18.4.3.7 Detection and quantification capabilities

Among the most important Performance Characteristics of the Chemical Measurement Process (CMP) are those that can serve as measures of the underlying *detection* and *quantification* capabilities. These are essential for applications in research, international commerce, health, and safety. Such measures are important for *planning* measurements, and for selecting or developing CMPs that can meet specified needs, such as the detection or quantification of a dangerous or regulated level of a toxic substance.

Equations 18.4.1-6 provide the basis for our considering the meaning of minimum detectable and minimum quantifiable amounts (signals, concentrations) in Analytical Chemistry. In each case, the determining factor is the distribution function of the estimated quantity (estimated net signal $\hat{S}$, concentration or amount $\hat{x}$). If normality can be assumed, it is sufficient to know the standard deviation of the estimated quantity as a function of S (or x). Detection limits (minimum detectable amounts) are based on the theory of hypothesis testing and the probabilities of false positives α, and false negatives β. Quantification limits are defined in terms of a specified value for the relative standard deviation. It is important to emphasize that both types of limits are CMP Performance Characteristics, associated with underlying *true values* of the quantity of interest; they are *not* associated with any particular outcome or result. The *detection decision*, on the other hand, is result-specific; it is made by comparing the experimental result with the Critical Value, which is the minimum significant *estimated value* of the quantity of interest.

Terminology. Unfortunately, a host of terms have been used within the chemical community to describe detection and quantification capabilities. Perhaps the most widely used is "detection limit" (or "limit of detection") as an indicator of the minimum detectable analyte net signal, amount, or concentration. However, because the distinction between the *minimum significant estimated concentration* and the *minimum detectable true concentration* has not been universally appreciated, the same term and numerical value has been applied by some, perhaps unwittingly, in both contexts. Despite this, the term "Detection Limit" is widely understood and quoted by most chemists as a measure of the inherent detection capability. As a result of coordinated efforts between IUPAC and ISO for the harmonization of "detection" concepts and terminology, the official IUPAC recommendation is restricted to the following terms and alternates:

For distinguishing a chemical signal from background noise -- ie., for making the Detection Decision: the *critical value* (L_C) of the appropriate chemical variable (*estimated* net signal, concentration, or amount); alternative: the *critical level*. As the measure of the inherent Detection Capability of a CMP: the *minimum Detectable (true) value* (L_D) of the appropriate chemical variable; alternative: the *detection limit*. As the measure of the inherent Quantification Capability of a CMP, the *minimum quantifiable (true) value* (L_Q); alternative: the *quantification limit*. Many other terms such as "Decision Criterion" for L_C, "Identification Limit" for L_D, and "Measurement Limit" for

L_Q, appear in the chemical literature. In the interest of *uniform international nomenclature*, however, only the terms and alternatives defined above are recommended.

Note: For presentation of the defining relations, L is used as the generic symbol for the quantity of interest. This is replaced by S when treating net analyte signals, and x, when treating analyte concentrations or amounts. Thus, L_C, L_D and L_Q may represent S_C, S_D and S_Q, or x_C, x_D and x_Q, as appropriate.

Specification of the Measurement Process. Just as with other Performance Characteristics, L_D and L_Q cannot be specified in the absence of a fully defined measurement process, including such matters as types and levels of interference *as well as* the data reduction algorithm. "Interference free detection limits" and "Instrument detection limits", for example, are perfectly valid within their respective domains; but if detection or quantification characteristics are sought for a more complex chemical measurement process, involving for example sampling, analyte separation and purification, and interference and matrix effects, then it is mandatory that all these factors be considered in deriving values for L_D and L_Q for that process. Otherwise the actual performance of the CMP (detection, quantification capabilities) may fall far short of the requisite performance.

Detection -- Fundamental Relations. The *statistical theory of hypothesis testing*, introduced in Section 18.4.3.6, serves as the framework for the treatment of Detection in Analytical Chemistry. Following this theory two kinds of errors is considered (really erroneous decisions): the error of the first kind ("type I," false positive), accepting the "alternative hypothesis" (analyte present) when that is wrong; and the error of the second kind ("type II," false negative), accepting the "null hypothesis" (analyte absent) when that is wrong. The probability of the type I error is indicated by α; the probability for the type II error, by β. Default values recommended by IUPAC for α and β are 0.05, each. These probabilities are directly linked with the one-sided tails of the distributions of the estimated quantities ($\hat{S}$, $\hat{x}$). A graphical representation of these concepts is given in Fig. 18.4.2, where the "driving force" in this hypothetical example is the ability to detect the release of specific chemical precursors of earthquakes (e.g., radon) at levels corresponding to earthquakes of magnitude L_R and above. Thus L_R is the "requisite limit" or maximum acceptable limit for undetected earthquakes; this is driven, in turn, by a maximum acceptable loss to society. (Derivation of L_R values for sociotechnical problems, of course, is far more complex than the subject of this report!) The lower part of the figure shows the minimum detectable value for the chemical precursor L_D, that must not exceed L_R, and its relation to the probability density functions (pdf) at L = 0 and at $L = L_D$ together with α and β, and the decision point (Critical Value) L_C. The figure has been purposely constructed to illustrate heteroscedasticity -- in this case, variance increasing with signal level, and unequal α and β. The point of the latter construct is that, although 0.05 is the recommended default value for these parameters, particular

circumstances may dictate more stringent control of the one or the other. Instructive implicit issues in this example are that (1) a major factor governing the detection capability could be the natural variation of the radon background (blank variance) in the environment sampled, and (2) a calibration factor or function is needed in order to couple the two abscissae in the diagram. In principle, the response of a sensing instrument could be calibrated directly to the Richter scale (earthquake magnitude); alternatively, there could be a two-stage calibration: response-radon concentration, and concentration-Richter scale.

A final point is that, with the exception of certain "distribution-free" techniques, Detection Limits *cannot* be derived in the absence of known (or assumed) distributions. As with all Performance Characteristics, the parameters used to compute L_C and L_D should be estimated from measurements in the region of interest -- in this case in the range between the blank and the detection limit. Similarly, experimental verification of computed detection limits is highly recommended.

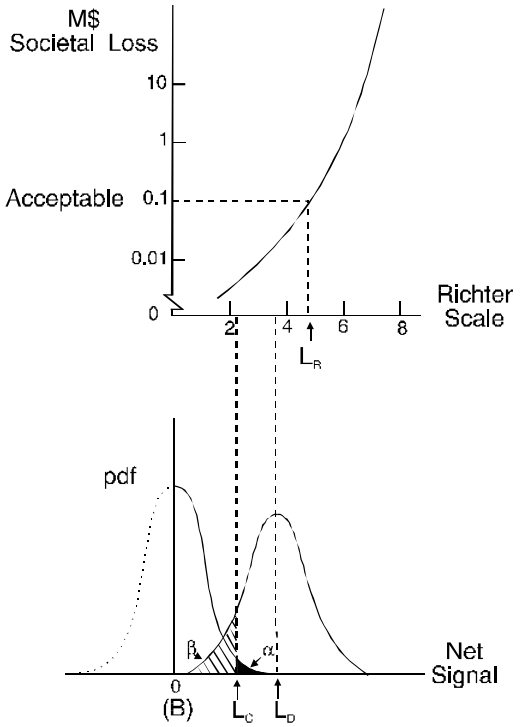

Fig. 18.4.2 Detection: needs and capabilities. Top portion shows the requisite limit L_R, bottom shows detection capability L_D.

Note: The single, most important application of the detection limit is for *planning* (CMP design or selection). It allows one to judge whether the CMP under consideration is adequate for the detection requirements. This is in sharp contrast to the application of the critical value for decision making, given the *result* of a measurement. The most serious pitfall is inadequate attention to the magnitude and variability of the *overall* blank, which may lead to severe underestimation of the detection limit.

Detection Decisions (L_C). The decision "detected" or "not detected" is made by comparison of the estimated quantity ($\hat{L}$) with the *critical value* (L_C) of the respective distribution, such that the probability of exceeding L_C is no greater than α if analyte is absent ($L = 0$, null hypothesis). The Critical Value is thus the minimum significant value of an estimated net signal or concentration, applied as a discriminator against background noise. This corresponds to a 1-sided significance test.

The above definition of L_C can be expressed as follows,

$$\Pr(\hat{L} > L_C \mid L=0) \leq \alpha \qquad (18.4.9)$$

Generally the equation is stated as an equality, but the inequality is given to accommodate discrete distributions, such as the Poisson, where not all values of α are possible. If $\hat{L}$ is normally distributed with known variance, Eq. 9 reduces to the following simple expression,

$$L_C = z_{1-\alpha}\,\sigma_o \qquad (18.4.10)$$

where $z_{1-\alpha}$ (or z_P) represents the (1-α)th percentage point or critical value of the standard normal variable, and σ_o is the standard deviation of the estimated quantity (net signal or concentration) under the null hypothesis (true value = 0). Taking the default value for α (0.05), $L_C = 1.645\ \sigma_o$.

Note that Eq. 18.4.9, *not* Eq. 18.4.10, is the defining equation for L_C, and the result ($1.645\sigma_o$) applies *only* if the data are normal with known variance and α is set equal to its default value. If σ_o is estimated by s_o, based on ν degrees of freedom, $z_{1-\alpha}$ must be replaced by Student's-*t*. That is,

$$L_C = t_{1-\alpha,\nu}\,s_o \qquad (18.4.11)$$

For $\alpha = 0.05$ and 4 degrees of freedom, for example, L_C would be equal to 2.132 s_o.

Notes:

(1) Some measurement systems impose an artificial hardware or software *threshold* (*de facto* L_C) to discriminate against small signals. In such cases statistical significance is problematic -- α may be quite small and perhaps unknown, but equations 18.4.12 and 18.4.13 below can still be applied to compute L_D, given L_C and β. The impact of such a threshold can be profound, severely eroding the inherent detection capability of the system.

(2) A result falling below L_C, triggering the decision "not detected" should not be construed as demonstrating analyte absence. (See section 18.4.3.6.) Reporting such a result as "zero" or as "$<L_D$" is *not* recommended; the estimated value (net signal, concentration) and its uncertainty should *always* be reported.

Minimum Detectable Value; Detection Limit (L_D). The *Minimum Detectable Value* of the net signal (or concentration) is that value (L_D) for which the false negative error is β, given L_C (or α). It is the true net signal (or concentration) for which the probability that the estimated value $\hat{L}$ does not exceed L_C is β. The definition of L_D can thus be expressed as

$$\Pr(\hat{L} \leq L_C \mid L=L_D) = \beta \qquad (18.4.12)$$

For normal data having known variance structure, this yields,

$$L_D = L_C + z_{1-\beta}\,\sigma_D \qquad (18.4.13)$$

For the special situation where the variance is constant between $L = 0$ and $L = L_D$, the right side of Eq. 13 reduces to $(z_{1-\alpha}+z_{1-\beta})\sigma_o$; if in addition α and β are equal, this gives $2z_{1-\alpha}\sigma_o$ which equals $2L_C$. Taking the default values for α and β (0.05), this equals 3.29 σ_o. If L_C employs an estimate s_o based on ν degrees of freedom (Eq. 18.4.11), then $(z_{1-\alpha}+z_{1-\beta})$ must be replaced by $\delta_{\alpha,\beta,\nu}$, the non-centrality parameter of the non-central-t distribution. For $\alpha = \beta$, this parameter is approximately equal to $2t$ and the appropriate expression (for constant variance) is,

$$L_D = \delta_{\alpha,\beta,\nu}\,\sigma_o \approx 2t_{1-\alpha,\nu}\,\sigma_o \qquad (18.4.14)$$

For 4 degrees of freedom, for example, the use of $2t$ would give $L_D = 4.26\ \sigma_o$. (The actual value for δ in this case is 4.067.) Note that σ_o *must be used* in Eq. 18.4.14. If only an estimate s_o is available, that means that the minimum detectable value is uncertain by the ratio (σ/s). Using the techniques of section 18.4.3.8, confidence limits may then be calculated for L_D. (A 95% upper limit for L_D, based on an observed s_o with 4 degrees of freedom, would be $\{4.07/(\sqrt{0.178})\}\ s_o$ or 9.65 s_o.

Notes:

(1) When ν is large, $2t$ is an excellent approximation for δ. For $\nu \geq 25$, with $\alpha = \beta = 0.05$, the difference is no more than 1 %. For fewer degrees of freedom, a very simple correction factor for $2t$, $4\nu/(4\nu+1)$, which takes into account the bias in s, gives values that are within 1 % of δ for $\nu \geq 5$. For the above example where $\nu = 4$, δ would be approximated as 2(2.132)(16/17) which equals 4.013.

(2) L_D is *defined* by Eq. 18.4.12 in terms of the distribution of $\hat{L}$ when $L = L_D$, the probability of the type-II error β, and L_C, with L_C being defined (Eq. 18.4.9) in terms of the distribution of $\hat{L}$ when $L = 0$, and the probability of the type-I error α. When certain conditions are satisfied, L_D can be expressed as the product of a specific coefficient and the standard deviation of the blank, such as 3.29 σ_B, when the uncertainty in the mean (expected) value of the blank is negligible, α and β each equal 0.05, and $\hat{L}$ is normally distributed with known, constant variance. L_D is *not defined*, however, simply as a fixed coefficient (2, 3, 6, etc.) times the standard deviation of a pure solution background. To do so can be extremely misleading. The correct expression must be derived from the proper defining equations (Eq. 18.4.9 and 18.4.12), and it must take into account degrees of freedom, α and β, and the distribution of $\hat{L}$ as influenced by such factors as analyte concentration, matrix effects, and interference.

(3) The question of detection has been treated extensively by H. Kaiser for spectrochemical analysis. In the earlier editions of the "Orange Book" the use of $3s_B$ is recommended as the "limit of detection". Although originally intended to serve as a measure of the detection capability, this quantity was then used as the "decision criterion" to distinguish an estimated signal from the background noise. Such a definition, which in effect sets L_C *and* L_D each equal to $3s$, corresponds for a normal distribution (large ν) to a type-I error probability of *ca*. 0.15 % but a type-II error probability of 50 % ! (See the Source Document [Currie, 1995] in section 18.9 for further comments and references.)

Signal Domain (S_C, S_D). In many cases the smallest signal S_D that can be reliably distinguished from the blank, given the critical level S_C, is desired, as in the operation of radiation monitors. Assuming normality and knowledge of σ, simple expressions can be given for the two quantities involved in Signal Detection. Eq. 18.4.10 takes the following form for the Critical Value,

$$S_C = z_{1-\alpha}\,\sigma_o \rightarrow 1.645\,\sigma_o \qquad (18.4.15)$$

where the expression to the right of the arrow results for $\alpha = 0.05$. From Eq. 18.4.3 the estimated net signal $\hat{S}$ equals y- $\hat{B}$, and its variance is

$$V\hat{S} = V_y + V_{\hat{B}} \rightarrow V_B + V_{\hat{B}} = V_o \qquad (18.4.16)$$

The quantity to the right of the arrow is σ_o^2, the variance of the estimated net signal when the true value S is zero. If the variance of $\hat{B}$ is negligible, then $\sigma_o \approx \sigma_B$, the standard deviation of the Blank. If B is estimated in a "paired" experiment -- i.e., $V_{\hat{B}} = V_B$, then $\sigma_o = \sigma_B\sqrt{2}$. Note that $\sigma_o \approx \sigma_B$, and $\sigma_o = \sigma_B\sqrt{2}$, are limiting cases. More generally, $\sigma_o = \sigma_B\sqrt{\eta}$, where $\eta = 1 + (V_{\hat{B}}/V_B)$. Thus, η reflects different numbers of replicates, or, for particle or ion counting, different counting times for "sample" vs blank measurements. (See section 18.4.3.8 for further discussion of the *blank*.)

The Minimum Detectable Signal S_D derives similarly from Eq. 18.4.13, that is,

$$S_D = S_C + z_{1-\beta}\,\sigma_D \qquad (18.4.17)$$

where σ_D^2 represents the variance of $\hat{S}$ when $S = S_D$. For the special case where the *variance is constant* between $S = 0$ and $S = S_D$, and $\alpha = \beta = 0.05$, the Minimum Detectable Signal S_D becomes $2S_C = 3.29\ \sigma_o$, or $(3.29\sqrt{2})\sigma_B = 4.65\ \sigma_B$ for paired observations. The treatment using an estimated variance, s_o^2 and Student's-t follows that given above. The above result is not correct for S_D if the variance depends on the magnitude of the signal. A case in point is the counting of particles or ions in accelerators or mass spectrometers, where the number of counts accumulated follows the

Poisson distribution, for which the variance equals the expected number of counts. If the mean value of the background is known precisely, for example, $\sigma_o^2 = \sigma_B^2$, which in turn equals the expected number of background counts B. This leads to approximate expressions of $1.645\sqrt{B}$, and $2.71 + 3.29\sqrt{B}$ for S_C and S_D (units of counts), respectively, for counting experiments with "well known" blanks. In more complicated cases where net signals are estimated in the presence of chromatographic or spectroscopic baselines, or where they must be deconvolved from overlapping peaks, the limiting standard deviations (σ_o and σ_D) must be estimated by the *same procedures used to calculate the standard deviation of the estimated (net) signal of interest.*

Note: The result for counting data given above is based on the normal approximation for the Poisson distribution. Rigorous treatment of discrete and other non-normal distributions, which is beyond the scope of this document, requires use of the actual distribution together with the defining relations Eq. 18.4.9 and Eq. 18.4.12.

Concentration Domain (x_C, x_D). For the special category of "direct reading" instrument systems, the response is given directly in units of concentration (or amount). In this case, the distinction between the signal domain and the concentration domain vanishes, and the treatment in the preceding section applies, with y, e_y, B, and S already expressed in concentration units. As before, the development of particular values for the critical level and detection limit requires distributional assumptions, such as normality, which should be tested. More generally, the transformation to the minimum detectable concentration (amount) involves one or more multiplicative (or divisive) factors, each of which may be subject to error. Collectively, these factors comprise the sensitivity A which relates the net signal to the physical or chemical quantity of interest x, as indicated in Eq. 18.4.5. We consider two cases.

Calibration function known ($e_{\hat{A}}$ negligible or constant). When the uncertainty about the calibration function $F(x)$ and its parameters is negligible, the minimum detectable concentration x_D can be calculated as $F^{-1}(y_D)$, where $y_D = B + S_D$. Problems arise only when the calibration function is not monotonic; and even if it is monotonic, some iteration may be needed if $F(x)$ is not linear in x. In the linear case where $F(x) = B + Ax$, and the uncertainty of the sensitivity, but not necessarily that of the blank, is negligible, the transformation from the minimum detectable signal to the minimum detectable concentration is simply

$$x_D = S_D/A \tag{18.4.18}$$

For normal data with constant, known variance, and $\alpha = \beta$, the Minimum Detectable Concentration x_D is thus $2S_C/A$. Taking the default value for α and β, this becomes $(3.29\ \sigma_o)/A$, where σ_o is the standard deviation of $\hat{S}$ when $S = 0$. For paired observations this is equivalent to $(4.65\ \sigma_B)/A$, where σ_B is the standard deviation of the blank. Since only the numerator in Eq. 18.4.18 is subject to random error, the detection test will still be

made using S_C. When variance is estimated as s^2, Student's-*t* (central and non-central) must be used as shown above.

When the assumed value of the sensitivity A is fixed, but biased -- as when an independent estimate of the slope from a *single* calibration operation, or a calibration material or a theoretical estimate having non-negligible error, is repeatedly used -- the calculated detection limit will be correspondingly biased. Bounds for the bias in A can be applied to compute bounds for the true detection limit. Since the biased estimate of A is fixed, it cannot contribute to the variance of $\hat{x}$.

Note: Repeated use of a fixed estimate for the blank is *not* recommended, unless $V_{\hat{B}} << V_B$, as that may introduce a systematic error comparable to the Detection Limit, itself. This is of fundamental importance in the common situation, especially in trace analysis, where the sensitivity estimate is derived from instrument calibration, but where the blank and its variance depend primarily on non-instrumental parts of the CMP including isolation of the analyte and even sampling. (See discussion of the *blank* in section 18.4.3.8.)

Calibration function estimated ($e_{\hat{A}}$ random). When the error in $\hat{A}$ is random, then its effect on the distribution of $\hat{x}$ must be taken into account, along with random error in y and $\hat{B}$. This is the case, for example, where sensitivity (slope) estimation is repeated with each application of the measurement process. For the common situation where x is estimated by $(y-\hat{B})/\hat{A}$ [Eq. 18.4.5], the minimum detectable concentration may be calculated from the defining equations 18.4.9 and 18.4.12, and their normal equivalents, using the Taylor expansion for the variance of $\hat{x}$ at the detection limit x_D: $V\hat{x}(x=x_D) \approx (V_o + x_D^2 V_{\hat{A}} + 2x_D V_{AB})/A^2$, with V_o as given in Eq. 18.4.16. For the heteroscedastic case (V_y varying with concentration), V_o must be replaced by $(V_y(x_D)+V_{\hat{B}})$ in the above expression, and weights used. The results for constant V_y and $\alpha = \beta$ are

$$S_C = t_{1-\alpha,\nu} s_o \qquad (18.4.19)$$

$$x_D = (\delta_{\alpha,\beta,\nu}\sigma_o/A)(K/I) \approx (2t_{1-\alpha,\nu}\sigma_o/A)(K/I) \qquad (18.4.20)$$

where: $K = 1 + r(B,A)(\sigma\hat{B}/\sigma_o)[t_{1-\alpha,\nu}(\sigma\hat{A}/A)]$

$$I = 1 - [t_{1-\alpha,\nu}(\sigma\hat{A}/A)]^2$$

When B and A are estimated from the *same* calibration data set, the estimates will be negatively correlated with $r(B,A) = -\hat{x}/x_q$, x_q being the quadratic mean. The ratio K/I may then range from slightly less than one to very much greater, depending on the calibration design and the magnitude of σ_y. The effect of the factor I in particular, can cause x_D to differ substantially from $2t_{1-\alpha,\nu}\sigma_o/A$. The extreme occurs when the relative

standard deviation of $\hat{A}$ approaches $1/t_{1-\alpha,\nu}$; then x_D is unbounded. When B and A are estimated independently, then $r(B,A) = 0$, and $K = 1$. If the relative standard deviation of $\hat{A}$ is negligible compared to $1/t_{1-\alpha,\nu}$, then K and I both approach unity, and x_D reduces to the form given in Eq. 18.4.18.

A note of caution: If the parameters used in equations 18.4.19 and 18.4.20 derive from a calibration operation that fails to encompass the *entire* CMP, the resulting values for S_C and x_D are likely to be much too small. Such would be the case, for example, if the response variance and that of the estimated intercept based on instrument calibration data alone were taken as representative of the total CMP, which may have major response and blank variations associated with reagents and the sample preparation environment.

Note: When an estimated value $\hat{A}$ is used in Eq. 18.4.20, it gives a rigorous expression for the maximum (non-detection) upper limit for a particular realization of the calibration curve. (This result derives from the distribution of $y - \hat{B} - \hat{A}x$ which is normal with mean zero and variance $V_y + V_{\hat{B}} + x^2 V_{\hat{A}} + 2xV_{AB}$.) Since $\hat{A}$ is a random variable, this means for the measurement process as a whole that there is a *distribution of limits* $x_D(\hat{A})$ corresponding to the distribution of $\hat{A}$'s. When A is used in Eq. 18.4.20, the resulting x_D can be shown to be approximately equal to the median value of the distribution of the maximum upper limits. (See Note-2 and the references cited in the Source Document [Currie], for important additional information on the distribution of the estimated concentration ($\hat{x}$) and multiple detection decisions, and their impact on the minimum detectable concentration.)

Multicomponent Detection. When a sensing instrument responds simultaneously to several analytes, one is faced with the problem of multicomponent detection and analysis. This is a very important situation in chemical analysis, having many facets and a large literature, including such topics as "errors-in-variables-regression" and "multivariate calibration"; but only a brief descriptive outline will be offered here. For the simplest case, where blanks and sensitivities are known and signals additive, $\boldsymbol{S}$ can be written as the summation of responses of the individual chemical components -- i.e., $S_i = \Sigma S_{ij} = \Sigma A_{ij}x_j$, where the summation index-j is the chemical component index, and i, a time index (chromatography, decay curves), or an energy or mass index (optical, mass spectrometry). In order to obtain a solution, S must be a vector with at least as many elements S_i as there are unknown chemical components. Two approaches are common:

(1) When the "peak-baseline" situation obtains, as in certain spectroscopies and chromatography, for each non-overlapping peak, the sum ΣAx can be partitioned into a one component "peak" and a smooth (constant, linear) baseline composed of all other (interfering) components. This is analogous to Eq. 18.4.2, and for each such peak, it can be treated as a pseudo one component problem.

(2) In the absence of such a partition, the full matrix equation, $\boldsymbol{S} = \boldsymbol{A}\boldsymbol{x}$, must be treated, with x_{kC} and x_{kD} computed for component-k, given the complete sensitivity matrix $\boldsymbol{A}$ and concentrations of all other (interfering) components.

These quantities can be calculated by iteratively computing, from the Weighted Least Squares covariance matrix, the variance of component-k as a function of its concentration, keeping all interfering components constant, and using the defining equations 9 and 12, or their normal forms, equations 18.4.10 and 18.4.13.

Minimum Quantifiable Value; Quantification Limit (L_Q). *Quantification limits* are performance characteristics that mark the ability of a CMP to adequately "quantify" an analyte. Like detection limits, quantification limits are vital for the planning phase of chemical analysis; they serve as benchmarks that indicate whether the CMP can adequately meet the measurement needs. The ability to quantify is generally expressed in terms of the signal or analyte (true) value that will produce estimates having a specified relative standard deviation (RSD), commonly 10 %. That is,

$$L_Q = k_Q \sigma_Q \tag{18.4.21}$$

where L_Q is the Quantification Limit, σ_Q is the standard deviation at that point, and k_Q is the multiplier whose reciprocal equals the selected quantifying RSD. The IUPAC default value for k_Q is 10. As with detection limits, the net *signal quantification limit* (S_Q) and *analyte (amount or concentration) quantification limit* (x_Q) derive from the relations in equations 18.4.1-5, and the variance structure of the measurement process. If the sensitivity A is known, then $x_Q = S_Q/A$; if an estimate $\hat{A}$ is used computing $\hat{x}$, then its variance must be considered in deriving x_Q. (See Note-1, below.) Just as with the case of S_D and x_D, uncertainties in assumed values for σ and A are reflected in uncertainties in the corresponding Quantification limits.

If σ is known and constant, then σ_Q in Eq. 18.4.21 can be replaced by σ_o, since the standard deviation of the estimated quantity is independent of concentration. Using the default value for k_Q, we then have

$$L_Q = 10\, \sigma_Q = 10\, \sigma_o \tag{18.4.22}$$

In this case, the quantification limit is just 3.04 times the detection limit, given normality and $\alpha = \beta = 0.05$.

Notes:

(1) In analogy with x_D, the existence of x_Q is determined by the *RSD* of $\hat{A}$. In this case the limiting condition for finite x_Q is RSD($\hat{A}$) < 1/k. If x is estimated with Eq. 18.4.5, and $\hat{B}$ and $\hat{A}$ are independent, and $\sigma(\hat{S})$ is constant with value σ_o,

then $x_Q = (k\sigma_o/A)/[1-(k\sigma_A/A)^2]^{1/2}$, where $(k\sigma_o/A)$ is the limiting result when the random error in $\hat{A}$ is negligible.]

(2) One frequently finds in the chemical literature the term "Determination Limit." Use of this term is *not* recommended, because of ambiguity.

Heteroscedasticity. If the variance of the estimated quantity is not constant, then its variation must be taken into account in computing detection and quantification limits. The critical level is unaffected, since it reflects the variance of the null signal only. Two types of σ variation are common in chemical and physical metrology: (a) σ^2 (variance) proportionate to response, as with shot noise and Poisson counting processes; and (b) σ (standard deviation) increasing in a linear fashion. This effect, which is too often ignored, can be very important. As shown in the Source Document [Currie], a CMP having a "well-known" blank and a 4% asymptotic RSD leads to an increase of L_D from $3.29\sigma_B$ to $3.52\sigma_B$, and an increase of L_Q from $10\sigma_B$ to $16.7\sigma_B$. If σ increases too sharply, L_D and/or L_Q may not be attainable for the CMP in question. This problem may be attacked through replication, giving σ reduction by $1/\sqrt{n}$, but caution should be exercised since unsuspected systematic error will *not* be correspondingly reduced!