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Review

Over a century of detection and quantification capabilities in analytical chemistry – Historical overview and trends

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ABSTRACT

The detection limit (L_D) and the quantification limit (L_Q) are important parameters in the validation process. Estimation of these parameters is especially important when trace and ultra-trace quantities of analyte are to be detected. When the apparatus response from the analyte is below the detection limit, it does not necessarily mean that the analyte is not present in the sample. It may be a message that the analyte concentration could be below the detection capabilities of the instrument or analytical method. By using a more sensitive detector or a different analytical method it is possible to quantitatively determine the analyte in a given sample. The terms associated with detection capabilities have been present in the scientific literature for at least the past 100 years. Numerous terms, definitions and approaches to calculations have been presented during that time period. This paper is an attempt to collect and summarize the principal approaches to the definition and calculation of detection and quantification abilities published from the beginning of 20th century up until the present. Some of the most important methods are described in detail. Furthermore, the authors would like to popularize the knowledge of metrology in chemistry, particularly that part of it which concerns validation of the analytical procedure.

Contents

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1. Introduction

It is certainly true that assignation of a critical level (L_C), detection limit (L_D) and a quantification limit (L_Q) is necessary to produce reliable results when analyzing samples at low concentration ranges (dependent on the capability of the equipment used to determine the analyte), not only when trace and ultratrace quantities of the analyte are measured. There are many different applications where assignation of detection and quantification capabilities is crucial, including health protection and doping control, radiochemistry, trace analysis of toxic elements in the environment, food and materials and verifying the purity of materials and products. However, determination of these parameters has proved to be troublesome over the years because both the number of determination methods adopted and the inconsistent terms related to them have caused confusion.

The aim of the presented paper is to trace the history of changes in the definition and determination of detection and quantification capabilities and to present the approaches to estimating L_D in modern analytical chemistry. A series of reviews on the estimation of methods of detection abilities have been published [1–6]. However, no comprehensive history of changes in approach to the estimation of detection abilities has yet been published. Currie (in 1968) [7] and Lavagnini and Magno (in 2007) [1] reported on a variety of terms used in the literature. In the present paper, the authors have also presented a list of terms that have been used in reference to L_C, L_D and L_Q in the literature discussed herein (Table 1). The purpose was to illustrate the multiplicity of terms which have basically the same meaning. Unlike Currie, Lavagnini and Magno, the authors have covered over a century of the history of terms used in connection with detection and quantification capabilities: from the early 20th century to the

Table 1
Different terms associated with detection and quantification capabilities used in the literature.

Authors	Term used	Refers to
Altshuer and Pasternack [14]	The minimum significant measured activity	Critical level
Currie [7]	The critical level	
IUPAC [24]		
Boqué and Heyden [2]		
Rajaković et al. [3]		
IUPAC [24]	Critical value	
Hubaux and Vos [16]	Decision limit	
Linnet and Kondratovich [38]	Limit of blank	
Loock and Wentzell [41]	Critical concentration limit	
Lavagnini et al. [40]	Critical limit	
Curthman and Rothberg [10]	The limit of the test	Detection limit
Feigl [11]	Erfassungsgrenze	
Kaiser [12,13]	Nachweisgrenze	
Altshuler and Pasternack [14]	The lower limit of detection/the minimum detectable true activity	
Wing and Wahlgren [15]	Detection sensitivity	
John et al. [46]	The limiting detectable sample concentration	
Currie [7]	The detection limit/limit of detection	
Hubaux and Vos [16]		
IUPAC [18]		
IUPAC [24]		
Voigtmann [17,19,26–29]		
EPA [35]		
ICH Q2(R1) [36]		
Lavagnini and Magno [1]		
(EC) No. 333/2007 [45]		
Boqué and Heyden [2]		
Rajaković et al. [3]		
Linnet and Kondratovich [38]		
Lavagnini et al. [40]		
Loock and Wentzell [41]		
IUPAC [24]	Minimum detectable value	
ISO 11843-1 [25]		
US EPA [35]	Instrument detection limit and method detection limit	
Currie [7]	Minimum working concentration	Quantification limit
Currie [7]	Determination limit	
IUPAC [24]	Minimum quantifiable value	
IUPAC [24]	Quantification limit/limit of quantification	
Lavagnini and Magno [1]		
(EC) No. 333/2007 [45]		
Rajaković et al. [3]		
Linnet and Kondratovich [38]		
US EPA [35]	Instrument quantitation limit and method quantitation limit	
US EPA [35]	Limit of quantitation/quantitation limit	
ICH Q2(R1) [36]		

present. As can be seen from Table 1, the terms critical level, detection limit/limit of detection and quantification limit/limit of quantification are the most commonly used these days.

Furthermore, the authors would like to draw scientists' attention to validation of the analytical procedures. The validation process should be a confirmation that the procedure is fit for a specifically intended use. L_D and L_Q are one of the most important parameters of the analytical procedure and thus deserve special attention. The present publication provides an opportunity to learn something more about over one hundred years of the history of detection and quantification capabilities. Moreover, some modern and universally accepted methods for estimating L_C, L_D and L_Q are demonstrated in the paper.

2. Important issues related to estimation of detection and quantification capabilities

Before discussing approaches in computing detection capabilities, the authors would like to highlight some information, crucial for a proper understanding and effective application of the methods to determine detection and quantification capabilities: (i) Neyman–Pearson hypothesis testing theory, (ii) how to correctly present results, (iii) statistical intervals and (iv) blank samples. A knowledge of these topics is important to properly use L_D and L_Q estimation methods and thus deserve special attention.

2.1. Neyman–Pearson hypothesis testing theory

Numerous statistical techniques rely on using methods of hypothesis testing, confidence intervals and estimations with the purpose of representation and interpretation of evidence in a given set of observations. Briefly, the Neyman–Pearson theory [8] focuses on using observations to choose from two hypotheses. The concept of the Neyman–Pearson theory means that a statistical test should be evaluated with regard to its error probabilities: the probability of rejecting hypothesis A in the case when it is true and the probability of accepting A when hypothesis B is true. A procedure with good probabilistic properties will manifest a satisfying performance on average, provided it is used repeatedly.

This theory explains how to find a test with the smallest Type II error value (β) for any fixed Type I error value (α). There is still a risk of making Type I errors but this risk is controlled by the fixed value. Any test with a smaller than assumed Type II risk entails a larger Type I risk. The Neyman–Pearson theory of hypothesis testing focuses on reducing the probabilities of making errors, thus providing a potent and strong paradigm that is widely present within today's statistical theory. Fig. 1 represents graphically the relationship between Type I and Type II errors, as well as L_C, L_D and L_Q.

2.2. How to correctly present results? About different types of domain

The way a result is presented depends on the data type used to estimate detection capabilities. They can be the theoretical values almost never known in real life (population parameters) or can be obtained experimentally, as the estimation of the true parameters (sample test statistics). Based on the first data type, the result is given in the theoretical domain. Whereas L_C and L_D are presented in the experimental domain, they are calculated from measurement data. It should be mentioned that the true L_C and L_D values are computed by using the true parameters. By using experimental data to calculate detection capabilities the results will only give an estimation of the true values. In both the experimental and the theoretical domain the detection capabilities can be presented in the response or concentration domain. Table 2 graphically indicates this issue (with appropriate notations). The authors use the notation system presented in Table 2. However, in the present paper, the authors also use the generic symbol L_C and L_D to represent critical level and detection limit, respectively.

2.3. Statistical intervals

Statistical intervals are elements of statistic that represent reliability of estimation of the population parameters or prediction of future sample values, dependent on parameters like variance, sample size or confidence level. The width of the intervals is extended by factors like high confidence level, small sample size and large variance. There are three types of intervals used in statistical inference: (i) confidence intervals, (ii) prediction intervals and (iii) tolerance intervals. Each type of the intervals provides different statistical information. Fig. 2 is an schematic

Table 2
Symbols used to present detection capabilities in the experimental and theoretical domain.

Type of domain	Critical level		Detection limit	
	Signal domain	Concentration domain	Signal domain	Concentration domain
Theoretical domain	Y_C	X_C	Y_D	X_D
Experimental domain	y_C	x_C	y_D	x_D

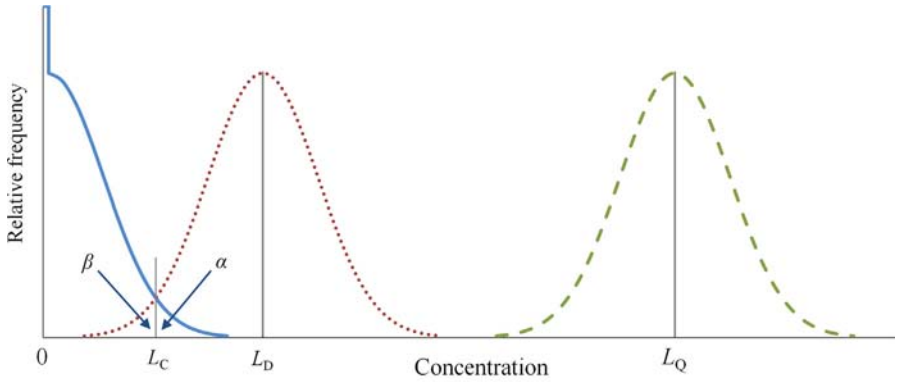

Fig. 1. Graphical representation of Type I and Type II errors, α and β respectively, and relationship between L_C, L_D and L_Q with truncation at zero. Relative frequency of results at (i) blank concentration (_), (ii) detection limit concentration (…), (iii) quantification limit concentration (---). Negative values are truncated and clustered in the zero concentration point, hence creating asymmetric distribution of values.

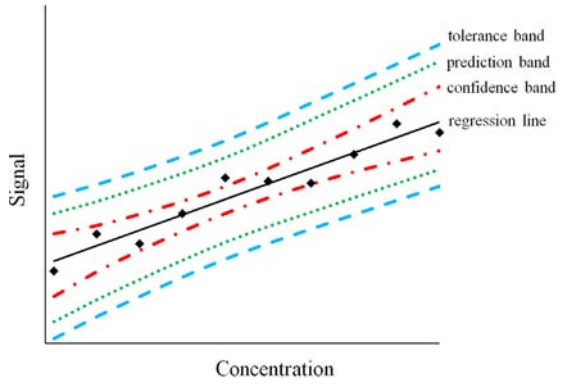

Fig. 2. Example of schematic representation of statistical intervals for 10 values presented as the continuous bands and their relation to each other: (i) regression line (_), (ii) confidence band (-•-), (iii) prediction band (…), (iv) tolerance band (---).

representation of mutual position of the discussed intervals presented as the continuous bands.

Confidence interval is a range of values that is likely to include the true population parameter, like mean or standard deviation, with a given confidence level. It should not be interpreted as the range that contains certain percentage of individual sample values. In analytical chemistry, confidence interval is the statistical tool that is most often used to describe in what range the mean of the sample is contained.

Prediction interval provides information about a range of values that will contain a single future response value with a given confidence level. It is always wider than confidence interval because it considers uncertainty of the prediction of single response and the uncertainty of the mean value. While describing the 95% prediction intervals one must remember that term "95%" refers to a confidence level, not to a coverage of sample values. Misinterpretation of this fact may lead to erroneous conclusions.

Tolerance interval is the widest of the presented intervals and it covers a specified proportion of the population with a given confidence level. The difference between the prediction intervals and the tolerance interval is that the first refers only to single future response value and the latter covers the certain part of the population.

Statistical intervals are usually calculated and presented as two-sided intervals. However, they can be expressed as one-sided intervals, either lower or upper, representing only one limiting value instead of two. Another aspect of intervals is the division to simultaneous and non-simultaneous intervals. Non-simultaneous interval is used when one only want to make the prediction for a single x-value, whereas simultaneous interval is chosen when prediction is supposed to cover the several positions of x-values simultaneously. The discussion on the proper use of above intervals along with suitable equations is presented in the tutorial by de Gryze et al. [9].

2.4. Blank samples

The role of blank is crucial when estimating detection capabilities. The value and standard deviation of the blank are inherently connected with basically every L_D estimation method. The precision of preparing and analyzing the blank solutions has the direct impact on the estimation of L_D value, especially when handling with samples containing analyte in concentrations close to the L_D level. The ideal blank should have a similar matrix and concentration of interfering compounds comparable to samples but contain none of the analyte and it is subjected to the sample preparation procedures. The signal from appropriate blank should take into account several variables crucial to proper estimation of detection capabilities such as instrumental noise, fluctuations of measurement conditions over long-term process of measuring, inhomogeneity, contamination from the reagents used in the sample preparation process and sampling procedure. Depending on the instrument or the analytical process the blank samples are used for calibrating the instruments, establishing the baseline or washing out the samples from instrument's tubing and containers. If the blank is intended to use in ways mentioned above, then it should contain the solvent without interfering components and it usually does not pass through the sample preparation procedures.

3. Historical background

The development of the definition and estimation of detection capabilities was strongly linked to the development of instrumental analysis. In the early 20th century, instrumental analysis became significant in the field of analytical chemistry. The first mention of detection abilities in the literature probably dates from this time [10,11]. Since then, there has been no doubt about the importance of determining L_D.

At the beginning of the 20th century, references to detection capabilities regarded only qualitative determination of substances present at low concentration in the sample (qualitative laboratory tests). Quantitative analysis of low-concentration compounds was still the future task. Some steps toward a detection of low quantities of substances were made by Curtman and Rothberg [10]. The authors described the determination of 'the limit of the test' – the smallest quantity of analyte that would give 'an unmistakable' signal under specified conditions. In 1923 in Mikrochemie, Feigl used the term *Erfassungsgrenze* which can be translated into English as detection limit [11]. Although some terms were used, the methods for estimating the detection capabilities were not specified. Kaiser made a major step forward in L_D calculation [12,13]. He proposed to estimate L_D by applying a mathematical statistic (for suitable equation see Table 3). The proposed method allows the computation of an experimental detection limit in the response and content domain. However, there is no mention of hypothesis testing in Kaiser's approach.

4. 1960s: a multitude of new ways to estimate detection limit and Currie's attempt at standardization

It was only in the 1960s that analytical chemists became much more involved with characterization of the analytical procedure. 'The smallest amount or concentration that can be detected' or other similar definitions were in use. However, the above definition is ambiguous and may lead to subjective results due to the potential ambiguity of using the expression 'the smallest'. Secondly, there is no clear answer when the analyst makes the decision that the analyte is 'detected'. These problems indicated a need for constructing an unequivocal definition of detection limit. Moreover, a variety of ways to describe detection and quantification abilities emerged at the time. Most of them were based on calculations of standard deviation of the blank sample. Altshuler and Pasternack suggested the use of standard deviation of the blank (σ_0) to calculate 'the lower limit of detection' [14]. Wing and Wahlgren evaluated 'the relative detection sensitivity' as 10% of the background [15].

In the 1960s many more methods emerged to calculate detection capabilities than those mentioned above. Consequently, as early as the late 1960s, Currie became aware that the number of terms and ways to calculate detection capabilities could be problematical (Tables 1 and 3, respectively). Moreover, as Currie noted, the L_D

Table 3
Historical and universally accepted approaches for estimation of the detection and quantification capabilities discussed in the present paper.

Authors	Description and comments	Equations
1960s		
Altshuler and Pasternack [14]	Computation of the lower limit of detection based on standard deviation of the blank	
Kaiser [13]	Calculation based on the signal response and standard deviation of the blank. The result presented in the content domain when y_D converted to concentration using the calibration function $\bar{y}_B$ – the mean value of the instrument blank response σ_0 – population standard deviation of the blank	$y_D = \bar{y}_B + 3\sigma_0$
Wing and Wahlgren [15]	'The relative detection sensitivity' computed as 10% of the background	
Currie [7]	The method is applied to following assumptions: homoscedastic, Gaussian measurement noise and ordinary least squares (OLS) regression k – coverage factor y_Q– quantification limit	$y_C = ks_0$ $y_D = 2ks_0$ $y_Q = 10s_0$
1970s and 1980s		
Hubaux and Vos [16]	Method based on the prediction interval of the calibration curve. According to Voigtman, the method produces biased results and is not recommended [17] s_r – sample standard error about regression, calculated with the equation listed below[b] $t_{1-\alpha,\ I\text{-}2}$ – Student's t corresponding to $I-2$ degrees of freedom and $(1-\alpha)$ confidence level b – slope of the calibration curve K – number of measurements performed on the unknown sample I – number of standard solution $\bar{x}$ – mean of I standards, calculated with the equation listed below[a] x_i – concentration of calibration standard	$x_C = \frac{s_r t_{1-\alpha,\ I-2}}{b}\sqrt{\frac{1}{K}+\frac{1}{I}+\frac{\bar{x}^2}{\sum_{i=1}^{I}(x_i-\bar{x})^2}}$[a,b] $x_D = x_C + \frac{s_r t_{1-\beta,\ I-2}}{b}\sqrt{\frac{1}{K}+\frac{1}{I}+\frac{(x_D-\bar{x})^2}{\sum_{i=1}^{I}(x_i-\bar{x})^2}}$[a,b]
IUPAC [18]	The value of k should refer to the number of replicates (20 replicate measurements and $k=3$ are recommended by the IUPAC) s – standard deviation	$x_D = ks/b$
Winefordner and Long [20]	Two approaches based on parameters of calibration curve , namely analytical sensitivity and interception and theirs standard deviations: (i) graphical approach and (ii) propagation of errors approach s_b – standard deviation of the slope s_a – standard deviation of the intercept a – intercept of the calibration curve	(i) $x_D = \frac{ks_0}{b \pm t_\alpha s_b}$ (ii) $x_D = \frac{k\sqrt{s_0^2+s_a^2+\left(\frac{a}{b}\right)^2 s_b^2}}{b}$
IUPAC and ISO steps to harmonization		
IUPAC [24]	Based on Neyman–Pearson theory of hypothesis testing, factors associated with preparation of calibration curve (number of standards, the range of the calibration curve, number of replicates performed on the blank, standards and the unknown sample) are considered. The correctness of the method was proved by Voigtman [17] η – function of the OLS parameters, calculated with the equation listed below[c] ν – degrees of freedom s_Q – standard deviation of the estimated value at the quantification limit x_Q – quantification limit content value	$x_C = \frac{t_{1-\alpha,\nu} s_0 \eta^{1/2}}{b}$[c] $x_D = \frac{(t_{1-\alpha,\nu}+t_{1-\beta,\nu})s_0\eta^{1/2}}{b}$[c] $x_Q = \frac{10s_0}{b}$
ISO [25,34]	Method based on the noncentrality parameter of the noncentral t distribution. For the assumptions: linear calibration function and homoscedastic, Gaussian measurement noise, x_C and x_D are estimated using the expressions listed alongside. Voigtman strongly advises against using this approach because of the bias J – number of parallel preparations for standard solutions δ – noncentrality parameter of non-central t distribution $t_{1-\alpha,\ IJ-2}$ – $(1-\alpha)$% quantile of Student's t distribution with $IJ-2$ degrees of freedom	$x_C = \frac{t_{1-\alpha IJ-2} s_{y/x}}{b}\left(\frac{1}{K}+\frac{1}{IJ}+\frac{\bar{x}^2}{\sum_{i=1}^{I}(x_i-\bar{x})^2}\right)^{1/2}$ $x_D = \frac{\delta(IJ-2,\alpha,\beta)s_{y/x}}{b}\left(\frac{1}{K}+\frac{1}{IJ}+\frac{\bar{x}^2}{\sum_{i=1}^{I}(x_i-\bar{x})^2}\right)^{1/2}$
Other approaches for computing detection and quantification capabilities from 1990s to present		
US EPA [35]	The computation of MDL is based on the one-tailed t-statistic at the 99% confidence level and s, in concentration units, for (7 or more) samples spiked at the estimated IQL	$IDL = \frac{3s_r}{b}$ $IQL = \frac{10s_r}{b}$ $MDL = t_{1-\alpha,K-1}s$ $MQL = 3MDL$
Linnet and Kondratovich [38]	Approach is nonparametric i.e. no assumptions are made regarding measurements distribution. Data from blank samples are ranked by increasing values and 95th percentile is taken $Perc_{1-\alpha}$ – $1-\alpha$th percentile of ranked blank net values n – number of blank samples	$L_C = Perc_{1-\alpha} = n(\frac{95}{100}+0.5)$ $L_D = L_C + c_\beta \times s$[d]
Lavagnini [40]	Nonparametric method involving Type I and II errors similar to Hubaux–Vos, based on the one-sided simultaneous tolerance interval. It uses Theil–Sen (TS) median-based regression technique combined with Lancaster–Quade (LQ) statistics	
Loock and Wentzel [41]	Method applicable with sensors calculated with mean and standard deviation. Parametric and homoscedastic sample measurements values are assumed	$y_D = \bar{y}_B + t_{\alpha,n-1}s_r$[b] $x_D = \frac{t_{\alpha,n-1}s_r}{b}$[b]

[a] $\bar{x} = \frac{1}{I}\sum_{i=1}^{I} x_i$.

[b] $s_r = \sqrt{\frac{\sum_{i=1}^{I}[\bar{y}_i-(a+bx_i)]^2}{I-2}}$ where $\bar{y}_i$ denotes the sample mean of replicates for standard.

[c] $\eta = \left(\frac{1}{K}+\frac{1}{I}+\frac{\bar{x}^2}{\sum_{i=1}^{I}(x_i-\bar{x})^2}\right)^{1/2}$.

[d] $c_\beta = z_{1-\beta}/\left[1-\frac{1}{4\times\nu}\right]$ where $z_{1-\beta}$ denotes the standard normal deviate derived from the 95th percentile of the standard Gaussian distribution.

values obtained by using different equations developed during the 1960s, applied to the same chemical measurement system, encompass nearly three orders of magnitude [7]. Because some methods quoted by Currie had no statistical background or the statistical explanation was incorrect, he proposed a new concept for estimating detection and quantification capabilities. Currie's reflections were based on the Neyman–Pearson hypothesis testing theory. Currie's concept was based on the following assumptions: the response variable has Gaussian distribution and is approximately linearly related to the explanatory variables (linear regression also known as ordinary least squares, OLS). Furthermore, the variance of the response variable is the same for all explanatory variables (homoscedasticity). The critical level was defined as the response of the instrument above which an observed signal may be reliably recognized as 'detected'. L_C depends only on Type I errors (false negatives are ignored). According to the desired confidence level, the value of the coverage factor (k) can be different. Therefore, when the probability of a false positive error is 0.05, $k=1.64$ (one-tailed t-test, infinite degrees of freedom). Currie's definition of L_D from 1968 is as follows: 'the "true" net signal level which may be *a priori* expected to lead to detection'. Unlike L_C, L_D depends on both false positive and false negatives [7]. For the assumption $\alpha=\beta$, L_D can be estimated according to the formula: $L_D=2L_C$. Whereas L_Q was defined as 'the level at which the measurement precision will be satisfactory for quantitative determination'. The corresponding equations for L_C, L_D and L_Q (with Currie's assumptions) are listed in Table 3. Currie's paper, published in 1968 had a significant impact on the conceptual development of detection and quantification capabilities. Unfortunately, it would be three decades after its publication before any steps were taken towards harmonization.

5. Approaches during the 1970s and 1980s

5.1. The Hubaux and Vos approach

In the article published in 1970, Hubaux and Vos presented a method based on the prediction interval of the calibration curve to estimate detection capabilities [16]. The aim was to compute L_C and L_D in the experimental domain by using information from a calibration curve. The values of these parameters (in the concentration domain) are estimated using the equations listed in Table 3. As the authors correctly noticed, the values of x_C and x_D depend on the precision and the preparation way of the calibration line (calibration range, number of standard solutions and number of replicates for calibration standards and for the unknown sample). However, because of some incorrect assumptions, the Hubaux and Vos method produces biased results and is not recommended: the use of prediction intervals to compute detection capabilities was a mistake. This was proved and explained by Voigtman by performing Monte Carlo simulations, which comprised tens of millions of independent calibration curve data sets [17]. The result was that experimental detection limits by Hubaux and Vos approach were significantly negative biased and produced too high false negative rates which was due to a long-standing error generated by using the prediction intervals.

5.2. The IUPAC method from 1978

In 1978 the IUPAC members defined the detection limit as 'the concentration or the quantity derived from the smallest measure that can be detected with reasonable certainty for a given analytical procedure' and suggested the equation listed in Table 3 to estimate L_D [18]. According to IUPAC s denotes the standard deviation of measurements for a blank sample (s_0). As can be seen by comparing the equations in Table 3, the IUPAC approach from 1978 is similar to Kaiser's method (actually, when $k=3$ the formulas are the same). In neither of the methods is there any mention of hypothesis testing theory. In the IUPAC model the computations are based on k, whose numerical value is not unambiguously specified. However, the k value should refer to the number of measurements. Therefore, by using the value recommended by IUPAC ($k=3$), there is a necessity to accomplish a sufficiently large number of measurements (minimum 20 replicates) [18]. The standard deviation mentioned above can be estimated as [19]: (i) s_0, (ii) s_r (see equation below Table 3) and (iii) sample standard error of the intercept of the calibration curve (s_a) given by the equation:

$$s_a = \frac{s_r}{I^{1/2}}\sqrt{1+\frac{\sum_{i=1}^{I} x_i^2}{I\sum_{i=1}^{I}(x_i-\bar{x})^2}} \quad (1)$$

Different possible ways to compute standard deviation leads to various x_D results. Therefore, it is always crucial to give not only the obtained L_D value but also the manner of the standard deviation designation when the discussed method is applied. This issue was later indicated and examined by Winefordner and Long in their paper of 1983 [20]. Kaiser's and the IUPAC approaches discussed above can be considered as the foundations of the traditional method of determination of detection capabilities. In fact, the commonly used blank determination method (L_D calculated as three times the standard deviation of the blank) [21–23] is a very simplistic way of applying the traditional model. However, the method is not sufficiently precise. When L_D is estimated as a standard deviation of the blank multiplied by 3, the factors associated with preparation of the calibration curve are not fully considered. The slope and intercept are subject to error. In case of using a blank determination method, random errors in the slope and intercept of the calibration line are omitted. However, the errors mentioned above are taken into consideration when the standard deviation is calculated as s_a or s_r instead of s_0.

In conclusion, the computations in the IUPAC method are based on empirical data and are easy to apply. However, as mentioned above, different modifications of the discussed concept arise from the several ways of calculating the standard deviation. As noted by Montville and Voigtman in 2003, this can result in an intentional selection of that modification which gives the lowest L_D value [19].

5.3. Winefordner and Long – verification of the IUPAC method

The purpose of this report is to evaluate the statistical significance of L_D value in accordance with the IUPAC definition. It is presented in a simple and general form with the intention that it is also directed towards researchers without extensive statistical knowledge [20]. Three methods of estimating L_D are compared in terms of their competence considering analytical sensitivity and its influence on L_D. For better visualization of the differences between those methods they are confronted with each other while dealing with data sets whose slope, intercept and standard deviations differ significantly.

The following issues relate to the IUPAC approach and have been commented upon by authors to a wide extent. Emphasis is put on using factor $k=3$, instead of $k=2$. It is necessary for the L_D value to be significantly different from the blank values. It is also recommended to include the k factor into the x_D value, not only into the y_D value since x_D is more frequently reported than y_D, e.g., $x_{D(k=3)}$. Besides the IUPAC model, two others are presented: (i) the graphical approach, which includes standard deviation of the slope in the L_D expression; and (ii) the propagation of errors' approach which concerns the standard deviation of the concentration. All three models are applied to four different experimental data sets and conclusions are drawn. Fig. 3 explains how L_D is obtained with the graphical approach. This method introduces

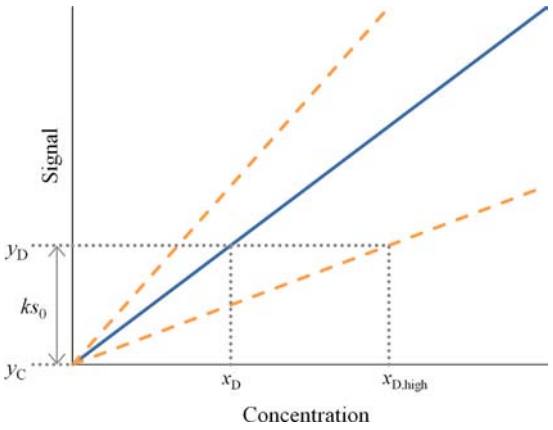

Fig. 3. Graphical representation of L_D estimation using the graphical approach presented by Winefordner and Long. The analytical calibration line (_) and confidence interval of the slope (---). The x_D value in the concentration domain is obtained by the straight line projected from y_D intercepting with the calibration line.

confidence interval of the slope marked with dashed lines. The L_D is then calculated by the equation presented in Table 3. In the case when the parameter related to the error of the slope, $t_\alpha s_b$, is close to 0 or when $b \gg t_\alpha s_b$, the value of x_D is obtained. However, when $t_\alpha s_m$ value grows, it increases the x_D value so it becomes $x_{D,high}$, as shown in Fig. 3. Having all dependencies in consideration, the larger value of $x_{D,high}$ is recommended while using the graphical approach. The propagation of errors method is more complicated than the other two methods and involves interception and its standard deviation besides the standard deviation of the slope and of the blank, see Table 3 for the proper equation. All parameters altogether contribute to discernibly larger x_D in comparison with other two methods. However, it is not a drawback since all parameters which have significant contribution to reliability of blank and standards signals measures are taken into consideration.

To conclude the results, the graphical approach provided the most erroneous values of L_D and should be used only for approximating L_D values. The IUPAC approach is advisable when the error of the blank significantly exceeds the error of the slope otherwise the L_D value will be artificially low. The propagation of errors is considered to be the most suitable due to its incorporation of analyte measurement errors into the L_D value. With regard to the above statements, both the IUPAC and the propagation of errors approaches are recommended by Winefordner and Long in the paper of 1983.

6. Modern approaches to the calculation of detection and quantification capabilities

As presented above, in the literature published up to the 1990s there were numerous inconsistent definitions and methods for determining L_D. ISO and IUPAC members saw a need to harmonize the definitions related to detection and quantification capabilities. Therefore, in the mid-1990s two important documents prepared by ISO and IUPAC members were issued [24,25]. Even though ISO and IUPAC specialists collaborated while preparing these documents, differences in approaches in defining and calculating detection and quantification abilities still appeared. Their proposed concepts are described below.

6.1. IUPAC concept

In an IUPAC document from 1995 (prepared by Currie) [24], some steps to harmonize an international terminology in the area of detection and quantification capabilities were taken. The suggestions for nomenclature are listed in Table 1. Currie recommends using the terms: 'critical value' or 'critical level', 'detection limit' or 'minimum detectable value' and 'quantification limit' or 'minimum quantifiable value'. The assumptions for computing detection and quantification capabilities are the same as for Currie's concept from 1968, the IUPAC method from 1978, the graphical approach or the propagation of errors approach discussed previously: homoscedastic, Gaussian measurement noise and OLS regression. The IUPAC concept from 1978 was developed to consider the theory of hypothesis testing, therefore the *t*-Student distribution was taken into consideration. The constant value of k was replaced with the Student t-value. The probability of false positives α and false negatives β, recommended by Currie, is equal to 0.05. This means there is a 5% chance that the researcher incorrectly decides that the analyte is present in the sample when it is not (during the detection limit estimation). The equations for x_C, x_D and x_Q are presented in Table 3. The method proposed by Currie is recommended for estimating detection and quantification capabilities. The correctness of the presented approach was tested and described by Voigtman not only for homoscedastic, Gaussian measurement noise and OLS processing of calibration curve data, but also for heteroscedastic, Gaussian measurement noise and weighted least squares (WLS) regression [17,26–29]. Currie's concept is useful for estimating detection capabilities in the theoretical domain as well as the experimental domain. The advantage is that the method is universal and can be adopted in industry and various fields of science (for example chemistry, medicine and toxicology). In subsequent papers, Currie draws the researcher's attention to the importance of a unification of methods to compute detection capabilities [5,30–32]. The articles are mainly related to the harmonization of L_C and L_D estimation, executed by IUPAC and ISO members in the mid-1990s. Currie briefly describes the history of detection capabilities, characterizes IUPAC and ISO approaches and the differences between them and communicates future challenges. The author pays attention to the role of the blank and its variance as the most crucial quantities when calculating detection and quantification capabilities [5,30,32,33]. Furthermore, Currie recommends reporting an estimated value with its uncertainty, even when the obtained result is below the L_C [24,30,32,33]. This prevents information loss. 'When a result is indistinguishable from the blank, based on a comparison of the result with the L_C, then it is important also to indicate that fact, perhaps with an asterisk or "ND" for not detected. But "ND" should never be used alone. Otherwise there will be information loss, and possibly bias if "ND" is interpreted as "zero"'[33].

In 1999 Currie published a historical overview of detection and quantification limits [5]. The author considers Kaiser's [12] and Currie's [7] articles as one of the early papers related to the detection limit. In the paper the problems arising from transformation of the signal detection and quantification limits to the concentration domain as well as the ill-defined blank were described. However, Currie mainly focuses on presenting the IUPAC recommendations from 1995 and some hints in the subject matter. In the present paper the authors describe the history of detection capabilities more broadly . Considerations of changes in nomenclature and computations are presented in Tables 1 and 3, including origins (from the 1900s) and trends of the last decade.

6.2. International Standard ISO 11843

In the ISO document that outlines the terms and definitions for describing detection capabilities [25], the expressions the critical value and the minimum detectable value are used. There are the same basic assumptions as used by the IUPAC and Currie method:

(i) the linear calibration function, (ii) Gaussian measurement noise, and (iii) constant variance (homoscedasticity). The ISO approach allows the L_C and L_D to be calculated in the experimental domain (in both the response and the concentration domain). The appropriate equations (for the concentration domain) are listed in Table 3. According to the ISO recommendations, at least a 5-point calibration curve should be prepared ($I=5$). When $\alpha=\beta$ and the appropriate large number of replicates is made, δ can be approximated as $2t_{1-\alpha,IJ-2}$, then $x_D=2x_C$ [34].

The ISO recommendations for calibration curve preparation are memorable and should always be adopted. However, Voigtman suggests that the methods proposed by the ISO [34] are biased. Voigtman verified the utility of the method based on critical values of the noncentrality parameter of the noncentral t distribution to estimate detection capabilities. As with the Hubaux and Vos approach, he carried out Monte Carlo simulation study using tens of millions of independent calibration curve data sets. The results showed that the method provides substantial bias in rates of false negatives [26]. For this reason, Voigtman strongly advises against using this approach: 'avoid use of "critical values of noncentrality parameter of the noncentral t distribution" methodology, since it is never applicable' [28]. A derivation of the x_D formula is misleading and results in a negatively biased x_D value (the x_D value is underestimated). Voigtman suggests using Currie's method to estimate detection and quantification capabilities because it gives unbiased results for all degrees of freedom. Concluding, Voigtman proved the ISO method to be mathematically incorrect. To the date, researchers did not deny Voigtman's statement regarding this method, which is still officially in use. The topic is still open to be discussed.

7. Other approaches for computing detection and quantification capabilities from the 1990s to present

7.1. The United States Environmental Protection Agency, US EPA approach

In 2000, the US EPA members proposed to distinguish the detection and quantification capabilities that refer to the measuring device and the analytical method [35]. In this concept, L_D and L_Q can be expressed as four different terms: (1) instrument detection limit (*IDL*), (2) method detection limit (*MDL*), (3) instrument quantitation limit (*IQL*) and (4) method quantitation limit (*MQL*). *IDL* and *IQL* refer to the limitations of the apparatus and can be estimated from measurements of blank samples or standard solutions. *IDL* and *IQL* values depend on the sensitivity and background noise of the instrument. The terms *MDL* and *MQL* refer to the minimum concentration of the analyte that can be reliably detected (*MDL*) or reliably quantified (*MQL*) by using the specific analytical method and can be estimated from measurements of real samples or spiked samples. In this instance, not only the instrumental noise and sensitivity, but also matrix effects and interferences are included.

In the root mean square error, the RMSE Method proposed by the US EPA [35] the equation to calculate *IDL* is a modification of the IUPAC formula from 1978 (RMSE is equal to s_r, see equation listed below Table 3). *IQL* is calculated as to 10-fold s_r divided by b. As mentioned above, the calculations of *MDL* and *MQL* are based on the measurements of matrix samples spiked with analyte concentration at the estimated *IQL* and the Student t-value is taken into consideration (one-tailed t-test for $\alpha=0.01$ and $K-1$ degrees of freedom). The equations proposed by the US EPA members are given in Table 3.

The EPA's intention was a specification of L_D calculations of pesticide residues in food. This was achieved by one of the EPA's programs called the Office of Pesticide Program (OPP). The primary objective of that study was an evaluation of health hazards to the population resulting from the presence of pesticide residues in food. The driving force behind the development of this program at the time was the requirements outlined in the Food Quality Protection Act (FQPA) in 1996. Certain ways of processing were assumed regarding measurements denoted as "Nondetects" which does not necessarily mean that the analyte is not present in the sample, it might occur below the L_D. The US EPA approach assumes a normal distribution of measurements.

7.2. Methods based on signal-to-noise ratio

Different concepts and calculation approaches to detection capabilities are based on the S/N ratio. They are mainly used in chromatography. The approach commonly used today was proposed by The International Conference on the Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and The European Pharmacopoeia. According to the ICH document [36], the L_D and the L_Q are designated by chromatograms from spiked samples at a low concentration level of the analyte and blank samples. The signal-to-noise ratio between 3:1 or 2:1 is generally considered a good estimate of L_D. The $S/N=10:1$ refers to the smallest concentration of the analyte which can be reliably quantified (L_Q). Based on the S/N ratio approach from 7th edition of the European Pharmacopoeia [37], L_D can be estimated using the following equation:

$$L_D=\frac{6H}{h} \tag{2}$$

The parameters H and h are presented in Fig. 4. H is obtained for the chromatogram of a blank sample with a small amount of analyte. The background noise is usually designated for a blank sample and observed around the retention time of the analyte. h is the maximum amplitude of the background noise. In addition, when the method based on the S/N ratio is applied, the appropriate chromatograms should be attached.

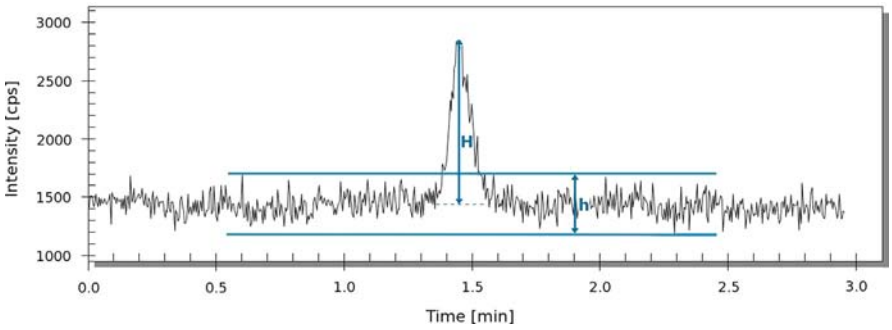

Fig. 4. Graphical representation of h and H parameters.

The signal-to-noise ratio is widely used in chromatographic methods because it is an easy tool to estimate detection capabilities. However, due to manual integration, application of S/N ratio approach results in subjective evaluation of L_D. Moreover, outcomes obtained with the discussed method depend mainly on the instrumental noise. Another example of successful application of the L_D estimation method for chromatographic data is the IUPAC concept (Fig. 4.)

7.3. Nonparametric methods

When distribution of variables in the population is not available or when the results of an analysis are scattered in a non-Gaussian manner, nonparametric statistical methods should be used to obtain a more reliable estimation of the detection limit. Nonparametric methods do not rely on predictable population parameters i.e. mean or standard deviation, which describe distribution of variables of interest. Nonparametric approaches belong to the so-called "robust methods" and are applied in cases when variables manifest non-Gaussian distribution, outliers are present or when certain assumptions according to variables distribution are not achieved. Nonparametric statistics are generally easier to handle than parametric methods, have fewer assumptions and can be implemented even when the use of the latter is justified, but one must keep in mind that they are usually less powerful than parametric statistics. Some analytical instruments tend to truncate negative response signals and present them as zero or small positive numbers thus generating asymmetric distribution of values which is a premise to apply the nonparametric approach for L_D determination. Fig. 1 is an example of asymmetric data distribution produced by instrument-based data truncation at a zero concentration value. All readings below zero were automatically assigned to zero or small positive value. Another important issue presented in Fig. 1 is graphical indication of α and β, representing Type I and Type II errors respectively, which should be taken into consideration while determining L_D.

The most popular nonparametric statistical method of obtaining L_D is ranking of ordered values. Linnet and Kondratovich in their paper of 2004 [38] propose a method that consists of using L_C calculated with the 95th percentile from repeated blank measurements and standard deviation of repeated sample measurements with relevant concentrations in order to obtain L_D. Later in the same year, The National Committee for Clinical Laboratory Standards (NCCLS) in collaboration with Linnet and Kondratovich published official guideline, EP17-A, providing protocols for determining the lower limit of detection of clinical laboratory methods [39]. The EP17 guideline method used therein is basically the same and is recommended for use in clinical laboratories and by manufacturers of in vitro diagnostic tests. Firstly, L_C is determined by estimation of the 95th percentile of ranked values for $\alpha=5\%$ as a default level of error, next L_D is calculated using the equations listed in Table 3. The authors also elaborate an example of verifying a claimed L_D of a given analytical procedure and evaluate the performance of L_D estimation procedures by a simulation consisting of 10 000 runs. Corresponding to the simulation result, the conclusion is that smaller sample size contributes to larger standard error (SE): for sample size $n=25$, SE of L_D is 52% and for $n=100$, $SE=27\%$. The presented L_D estimation procedure is in accordance with the idea for establishing L_D as described by the ISO guidelines, mainly considering both Type I and II errors. The method becomes general by focusing on concentrations and is not dependent on a specified type of calibration function. It is also applicable with asymmetric blank distribution. The drawback of the described procedure is that it gives a less precise estimation of the L_C compared to fully parametric procedures.

Lavagnini et al. have recently proposed the use of the nonparametric Theil–Sen (TS) median-based regression technique combined with Lancaster–Quade (LQ) statistics [40]. This is applied to receive (i) detection limit of an instrumental method; (ii) quantification of the uncertainty of a discriminated variable in the inverse regression; (iii) comparison of methods. The method therein described is based on a one-sided simultaneous tolerance interval to obtain the L_D. The procedure involves Type I and Type II errors and is similar to the Hubaux and Vos approach [16]. Firstly, the $(1-\alpha)100\%$ one-sided simultaneous tolerance interval is calculated by the following equation:

$$y^{\pm}_{tol,1-\alpha}(x) = y^{\pm}_{C,1-\alpha}(x) \pm N(P)\left(\frac{v}{{}^{\alpha}\chi^2_v}s^2\right)^{1/2} \quad (3)$$

where $y^{\pm}_{tol,1-\alpha}(x)$ denotes the limits of the $(1-\alpha)100\%$ tolerance interval, $y^{\pm}_{C,1-\alpha}(x)$ the limits of the $(1-\alpha)100\%$ confidence band, $N(P)$ the one-sided P percentile point of the unit normal distribution and ${}^{\alpha}\chi^2_v$ the lower α percentile point of the χ^2 distribution. The next step is finding the upper limit $y^{+}_{tol,1-\alpha}(0)$, that is limiting value at zero concentration which is correspondent to the L_C according to Currie. The limiting value is explained as the upper value in the signal domain defined by confidence interval at $(1-\alpha)100\%$ confidence level that is associated with concentration at zero level. The L_D is then given by the projection on the x-axis of the intersection of a straight line $y=y^{+}_{tol,1-\alpha}(0)$ with the lower $(1-\beta)$ 100% one-sided tolerance band of the calibration curve. This operation is presented in Fig. 5.

In the view of the authors, the nonparametric Theil–Sen regression approach is easy to use and compute and is devoid of restrictive statistical constraints and is therefore a robust method. The values of L_D obtained with the TS–LQ approach are larger than those obtained with WLS regression. This is explained by considering the presence of two opposite effects: robustness of the nonparametric TS method and the influence of decreasing variance of the WLS tolerance interval at low concentration. Nevertheless the authors point out that these drawbacks do not affect the advantage achieved by the use of the TS–LQ technique in different analytical problems.

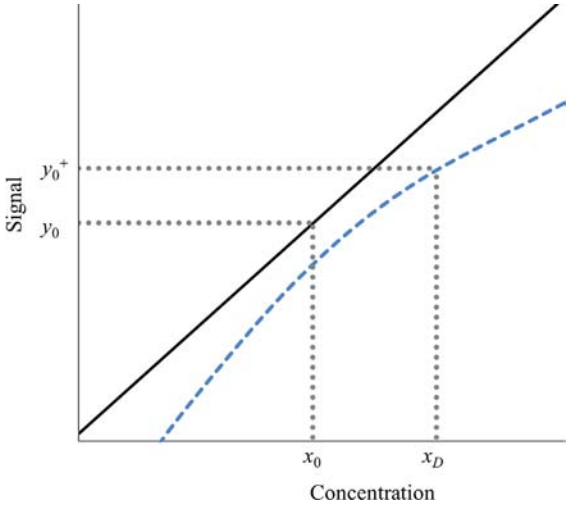

Fig. 5. Graphical representation of L_D estimation using nonparametric Theil–Sen approach presented by Lavagnini et al. TS calibration line (_) and lower $(1-\beta)100\%$ one-sided tolerance band (---). The interception of straight dotted line, projected from y_0^+, with the lower tolerance band indicates the position of L_D in the concentration domain. The point y_0^+ represents the upper limit of the $(1-\alpha)100\%$ one-sided simultaneous tolerance interval at zero concentration level.

7.4. Detection limits of chemical sensors

In the publication [41] the authors propose two methods for calculating the limits of detection that are applicable with sensors such as fiber optic sensors, photoacoustic sensors, absorption sensors and refractive index sensors. The explained methods of L_D calculation are (i) method 1: based on the standard deviation at low concentrations and (ii) method 2: determination by using a calibration curve. Examples in the form of spreadsheets are available online.

The first method accords with the guidelines of the American Chemical Society [42] and consists of (i) repeatedly measured and averaged blank value; (ii) measurements of samples containing 1–5 times higher analyte concentrations than the expected L_D and calculation of mean and standard deviation; (iii) calculation of signal at the L_D with an equation involving an average signal of blanks, α-quantile of Student's t-function and standard deviation; and (iv) computation of the concentration of L_D based on the sensitivity, i.e. slope of the calibration curve (see Table 3).

The above method represents a parametric approach which assumes that the errors are normally distributed. The second method is proposed for cases when researchers want to compare their own sensor system with a previously published system which has not been yet characterized with method 1. To obtain the L_D according to the second method, one must go through a series of equations involving variables such as the slope of linear fit, intercept of calibration curve, average standard deviation and uncertainty of the concentration measurements. This method also assumes a normal distribution of errors and, moreover, constancy of standard deviations of the signal for all concentration measurements. The authors also outline in the form of a graph the influence of the sensor resolution limit on determination of the L_D. To demonstrate practical applications and limitations, as well as differences between the discussed methods, both are applied to experimental data derived from other publications and summarized by the authors. In conclusion, the second method is described as requiring many assumptions and producing only an estimation of the L_D. Therefore, the first method, involving repeated measurements near the suspected L_D, is the most recommended.

7.5. Multivariate detection limits approaches

The value of L_D in the most cases refers to the univariate measurement signal, by which it is assumed that signal is highly selective for the specific analyte, and that possible influence of the interferences is negligible. However, while considering more complex data from spectral analysis or hyphenated techniques the estimation of detection limit may dependent on more than one variable. This situation is often encountered in the field of chemometrics and environmental analysis or industrial processes where multivariate calibration methods and related figures of merit serve a great benefit in data processing and statistical inference. Multivariate analysis handles unselective data to build a valid model, capable to make predictions of certain variables concerning the analyte of interest. Multivariate methods operate the multiple data simultaneously to predict the concentration of analyte and thus are able to compensate contribution of interferences and provide the quantitative information from unselective data with good results. The multitude of multivariate L_D calculation approaches is due to complexity and diversity of multivariate regression models and analytical data. Several reviews regarding the issue of multivariate approaches are presented below.

The topic of detection capabilities for multivariate calibration methods is presented in the IUPAC Technical Report by Olivieri et al. [43] where three different approaches are described using real experimental data. As the authors explain, L_D is strictly connected with uncertainty estimation on the concentration levels that can be statistically distinguish from zero concentration with a given probability of false detection. One of the methods therein presented is an error propagation-based formula for standard error of prediction to zero concentration level. This formula employs all sources of errors in the signal and concentrations data of calibration and prediction samples. This method is described as a sample specific, meaning that the level of interferences in the sample influences the L_D. This approach was also compared with Monte Carlo simulations and with empirical model consisting of repeated analysis of spiked samples resulting with mutual accordance. Another approach involve transformation of multivariate models to univariate forms. The condition that must be fulfilled here is that the multivariate model must be able to efficiently isolate signal of the selected analyte. The third method uses the neural network to optimize the probabilities of α and β simultaneously for a fixed threshold concentration. The procedure requires a set of samples with concentrations above and below the selected threshold level.

Several different approaches have been reviewed by Boque and Rius in 1996 [44]. The authors provide information on limitations, applications and calibration assumptions for each method along with suitable equations. The methods therein presented are (i) net analytical signal approach, including extension to inverse calibration models, (ii) confidence intervals for concentration approach, (iii) detection limits for coeluting species and previously mentioned, (iv) error propagation approach, and (v) transformation to univariate form. Another review worth mentioning was presented by van der Voet [6]. Author briefly describes several methods of L_D estimation, for example: (i) consideration of only one signal while ignoring the others, (ii) application of a univariate approach to each signal separately and (iii) development of decision criteria in the multivariate space.

8. Conclusions

Over the course of a hundred years of detection and quantification capabilities in analytical chemistry, researchers have proposed a variety of methods for computing L_C, L_D and L_Q (see Table 3). Owing to the application of metrology in chemical sciences, methods with no statistic foundations have been rejected automatically. For example, there are no sound reasons for estimating the L_D by using methods mentioned by Currie: detection limit compute as 10% of the background or twice the background [7]. Moreover, it was proved that some of the approaches (Hubaux and Vos and ISO) generate results with bias [17,26]. However, the methodology based on the noncentrality parameter of the noncentral t distribution [34] is still widely used and accepted.

The researchers must be aware of the fact that there is no one universal equation suitable in all situations. The choice of the calculation approach should be well thought out and reasonable and it should mainly depend on the statistics of the measurements: distribution of repeated measurements, the nature of measurement noise (homoscedastic or heteroscedastic) and processing method (ordinary least square or weighted least square). Depending on the very nature of the analytical data there is a great choice of various approaches of L_D estimation. There might be beneficial to incorporate less traditional and popular approaches. If the data fails to fit any model of prediction, one should consider nonparametric methods which are more robust than parametric methods. The multivariate method might be used when more than one component of the sample contributes to the analytical signal. The knowledge of statistical behavior of data is vital to minimize the possibility of misestimation of L_D. Regardless of the L_D and L_Q estimation method certain information should always be reported:

(i) the method used to estimate detection and quantification capabilities and (ii) the number of replicates (for statistical reasons, it is crucial to have a sufficiently large number of measurements). To conclude, before we compute detection capabilities, we should characterize the measurement system and choose the most useful concept to calculate L_D in our specific case.

The terms and approaches for the determination of detection and quantification capabilities remain one of the most controversial issues in analytical chemistry. Despite the fact that many articles about detection capabilities have been published so far, there is still no total agreement between researchers in this field. The present paper was written because the authors still recognize a need to publicize the issue of standardization of terms and computations of detection and quantification capabilities. Furthermore, the principal terms and equations relating to L_C, L_D and L_Q published from the beginning of 20th century up until the present are presented.

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