calculated:

$$\left(\frac{\partial C_x}{\partial C_p}\right)^2 u_p^2 = C_x^2 \left(\frac{u_p}{C_p}\right)^2 = \left(0.3\% \frac{u_x}{30\%}\right)^2 = 10^{-4} u_x^2 \tag{A5}$$

and the value of this term is much smaller relative to the variance of C_x according to eq 5; hence, the contribution of this term to the variance of C_x is neglected and eq A3 is simplified to yield the following relation:

$$u_x^2 = \left(\frac{\partial C_x}{\partial C_a}\right)^2 u_a^2 + \left(\frac{\partial C_x}{\partial C_b}\right)^2 u_b^2 + 2\frac{\partial C_x}{\partial C_a}\frac{\partial C_x}{\partial C_b} u_a u_b \rho_{a,b} \tag{A6}$$

The partial derivatives $\partial C_x / \partial C_a$ and $\partial C_x / \partial C_b$ are solved through

the following:

$$\frac{\partial C_x}{\partial C_a} = \frac{(B_p A_x - A_p B_x) C_b C_p}{(C_b A_x - C_a B_x)^2} = \left(\frac{C_p}{C_b}\right)\frac{B_p A_x - A_p B_x}{(A_x - R_m B_x)^2} \quad \text{(A7)}$$

$$\frac{C_p}{C_b} = \frac{C_{bp}}{B_p(C_{bp} + C_{bx})} = \frac{1}{B_p(1 + C_{bx}/C_{bp})} \quad \text{(A8)}$$

$$\frac{C_{bx}}{C_{bp}} = \left(\frac{A_p}{B_p} - R_m\right)\left(R_m - \frac{A_x}{B_x}\right)^{-1} \quad \text{(A9)}$$

Substituting C_p and C_b in eq A7 solves the partial derivative term:

$$\frac{\partial C_x}{\partial C_a} = \frac{1}{A_x - R_m B_x} \quad \text{(A10)}$$

Similarly,

$$\frac{\partial C_x}{\partial C_b} = \frac{(A_p B_x - B_p A_x) C_a C_p}{(C_b A_x - C_a B_x)^2} = \frac{-R_m}{A_x - R_m B_x} \quad \text{(A11)}$$

Substituting the partial derivatives in eq A6 and then taking the square root yields the uncertainty expression of eq 2.

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