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General procedures for limit of detection calculations in the industrial hygiene chemistry laboratory*

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Introduction

Limits of detection applicable to the analysis of industrial hygiene samples are of critical importance to the practicing industrial hygienist because unrealistically high analytical limits of detection can result in data which are meaningless with respect to any attempt to determine whether occupational exposure standards have been exceeded, and on the other hand, analytical approaches characterized by relatively low limits of detection provide extremely useful information which the practicing industrial hygienist can use with confidence in establishing safe working conditions.

In the industrial hygiene chemistry laboratory, chemists have historically been concerned with limits of detection of the analytical processes, but frequently all that was reported to the industrial hygienist was a general limit of detection of the process. As a result of recent interest by government agencies and, in particular, the industrial hygienist in the field, limits of detection are now routinely calculated and provided for each analysis separately.

While there is basic agreement as to the definition of the limit of detection, the actual implementation of calculations resulting in the determination of such a value is not as well specified. This paper presents a useful strategy for routine limit of detection calculations.

The limit of detection of an analytical process has been defined to be three standard deviations above the background instrument response. The purpose of this paper is to provide a bridge between this definition and the actual implementation of limit of detection calculations in the industrial hygiene or environmental chemistry laboratory. Methods are illustrated which incorporate into the limit of detection computations the shape of the calibration curve, the accuracy of prediction of the calibration curve, and the variability of instrument responses. The methods presented are widely applicable and can be easily added into existing analytical programs. **Burkart, J.A.:** General procedures for limit of detection calculations in the industrial hygiene chemistry laboratory. *Appl. Ind. Hyg.* 3:153-155; 1986.

Background

The 1980 American Chemical Society guidelines⁽¹⁾ for limits of detection and a more recent article⁽²⁾ summarize the basic approach to limit of detection (LOD) and limit of quantitation (LOQ) problems. These limits are calculated to be the concentration equivalent of K standard deviations from the background instrument response, where K is generally taken to be three for LOD and ten for LOQ.

The first problem that arises is in the determination of which standard deviation to use. Ideally, the standard deviation would be the standard deviation of instrument responses to blank samples, but in everyday laboratory practice this standard deviation may not be readily available. If any blanks are run, it is usually only two or three rather than the six or more which would likely be neces-

sary for accurate estimation of the blank standard deviation.

In the absence of a pure blank standard deviation, the standard deviation to be used then should incorporate any information on blank samples, plus information from low concentrations near the blanks, and should take into account how well the calibration curve fits the data. A method has been described which utilizes the standard error of the calibration curve and the standard deviation of the blanks, but only for a linear calibration curve.⁽²⁾

Nonlinear calibration curves provide a second problem not usually addressed. While simple linear calibration curves are definitely the rule, occasionally some instruments, methods, and analysts require the use of quadratic or exponential or weighted regressions to describe results. The important point is

TABLE I
Calibration curve data set for methyl ethyl ketone (MEK)

Standards	Instrument response		No. of replicates
	Quantity of MEK standards (mg)	Mean area	
0.0080	0.00680	0.00037	6
0.0160	0.01507	0.00034	6
0.0320	0.03165	0.00020	6
0.0800	0.08008	0.00046	6
0.1599	0.15852	0.00071	6
0.1999	0.19905	0.00055	6
0.3999	0.39956	0.00266	5
0.7997	0.78733	0.00349	6
1.5994	1.58735	0.00970	6
2.4015	2.38198	0.00783	6
3.9985	3.97974	0.00736	5
7.9970	8.13460	0.01919	5

to use the curve which truly fits the underlying distribution of the data, since limits of detection can be artificially altered by the indiscriminate choice of a calibration curve.

A third problem is attributed to the well recognized phenomena that, over a wide range of concentrations of standards, the variability of the instrument response frequently increases with increasing standard concentrations. Table I provides a data set which illustrates this. Using the standard error of the whole calibration curve will result in a larger standard deviation than would be obtained from lower concentrations only, thereby unrealistically increasing the LOD.

Since the determination of an LOD should be concerned with response variability in the low range of concentrations, any efficient method for determining a LOD should utilize the fitted calibration curve primarily with respect to the lowest concentrations. Use of a weighted calibration curve is also appropriate to reduce the effect of high concentration variability.

Other considerations in estimating the true variability of a process include the preparation of standards directly on the appropriate sample medium, wherever possible, to account for effects due to preparation of standards, to background on the medium, and to desorption efficiency. If replicate measurements are used, ideally they should be analyses of replicate preparations, not merely replicate injections of the same preparation.

Methods

Typically, in our industrial hygiene and environmental chemistry laboratory, calibration curves are determined from

a data set composed of six to eight chosen standards, replicated approximately twice. Four types of calibration curves may be used. Linear, quadratic, and exponential equations are used to fit curves of increasing functions of response with increasing concentrations. Although it is not widely used, an example of a decreasing function of response with increasing concentration is the Nernst equation, which is used for specific ion electrode analyses.

To calculate a concentration limit x_L (LOD or LOQ) one must first determine

Type of Calibration Curve	Equation
Linear	$y = a + bx$ (1)
Quadratic	$y = a + bx + cx^2$ (2)
Exponential	$y = a + b(1 - e^{-cx})$ (3)
Nernst	$y = a - b \log(c + x)$ (4)

where:

- y = Instrument response
- x = Concentration of standard
- a = Intercept or background instrument response derived from calibration curve
- b,c = Coefficients of concentration or functions thereof derived from calibration curve

$$\begin{aligned} \text{Linear} \quad y_L &= a + KS = a + bx_L \\ \text{then} \quad x_L &= (KS - a) / b \end{aligned} \quad (6)$$

$$\begin{aligned} \text{Quadratic} \quad y_L &= a + KS = a + bx_L + cx_L^2 \\ \text{then} \quad x_L &= \frac{-b + \sqrt{b^2 + 4KS c}}{2c} \end{aligned} \quad (7)$$

$$\begin{aligned} \text{Exponential} \quad y_L &= a + KS = a + b(1 - e^{-cx_L}) \\ \text{then} \quad x_L &= c^{-1} \ln(1 + KS/b) \end{aligned} \quad (8)$$

the corresponding response value y_L . This calculation requires the basic definition of LOD plus an estimate of the standard deviation (S) which will be described later:

$$y_L = a + KS \quad (5)$$

where:

a = the background instrument response

K = 3 for LOD and K = 10 for LOQ

Equating equation (5) with calibration curves (1) through (3) one may solve the equations for x_L , the limit of concern.

In the case of fitting a decreasing function such as the example of the Nernst equation, K standard deviations should be subtracted from the background response.

$$y_L = a - b \log c - KS \quad (9)$$

Then equating (9) and (4) the LOD or LOQ for Nernst is found:

$$\begin{aligned} \text{Nernst} \quad y_L &= a - b \log c - KS \\ &= a - b \log(c + x_L) \end{aligned}$$

$$\text{then } x_L = c(10^{KS/b} - 1) \quad (10)$$

LODs using other calibration functions can be derived using a similar approach. Weighted curves are sometimes used to get a better estimate of

the LOD since lower standards are weighted more than higher concentrations. Weighted versions of the above equations require only that the coefficients derived from the weighted analyses be substituted. Since this approach allows for different types of curves, only the choice of standard deviation remains to be made. The standard error of the calibration curve is a logical choice since it is composed of the error in the fit of the calibration curve plus the variability among replicate measurements (which at low concentrations should approximate the blank variability). To address the problem of overestimating the LOD by including data from all concentrations, a reduced data set is chosen comprised of data from the lowest concentrations only. Ideally, the results for particular analytes or instruments should be monitored to determine a boundary below which replicate variability remains fairly constant. In Table I this boundary could be placed at 0.08 mg or at 0.2 mg.

Alternatively, as would likely occur in practice, a good rule of thumb would require that five unreplicated concentrations, or the lowest three concentrations, if they are replicated, be included in the reduced data set. The standard error of the reduced calibration curve (S) would be:

$$S = \left[\sum_{i=1}^{N'} (\hat{y}_i - y_i)^2 / (N' - m) \right]^{1/2} \quad (11)$$

where:

\hat{y}_i = Predicted instrument response from the calibration curve fitted to complete data set for reduced data set points

y_i = Actual instrument response for reduced data set points
 N = Number of data points in the reduced data set
 m = Number of coefficients estimated in the calibration curve ($m=2$ for linear, $m=3$ otherwise)

The predicted values \hat{y}_i come from the fit of the calibration curve to the complete data set, but the standard error is only computed using the lowest concentrations with the least variability (the region where the LOD will be found).

A weighted quadratic calibration curve was fitted to the data in Table I resulting in the equation:

$$y = -0.000847 + 0.993287x + 0.000087x^2 \quad (12)$$

Using a boundary of 0.08 mg, the standard error of regression over the four lowest concentrations was computed to be 0.00220. Solving for the LOD by equation (7):

$$\text{LOD} = \frac{-0.993287 + \sqrt{(0.993287)^2 + 4(3)(-0.000087)(0.00220)}}{2(-0.000087)} = 0.007$$

If it could be argued that the pooled replicate standard deviation (0.00035 in this example) is an accurate estimate of the standard deviation of blanks, then an alternate method for LOD calculation using the basic definition would be:

$$\text{LOD} = 0 + 3(0.00035) = 0.001$$

This may be more realistic for low concentration level analyses but does not consider the calibration curve, and in practice the calibration curve is used to estimate low level results.

Summary

Methods for computing analytical LODs and LOQs have been presented based on accepted definitions of these quantities. The methods allow one to account for the shape of the calibration curve, to incorporate the accuracy of prediction, and to address the problem of heterogeneity of variance of responses in a calibration curve.

Recommendations

The methods discussed in this paper are widely applicable to routine laboratory calibration curves, can be easily added to curve fitting programs, and are recommended for general use. In some situations, a more statistically rigorous LOD method, such as proposed by Hubaux and Vos,⁽³⁾ may be warranted, although the Hubaux and Vos method does not deal with nonlinear curves or heterogeneity of variance. A simple alternative approach would be to merely replicate the responses to a blank standard sufficiently to accurately compute a blank mean and standard deviation and from these to compute the LOD as the mean plus three standard deviations.

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\$90 million per day for workplace accidents

Workplace accidents in 1984 cost the economy \$33 billion in lost wages, medical expenses, property damage and indirect costs. The National Safety Council estimates the total excludes the effects of exposures to toxic substances, which can cause occupational illnesses that don't become evident for years. (Source: *Wall Street Journal*, March 18, 1986, p. 1)