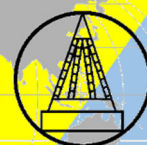

Eurachem 

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Cooperation on International Traceability in Analytical Chemistry

EURACHEM / CITAC Guide

**Setting and Using
Target Uncertainty in
Chemical Measurement**

STMU 2015



A focus for analytical chemistry in Europe



Eurachem/CITAC Guide Setting and Using Target Uncertainty in Chemical Measurement

First edition

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Foreword

The Eurachem/CITAC Measurement uncertainty and traceability working group prepared this document to complete a sequence of guidelines that aims at promoting the production of measurement results traceable to an adequate reference and, reported with reliable and sufficiently low uncertainty for the intended use of the measurement. These features are essential for the adequate interpretation of the measurement result which is discussed in the Eurachem/CITAC guide, ‘Use of uncertainty information in compliance assessment’.

This document discusses how to set a maximum admissible uncertainty, defined in the third edition of the International Vocabulary of Metrology as the “target uncertainty”, to check whether measurement quality quantified by the measurement uncertainty is fit for the intended purpose.

This guideline is applicable to analytical fields where the target uncertainty is not set by the regulator or the client, or a minimum difference of the studied parameter in the same or different items must be detected in R&D work. This guide discusses how to set the target uncertainty for process development and for applied or fundamental research using information about the smallest difference or system trend that must be distinguished in a reliable way.

This guideline can also be useful for authorities and stakeholders that feel the need to define or upgrade criteria for measurements quality. The setting of target values for the so called conventional performance characteristics (precision, trueness, etc.) can miss the control of important uncertainty components included in sound uncertainty evaluations.

The Eurachem/CITAC working group believes this document fills a gap in the current list of guidance for measurements in chemistry and can contribute to ensuring measurements play their role in the management of socio-economic interests and in the technological and scientific developments of society.

1 Introduction

All measurements are performed with a goal, ranging from the assessment of the compliance of a product with a specification to the characterization of a new material. The adequate fulfilment of this goal depends on the fitness of measurement uncertainty [1-4] for its intended use. For example, the assessment of the compliance of a gold alloy with a specification for gold content must be performed with a low uncertainty due to the price of this component. The measurement of glucose in blood should be affected by an uncertainty low enough to allow the reliable detection of deviations from the glucose values for a population of healthy individuals. The characterisation of a meteorite must be performed with an uncertainty small enough to distinguish the composition from other minerals. Therefore in setting the measurement requirements, in addition to specifying performance characteristics such as recovery, repeatability and bias it is also necessary to set a target value for the uncertainty [5].

According to the latest edition of the International Vocabulary of Metrology [1], the “upper limit” of the uncertainty “decided on the basis of the intended use of measurement results” is designated “target uncertainty”.

The decision on the fitness of a measurement procedure for the intended use depends not only on the measurement uncertainty, but also on other information, such as the analytical range and the uncorrected recovery in some fields, or the cost and duration of analysis.

In some analytical fields, the specification and/or the legislation define the target uncertainty required for compliance assessment [6, 7]. However, important measurements in many other fields are performed without this parameter having been set. The fact that the uncertainty is reported with the measurement result does not guarantee its fitness for the intended use.

2 Scope

This document provides guidance to analysts, regulators and other end-users of analytical information on setting the target measurement uncertainty.

Section 4 gives the inputs that are available to help set the target uncertainty.

Sections 5 covers the use of this information to set the target value.

Section 6 covers how to set the target uncertainty for a range of quantity values when it is initially defined for just some quantity values.

The estimated uncertainty can vary due to the variability of uncertainty component estimation and section 7 covers how the uncertainty of the uncertainty estimation can

affect the decision about the measurement's fitness for the intended use. Section 8 covers how the uncertainty might be reduced if the estimated uncertainty turns out to be larger than the target value and section 9 describes how to use the target uncertainty to guide measurement procedure validation by suggesting target values for specific performance characteristics.

Section 10 presents examples of setting the target uncertainty using the different types of information and algorithms presented in previous sections.

Section 3 (Terminology) discusses the relevant aspects of terminology used in this guide.

3 Terminology

This document uses terminology presented in the latest edition of the International Vocabulary of Metrology (VIM) [1].

The VIM (see entry 2.6 [1]) defines target measurement uncertainty as “measurement uncertainty specified as an upper limit and decided on the basis of the intended use of measurement results”.

Measurements are frequently performed to check if the measurand value (see entry 2.3 [1]) is above or below a maximum or

minimum permissible quantity value. The term “specification limit” or simply “limit” will be used for either one of these cases.

In this document, the generic term “quantity” is preferred to some specific examples like concentration, mass fraction, depletion rate, pH, etc.

The interpretation and application of VIM concepts to measurements in chemistry is discussed in a Eurachem guide [2].

4 Selecting inputs for setting the target measurement uncertainty

Where there is a defined maximum and/or a minimum limit for the measurand, typically in a legislation or technical specification, this document should be checked for guidance about the acceptable magnitude of the uncertainty (section 5.1.1). This information can also be available in guidelines and reports on the assessment of the compliance with the legislation or specification. The origin of such references and links to above-mentioned legislation and technical specification should be checked.

The target uncertainty can be inferred from the compliance interval, defined by a minimum and a maximum limit (section 5.1.2), or from the quantity value, above or below a single limit, beyond which there should be a low probability of an incorrect compliance decision (section 5.1.4).

In some fields, target values of measurement performance characteristics, such as limit of detection, precision and mean analyte recovery, are defined. In those cases, if these performance characteristics reflect the most relevant random and systematic effects affecting measurements, they can be converted into a target uncertainty (section 5.1.3). This target uncertainty is an additional requirement to the defined performance characteristics, which has the advantage of summarising in one parameter requirements for all sources of uncertainty, including some

that usually remain unchecked since they do not show up in conventional performance characteristics.

When target values are not defined for the relevant performance characteristics, the target uncertainty may be determined from how measurement performance is assessed from results of proficiency tests (section 5.2.1) if the performance score is estimated considering the intended use of the measurement. The results of collaborative studies or other interlaboratory comparisons can be used to define the target uncertainty (section 5.2.2) if it is concluded that the agreement between results is adequate for the purpose of the analysis. In some cases, it may be worthwhile to determine the target uncertainty from a study of the economic benefits of controlling products or processes with a more expensive measurement procedure that has a lower uncertainty (section 5.3).

If a trend in the composition of a system needs to be studied or differences in analysed items must be distinguished, the minimum change of the quantity value to be discriminated can be used to define the target uncertainty (section 5.4).

In some cases, the target uncertainty may have to be derived from one defined for technically similar, or related, decision problems (section 5.5).

5 Using existing information for setting the target uncertainty

This section details how to use different types of references or data outlined in section 4 to set the target measurement uncertainty. The sequence of presented types of data progresses from the ideal source of the target uncertainty to those less likely to be harmonised.

5.1 Legislation or product specification

Ideally, the target uncertainty is explicitly set in a reference document (section 5.1.1). On other occasions, this value is implicit from target values of other performance characteristics (section 5.1.3) or from the specification limit (sections 5.1.2 and 5.1.4).

5.1.1 Defined target uncertainty

The ideal case is where the legislation or a specification defines the target uncertainty. Unfortunately this is rarely the case at present. Current examples include:

- Commission Regulation (EC) 333/2007 [6] defines the target standard uncertainty (designated “maximum standard measurement uncertainty”) for the determination of Pb, Cd, Hg, inorganic tin, 3-MCPD and benzo(a)pyrene in foodstuffs. Defined target uncertainty is a function of the limit of detection and the maximum specification limit, Q^{\max} , (designated “concentration of interest” in the Regulation).
- Directive 2008/50/EC on ambient air quality and cleaner air for Europe [7] defines the target relative expanded uncertainty for measurements of relevant parameters. Target uncertainty is different for “fixed” and “indicative” measurements. Fixed measurements are performed in zones where the risk of pollutants exceeding limits is high. Indicative measurements are performed to enable the assessment of the geographical distribution of the pollutants.

Usually, the target uncertainty is set for measurement results close to the specification limit.

5.1.2 Defined compliance interval

In some analytical fields, the specification limit is defined without guidelines about the quality of measurements performed to check compliance with that level.

If a single minimum or maximum specification limit is defined, at least, the measurement quality close to this level should be assessed.

If a compliance interval for the quantity is defined (i.e. a minimum and maximum limit), measurement performance within and close to this interval should be assessed.

The target uncertainty for checking compliance with a single specification limit (minimum or maximum) should be defined considering the criteria discussed in the following sections.

If a compliance interval is defined for the measurand, such as the content of an active substance in a medicine or pesticide in a formulation for crop protection, the analyst can infer that the uncertainty should be small enough to distinguish quantities within this interval. If the compliance interval is defined by a maximum Q^{\max} and a minimum Q^{\min} quantity, the target expanded uncertainty, U^{tg} , should typically be 8 times smaller than the interval range:

$$U^{tg} = \frac{Q^{\max} - Q^{\min}}{8} \quad (1)$$

The factor 8 is selected since, in theory, this would allow the simultaneous accommodation of four non-overlapping measurement results reported with expanded uncertainty, considered the minimum discrimination ability within this interval. A value larger or smaller than 8 gives rise to an uncertainty estimate that seems to be too strict or too flexible for the typical purpose of a compliance interval.

5.1.3 Defined measurement performance characteristics

In some legislation or technical specifications, target values of measurement performance characteristics related to relevant uncertainty components are defined. Maximum limit of detection and/or quantification, maximum difference of results of duplicate measurements or maximum coefficient of variation of results of replicate measurements obtained under different precision conditions, and permissible recoveries, are some of those examples.

Example 1:

AOAC publish target method performance characteristics for an extensive list of analytes in their SMPR (Standard Method Performance Requirements) programme that are suitable for estimating target uncertainty. Recent requirements now include Target Uncertainty [8].

Occasionally, performance characteristics are presented using terminology different from that presented in the VIM [1] (Example 2). Therefore, analysts should check how terms are defined in the reference before checking measurement performance. If these documents are not clear about relevant details, such as the precision conditions, other documents or reports of the application of the reference should be consulted.

Example 2:

Directive 98/83/EC [9] on the quality of drinking water defines maximum values for the trueness but this is not the same as the definition in VIM [1].

If target values of measurement performance characteristics reflecting relevant random and systematic effects are defined, these can be used to estimate the target uncertainty. The target uncertainty is an additional requirement to the mandatory ones set in the regulation or specification. The target uncertainty also allows an assessment of whether the uncertainty components assumed to be

negligible in the regulation or specification are in fact negligible.

Table 1 presents some performance characteristics for which target values are occasionally quoted and which can be used for defining target values for the uncertainty associated with either random or systematic effects.

The target limit of detection (LOD^{tg}) defines a target value for the standard deviation, s^{tg} , of results, obtained under specified precision conditions, between the “zero value” and the limit of quantification (LOQ), where precision is expected to be approximately constant. The target value for the standard deviation will be equal to $s^{tg} = LOD^{tg}/3$ or $s^{tg} = LOD^{tg}/3.3$ depending on the convention used for calculating LOD. The LOD can be estimated as 3 or 3.3 times the standard deviation of measurement results obtained under repeatability or intermediate precision conditions (repeatability or intermediate precision standard deviations in short). The target precision of measurements performed close to the LOD is applicable, at least, up to LOQ, since both limits are together in a narrow quantity range.

The s^{tg} defined from a target LOQ, LOQ^{tg} , ($s^{tg} = LOQ^{tg}/10$) is usually applicable between LOD and $5LOQ$.

If LOD^{tg} and/or LOQ^{tg} are defined for intermediate precision conditions, the resulting standard deviation (i.e. s^{tg}) is adequate to quantify relevant random effects affecting measurements. The repeatability standard deviation underestimates random effects observable in various runs.

A SANCO document [14] proposes that when a target value for the reproducibility standard deviation is not available, it can be taken to be approximately 3/2 times larger than the corresponding repeatability standard deviation. Section 5.2.2 describes the use of target values for the reproducibility standard deviation to estimate the target uncertainty.

For measurements performed above the LOQ, the target coefficient of variation or target range of replicate measurements (Table 1) can be used to estimate the target intermediate precision standard deviation, s^{tg} . The target standard uncertainty of relevant

random effects, u_{ra}^{tg} , is estimated as s^{tg} (that is, $u_{ra}^{tg} = s^{tg}$).

The permissible mean error $|\bar{E}|^{tg}$, defined as the maximum range between the mean of replicate measured quantity values and the reference value observed from the analysis of reference materials during validation, can be used to estimate the target standard uncertainty associated with the uncorrected bias, u_{sy}^{tg} , as $(u_{sy}^{tg} = |\bar{E}|^{tg} / l)$, where l depends on the assumed distribution for $|\bar{E}|^{tg}$. This formula is applicable when bias is estimated from a large number of measurements of reference materials (Table 1).

The target combined uncertainty, u_c^{tg} , reflecting the combination of the estimation of precision and uncertainty on bias, calculated using uncertainty propagation law is:

$$u_c^{tg} = \sqrt{(u_{ra}^{tg})^2 + (u_{sy}^{tg})^2} \quad (5)$$

where u_{ra}^{tg} can be estimated from target values for the LOD, LOQ, coefficient of variation or range of replicate measurements, or any other parameter describing the same effect. The u_{sy}^{tg} can be estimated from the permissible mean error or an equivalent parameter.

The comparison of the target uncertainty with the uncertainty on the measurement result is discussed in section 7.

Table 1: Measurement performance characteristics for which defined target values can be used to estimate the target uncertainty.

Measurement performance characteristic	Description
Limit of Detection (LOD)	<p>The Limit of Detection (LOD) can be estimated under repeatability or intermediate precision conditions. For instrumental methods of analysis requiring daily calibration of the instrumentation, LOD estimated under repeatability conditions is only applicable to the daily run. The LOD estimated from the precision of measurements from different calibrations can be applicable to a longer time scale. At this quantity level, the measurement relative standard deviation is 33 % or 30 %, if the LOD is calculated by multiplying the measurement standard deviation by 3 or 3.3, respectively [10]. Since precision is constant in a narrow quantity range, the standard deviation of measurements at the LOD can be used to estimate precision between “zero value” and the Limit of Quantification (LOQ) (approximately 3 or 3.3 times larger than LOD). Only rarely is the uncertainty from systematic effects important for measurements close to LOD (i.e. between the “zero” and two times the LOD: [0, 2LOD]).</p> <p>The standard deviation utilised in LOD calculations is $LOD/3$ or $LOD/3.3$ depending on the convention used for estimating LOD.</p> <p>Therefore if a target LOD, LOD^{tg}, is defined, the target standard deviation for precision, s^{tg}, under the precision conditions specified in the estimation of LOD is:</p> $s^{tg} = \frac{LOD^{tg}}{3} \quad \text{or} \quad s^{tg} = \frac{LOD^{tg}}{3.3} \quad (2)$ <p>depending on how LOD is calculated.</p>

<p>Limit of Quantification (LOQ)</p>	<p>The calculation of the Limit of Quantification (LOQ) is similar to that performed to estimate LOD, where the multiplying factor of the standard deviation is 10 instead of 3 or 3.3. At this concentration level, systematic effects can be relevant.</p> <p>The standard deviation obtained under the same precision conditions as those used in the estimation of the LOQ, is $LOQ/10$. Usually, the estimated standard deviation can be applied between LOD and two to five times LOQ.</p> <p>Similarly to Eq.(2), if a target LOQ, LOQ^{tg}, is defined:</p> $s^{tg} = \frac{LOQ^{tg}}{10} \quad (3)$ <p>where s^{tg} is the target precision under the conditions specified in the definition of the LOQ^{tg}.</p>
<p>Range of replicate measurements</p>	<p>Whenever a target range for results from duplicate measurements is defined, the confidence level and precision conditions used should be checked. If a confidence level is not stated, a value of 95 % should be assumed. Since the repeatability or intermediate precision limits, estimated for a confidence level of 95 %, are 2.8 times larger than the standard deviation of measurements under the same precision conditions, the target range can be converted to a target standard deviation by dividing it by 2.8.</p> <p>If the target value of the range of results from more than duplicate measurements is defined, multiplying factors used to estimate the critical range from the precision estimation should be used to calculate the precision from the defined target range [11].</p>
<p>Coefficient of variation</p>	<p>If a target coefficient of variation is defined without specifying the precision conditions used (typically repeatability or intermediate precision conditions), it can be assumed that the more informative intermediate precision is reported. Many references to measurement performance characteristics do not use the terminology of the latest, or even previous, VIM editions, requiring a careful check of the meaning of the terms. In the past, the term reproducibility was used for the concept designated as intermediate precision in the latest VIM edition. According to the latest edition of the VIM [1], reproducibility refers to the agreement of results, of the same measurand, obtained from different laboratories using the same or different measurement procedures.</p> <p>Some documents define precision requirements as a target value for two times the standard deviation of results estimated under defined conditions [9].</p> <p>The repeatability standard deviation only reflects random effects under specific environmental and operational (i.e. for an analyst/equipment combination) conditions, and the intermediate precision will not reflect systematic effects, relevant in some measurements, such as the so called laboratory or method bias [12].</p>

Maximum permissible error

Some references define the maximum permissible bias affecting measurements. More frequently, maximum and minimum permissible relative signed errors are defined. Relative errors are usually expressed via recoveries (i.e. the ratio between estimated and expected quantity values).

In some analytical fields, permissible single and mean recoveries are defined for different situations [13]. Permissible recoveries for a single test are defined to check the quality of measurements for a batch of samples controlled through the analysis of a single recovery test. The permissible mean recovery is used, during measurement procedure validation, to check if bias is acceptable. Permissible error ranges are wider for single recovery tests than for mean recovery tests.

Since mean error is an estimation of measurement bias, it can be used to quantify approximately bias uncertainty component. If a maximum (\bar{E}_{Max}) and a minimum (\bar{E}_{Min}) mean error are defined, above and below a null or mean value, the standard uncertainty of an uncorrected bias can be calculated by reducing the confidence level of the half error range ($(\bar{E}_{Max} - \bar{E}_{Min})/2$) by dividing it by an adequate factor dependent on the selected distribution of the range. If a triangular or rectangular distribution with 100 % confidence level is considered, the factor $\sqrt{3}$ or $\sqrt{6}$ should be used respectively. The triangular distribution is preferable whenever the mean error is expected to be more probable in the middle of the interval $[\bar{E}_{Min}; \bar{E}_{Max}]$. Equation 4 gives an estimation of the target standard uncertainty of the bias, u_{sy}^{tg} , on measurements not corrected for mean error:

$$u_{sy}^{tg} = \frac{\bar{E}_{Max} - \bar{E}_{Min}}{2\sqrt{6}} \quad (4)$$

5.1.4 Defined decision risk

As was pointed out in the Introduction, an important reason for setting a target uncertainty is the use of uncertainty in the assessment of compliance as described in detail in reference [15]. The key to the assessment of compliance is the concept of “Decision rules”. These rules give a prescription for the acceptance or rejection of a product based on the measured quantity value, its uncertainty and the specification limit or limits, taking into account the acceptable level of the probability of making a wrong decision. On the basis of the Decision rules, an “Acceptance zone” and a “Rejection zone” are determined, such that if the measured quantity value lies in the acceptance zone, the product is declared compliant and, if in the rejection zone, it is declared non-compliant. In essence, the effect of applying the decision rule is to increase or decrease the limit, Q , by an amount ku , called a guard band. The value of k and whether the guard band is added or subtracted from Q depends on the choice of the decision rule. The target value for the standard uncertainty u is then chosen on what is an acceptable value of the size for the guard band.

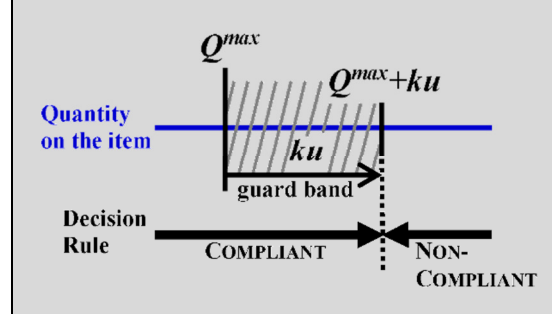
For example, when checking compliance against a maximum limit, Q^{\max} , where the decision rule requires a high probability that the limit is exceeded before declaring non-compliance, the guard band is added to Q^{\max} . This means that a measurement result as large as $(Q^{\max} + ku)$ will lead to a declaration of compliance [15] and a target value for u has to be chosen so that this is acceptable (Figure 1).

If a quantity value, q^{\max} , in the analysed item larger than Q^{\max} is defined, above which an item should be correctly declared as non-compliant with a probability larger than P_1 , it can be used to define the target uncertainty.

A specific scenario of controlling the risk of accepting an item where the compliance decision is taken from the measured quantity of a laboratory sample, but no allowance is made for how representative the measured value is in relation to a sampling target, is discussed below. In most regulations, a compliance decision is taken from the result of a measurement on a laboratory sample collected following a regulated procedure and, therefore, sampling uncertainty or

representativeness of the sample is not to be questioned. If the measurement aims at inferring information about the composition of a large sampled population, the target uncertainty must include the sampling and post-sampling uncertainty.

Figure 1: Decision criterion for the compliance of the quantity of an item with a maximum quantity, Q^{\max} , where a “guard band” ensures a decision that the measured quantity value has a low probability of incorrectly deciding non-compliance.



For example, when the following conditions for deciding product compliance are applicable (C1 to C4):

C1) Measurement distribution: The values attributable to the measurand Q , derived from a measured quantity value q , have an approximately normal distribution.

C2) A maximum limit, Q^{\max} , is defined.

C3) Decision rule: The product is considered not compliant if there is, at least, a high probability P_1 that the value of Q exceeds Q^{\max} , i.e. if the measured quantity value, q , minus an adequate multiple of its standard uncertainty, ku , is above Q^{\max} (i.e. $(q-ku) > Q^{\max}$). The multiplying factor, k , of the standard uncertainty, u , will be typically the one-tailed Student's t , t_1 , for the confidence level P_1 and degrees of freedom of u [15]. The quantity ku is the guard band for the compliance assessment and a maximum value of u has to be specified to keep the size of the guard band to an acceptable level.

C4) Decision risk: One way of setting a maximum value of u implicitly is to set a limit on the maximum measured quantity value, q^{\max} , that is acceptable for the sample to be declared compliant, e.g. $q^{\max} = Q^{\max}(1+x)$. In setting the value of x it must be borne in mind

that for a measured quantity value of $Q^{\max}(1+x)$ there is a 50 % probability that the value of Q exceeds this and a probability of $(1-P_1)$ that it exceeds $Q^{\max}(1+2x)$.

In this case, u^{tg} is estimated by the following equation:

$$u^{\text{tg}} = \frac{q^{\max} - Q^{\max}}{t_1} \quad (6)$$

If a minimum limit, Q^{\min} , is the defined condition, the decision rule is equivalent to C3 for values smaller than Q^{\min} (i.e. $(q+ku) < Q^{\min}$), and a maximum value of u is set implicitly in a similar way, then u^{tg} is estimated by Eq.(7):

$$u^{\text{tg}} = \frac{Q^{\min} - q^{\min}}{t_1} \quad (7)$$

where q^{\min} is the minimum measured quantity value that is acceptable for the sample to be declared compliant.

5.2 Proficiency or agreement evaluation criterion

If reference documents of the specification limit(s) for the measurand do not define measurement quality requirements, this information can be inferred from how measurements are assessed in proficiency tests (5.2.1), or from the dispersion of results from different laboratories when it is adequate to assess the agreement of such results (5.2.2).

5.2.1 Proficiency tests

In most analytical fields, performance in proficiency tests is evaluated by calculating z-scores, z , estimated from the ratio between the measurement error and an assigned standard deviation:

$$z = \frac{x_i - X_{\text{Ref}}}{\sigma} \quad (8)$$

where x_i is the value reported by the laboratory, X_{Ref} is the reference value and σ is the standard deviation defined for this assessment. When σ is set by the proficiency test provider to examine whether the methods being studied are fit for their intended use it can be used to define the target standard uncertainty ($u_c^{\text{tg}} = \sigma$). In the analysis of drinking water for major components, a σ of 7.5-10 % of X_{Ref} is generally used [16, 17].

For the European monitoring of pesticide residues in foodstuffs, σ is 25 % of the reference value X_{Ref} [13].

5.2.2 Measurement reproducibility

Whenever measurement reproducibility, s_R , or reproducibility limit, R (where $R=2.83s_R$) [11], is available in the standard procedure or in the report of an interlaboratory comparison for a particular method, which has been accepted as fit for its intended purpose, then s_R can be used in setting the target standard uncertainty for the specific quantity value. This experimental data can be converted to a target performance value if the estimated s_R is considered fit for the assessment of the agreement of results from various laboratories (e.g. through the calculation of the reproducibility limit). If s_R is obtained from a collaborative study where the agreement between measured quantity values is acceptable, s_R can be readily used in setting u_c^{tg} ($u_c^{\text{tg}} = s_R$). However, if s_R is estimated from results of laboratories for which it is concluded that serious lack of agreement of results is observed, this interlaboratory information will not be adequate to define u_c^{tg} .

The conditions under which the reproducibly study was carried out should be examined to determine if other uncertainty sources need to be considered to estimate u_c^{tg} . In some cases, reproducibility is estimated for the last stages of the measurement process and an assessment of the uncertainty of relevant pre-analytical and/or early analytical steps should be made.

For rational measurements¹, where bias attributed to the physical-chemical principles

¹ Rational measurements are measurements of measurands (rational measurands) defined independently of the measurement procedure used. In contrast, empirical or operationally defined measurements are measurements of measurands (empirical measurands) defined for a specific measurement procedure.

The determination of total gold in a sample of mining product is an example of a rational measurement since different procedures can be used to measure the same quantity. Different sample preparation procedures can be performed prior to the quantification stage.

of the procedure, δ , can be significant, if s_R is not estimated from an adequate diversity of measurement procedures², a target bias, δ^{tg} , should be considered in the calculation of u^{tg} . In this case, s_R and the bias, δ^{tg} , should be combined according to Eq.(9) [18]:

$$u^{tg} = \sqrt{s_R^2 + (\delta^{tg}/l)^2} \quad (9)$$

where l is $\sqrt{3}$ or $\sqrt{6}$ assuming δ^{tg} has a rectangular or triangular distribution and a confidence level of 100 %. This equation is not adequate to define target performance values if the observed dispersion of results from laboratories is considered too high for the usual purpose of the measurements.

In the food sector, the Horwitz equation [19] or the Horwitz modified equation [20] is used to define the target reproducibility, s_R^{tg} , for the analysis of minor or major, inorganic or organic components. Therefore, this relation can also be used to define the target uncertainty. However, since the Horwitz equation is a predictive model of the reproducibility, which takes into account the mass fraction of the analyte, the adequacy of the target uncertainty for the intended use of the measurements should be verified.

5.3 Cost/benefit studies

Fearn et al. [21] discussed the use of models of the variation of measurement cost with uncertainty, of the economic impact of wrong decisions from measurements, and of the probability distribution of the measured quantity in studied items, to select measurement conditions capable of minimising the overall cost of the performed control. However, this approach is difficult in cases where the economic impact of measurement is difficult to quantify or model.

On the other hand, the determination of aqua-regia extractable gold in a sample of mining product, using procedure A, estimates an empirical quantity that depends on the relative proportions of the analytical portion and the acid mixture, and the temperature conditions defined in procedure A. The procedure A defines the measured quantity.

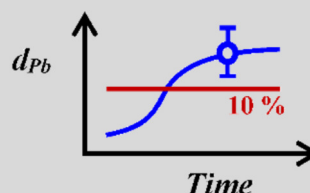
² According to the VIM [1], measurement reproducibility refers to the agreement of results from different laboratories that use the same or a different measurement procedure to determine the same measurand.

5.4 Magnitude of studied trends

Many important measurements are performed to measure a trend, to distinguish items with different origins, or where there is no or little information about the composition of an analysed item. The monitoring of the depletion of a contaminant in river water, the study of the distribution of a drug in different organs of test animals, and the determination of the composition of a meteorite, are just some examples. In these cases, the measurement quality should be adequate to detect meaningful trends or differences of items to be analysed. Measurement standard uncertainty should be, at least, 4 times smaller than trends or differences that need to be detected (see next paragraph for the deduction of this factor) (Example 3).

Example 3:

If a lead depletion (d_{pb}) in contaminated soil of more than 10 % needs to be detected, a measurement procedure should be developed to ensure the calculation of the depletion rate with a standard uncertainty not larger than 2.4 % (i.e. $2.4\% = 10\%/4.2$).



The multiple of 4 comes from the equation used to check the compatibility of measurement results at a confidence level of 99 % [1]. Usually, these assessments are performed at a confidence level of 99 % to ensure type I error probability (i.e. the probability of rejecting a true equivalence) is only 1%.

For two measurement results $[(x_A \pm k_A \cdot u_A)$ and $(x_B \pm k_B \cdot u_B)$, where x_i , k_i and u_i are the measured quantity value, the coverage factor and the standard uncertainty of measurement i ($i=A$ or B), the standard uncertainty, u_d , of the difference ($x_A - x_B$) is:

$$u_d = \sqrt{(u_A)^2 + (u_B)^2} \quad (10)$$

In order for the difference to be significant at a 99 % confidence level:

$$\rho_{AB} = |x_A - x_B| > t_d \sqrt{(u_A)^2 + (u_B)^2} \quad (11)$$

where ρ_{AB} is the range of values and t_d is the critical value of Student's t for a confidence level of 99 % and the degrees of freedom associated with u_d .

If x_A and x_B are estimated with a high number of degrees of freedom, k_d is approximately 3. Assuming that u_A and u_B are equal ($u_A = u_B = u$) since x_A and x_B are similar, the measurement results are not metrologically compatible, and therefore can represent different quantity values, if the following condition is valid:

$$\rho_{AB} > 3\sqrt{2}u \quad (12)$$

Therefore, the target standard uncertainty, u^{tg} , required to distinguish a minimum range, ρ^{min} , between x_A and x_B , is ($\rho^{\text{min}}/(3\sqrt{2})$); i.e. u should be, at least, ($3\sqrt{2}=4.2$) times smaller than ρ^{min} to distinguish this minimum range.

If u_d is expected to be associated with a low number of degrees of freedom, k_d must be adjusted accordingly.

If some systematic effects that affect the determination of x_A and x_B are known to be the same, those should not be included in the estimation of u_d . For instance, if the determination of lead content in a soil before and after a treatment is performed in the same laboratory and using the same calibration, some systematic effects affecting x_A and x_B individually will not affect ρ_{AB} . In that case, instead of combining estimated u_A and u_B , using Eq.(10), it is preferable to assess the function ρ_{AB} with all their shared and independent variables (Example 4). Numerical methods for combining uncertainty components, such as the Kragten and Monte Carlo methods [4] are particularly useful in these complex situations.

Example 4:

If the same calibration is used to measure spectrophotometrically the Chemical Oxygen Demand (COD) of a wastewater before and after a specific treatment, and both sample solutions are diluted to be measured in a similar concentration range, the bias associated with calibration cancels in the estimated trend of the COD value.

5.5 Information from a different scope

Many analytical measurements are performed where target values of measurement performance characteristics are not available, and proficiency tests or other comparisons are not regularly promoted. In these cases, target uncertainty can be defined by considering target values for performance characteristics of measurements for similar or related purposes.

The specification limits and target measurement uncertainties are defined considering the use of the measured quantity, ranging from the management of individual or public health needs to the management of financial interests. If similarity between uses is identified, the target uncertainty defined for one “analyte/matrix/measurement goal” combination can be used to define target uncertainty in other analytical problems. This extrapolation is easier the more similar or closely related the analytical problems are.

When a clear difference in the demand of the control of two quantities is observed, this can be used to justify a defined proportion between the respective target measurement uncertainties (Example 5 and 6).

Example 5:

The target uncertainty associated with the quantification of gold in pure gold alloys, should be smaller than that defined for the analysis of gold in mining products.

Example 6:

The target uncertainty of measurements of lead in drinking water, should be smaller than that associated with measurements of lead in wastewaters.

This extrapolation is less obvious if different parameters are studied but it is also possible (Example 7).

Example 7:

The target uncertainty of measurements of contaminants in air aerosols, such as total lead, should be smaller than that for the measurement of sulphate in the water soluble fraction of aerosols used to identify its anthropogenic or natural origin [22].

Target uncertainty can also be transferred within the same analytical sector. Usually these values vary from major to minor components. In some cases, target measurement uncertainties for organic parameters are larger than for inorganic parameters due to analytical limitations.

Any use of the target uncertainty from another analytical field should be clearly justified. Consecutive extrapolation of the target uncertainty between various analytical problems should be avoided since it tends to become less likely to be harmonised.

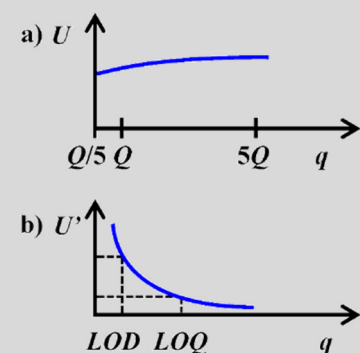
In some cases the definition of the target uncertainty should balance the need to ensure acceptance, by an individual or the community, and the achievability of the target uncertainty considering the state-of-the-art of measurement procedures. Those without an analytical or metrological background in the particular field of measurement, tend to request unrealistically low uncertainty. In these cases, the analyst should elucidate why the proposed target uncertainty is adequate.

6 Variation of target uncertainty with the quantity value

If the target uncertainty is, or can be, defined only for some quantity values and the measurement performance must be checked over an interval of quantity values, the expected variation of the uncertainty with the quantity can be used, together with the value of u^{tg} defined for some specific quantities, to define u^{tg} for the whole interval.

The uncertainty, U , tends to slightly increase with the quantity, being approximately constant over narrow quantity intervals. For simplicity, in many cases, it can be assumed that uncertainty is constant between five times less ($Q/5$) and five times more ($5Q$) than a quantity value Q (i.e. from $Q/5$ to $5Q$) (Figure 2a).

Figure 2: Expected trends of the variation of absolute (U) or relative (U') uncertainty with quantity value (q). The Q is the quantity value for which target uncertainty is defined.

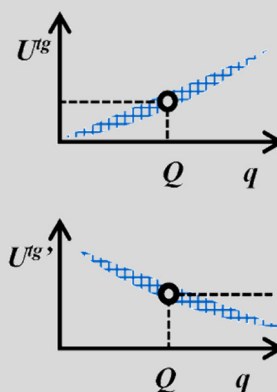



The relative uncertainty, U' , decreases as the quantity value increases, this reduction being pronounced from LOD to about $2LOQ$. Above $2LOQ$, the relative uncertainty tends to be approximately constant (Figure 2b).

These frequent trends [22-23] suggest that a target relative uncertainty set at a quantity value is feasible above that level, and a target uncertainty is applicable down to five times below this level (Example 8). In many cases, the target uncertainty can even be applicable further below since uncertainty tends to decrease with quantity reduction.

Example 8:

If target uncertainty is defined for the quantity value Q , the same target uncertainty can be used below Q , and the respective target relative uncertainty can be used above Q :



where  represents the expected trend of U or U' with the quantity value.

Since the target uncertainty is particularly important at the specification limit, any extrapolation to this critical value should involve a consideration of the adequacy of the target uncertainty.

7 Comparison of the estimated uncertainty with the target uncertainty

In principle, the uncertainty should be smaller than the target value, but if the target uncertainty is not defined in a regulation or specification, an additional tolerance of 20-30 % can be considered to allow for the variability of the uncertainty estimation process. The GUM [3] discusses that analysts should be aware of the variability of the uncertainty estimation process, illustrating it with the variability of the estimation of the

standard deviation of a population from a small number of results (paragraph E.4.3 in [3]).

The tolerance of 20-30 % is defined considering the usual degrees of freedom of standard uncertainties of measurements in chemistry and models of their variability.

8 Measurement uncertainty optimization

Measurement uncertainty must be reduced when the comparison with the target uncertainty proves that the measurement is not fit for the intended use. Measurement uncertainty can be reduced if relevant uncertainty components can be minimized. The so called bottom-up approach [12] for the evaluation of the uncertainty produces models most suitable for this optimization, where direct links between improvements on the

analytical steps or effects and global uncertainty reduction can be established. Whenever this information is not available and/or changes in measurement procedure or the reference materials used do not reduce the uncertainty to an adequate level, if the precision component is significant the analyst can reduce the uncertainty by reporting the mean of replicate measurements of samples.

9 Using the target uncertainty to guide validation

The defined target uncertainty can be used to guide the validation of the measurement procedure by suggesting target values for the various performance characteristics, determined prior to uncertainty evaluation, such as repeatability, intermediate precision, limit of quantification or mean recovery. The algorithms used to convert these performance data into an uncertainty component should be used in this assessment (Table 1).

Usually, the in-house validation or verification of a procedure involves the assessment of repeatability, intermediate precision, trueness, linearity, limit of quantification and uncertainty.

The repeatability standard deviation should not be larger than 1/5 to 1/3 of the target standard uncertainty to allow for the expected contribution of the other uncertainty components.

The intermediate precision standard deviation, a major uncertainty component in most measurements in chemistry, should not be larger than 1/3 to half [24] the target standard uncertainty.

The target uncertainty can guide the definition of the target limit of quantification if this limit is estimated under intermediate precision conditions. Since the coefficient of variation in the LOQ is 10 % [25], the quantity value where this precision is expected should correspond to the LOQ. Assuming that the squared intermediate precision constitutes half the squared standard uncertainty, the expected relative standard uncertainty in the LOQ is 14 % ($0.14 = \sqrt{(0.1)^2 + (0.1)^2}$). Accordingly, the predictive models of the uncertainty close to the LOQ can be used to define the target value for the limit (Example 9).

Trueness tests involve the determination of measurement error (i.e. measured quantity value minus a reference quantity value). Unlike trueness, error is a quantitative property. The error observed during measurement linearity evaluation or during the analysis of a reference material should be not larger than half the target standard uncertainty. The criteria for the observed errors seem to be less strict than for precision but reflect how this component contributes to the uncertainty (Table 1).

Example 9:

For the determination of the chemical oxygen demand of wastewaters to check compliance with Directive 91/271/EEC, a target relative standard uncertainty of 10 % is defined [23] for the limit of 125 mg L⁻¹ [26]. Therefore, at 125 mg L⁻¹ the target standard uncertainty is 12.5 mg L⁻¹. Since uncertainty should be approximately constant between 25 mg L⁻¹ and 625 mg L⁻¹ (i.e. five times less and more than 125 mg L⁻¹), the u' is 14 % at 89 mg L⁻¹ ($0.14 = 12.5/89$). Hence the maximum value for the limit of quantification would be 89 mg L⁻¹.

The present criterion for the various performance characteristics should be only indicative since the smaller magnitude of an effect can allow a more flexible assessment of the other ones.

10 Examples

The following sections present examples of the definition of the target measurement uncertainty in scenarios previously described.

10.1 Defined compliance interval

In the European Union, the quality of bathing water in running or still, fresh water or seawater, is regulated by Directive 76/160/EEC [27] which is the basis of national monitoring programmes. This legislation establishes limits for microbiological and physical-chemical parameters, and some pollutants. The pH of bathing water should be between 6-9 but provisions exist for exceeding these limits under certain conditions. Therefore, the determination of the pH in bathing water should be capable to distinguish pH values within this interval. According to the methodology proposed in section 5.1.2, the expanded uncertainty should be smaller than or equal to $[(9-6)/8]=0.38$ pH units (i.e. $U^{tg}=0.38$). This performance is easily achievable by potentiometric determinations with a combined glass electrode.

10.2 Defined measurement performance characteristics

In the European Union, the monitoring of the quality of drinking water must be supported by measurements performed by procedures fulfilling requirements presented in Council Directive 98/83/EC [9]. This directive sets maximum values for the “Limit of detection”, “Trueness” and “Precision” defined differently from the latest edition of the VIM [1]. These defined maximum values for the performance characteristics are multiples of the “parametric value”, that is, the regulatory limit for the measurand of interest.

In Directive 98/83/EC, “trueness” is defined as the difference between the mean value estimated from a large number of repeated measurements and the conventional true value and since this is not known it requires some interpretation. The precision φ is “twice the relative standard deviation” of measurements performed “within and between batch”. Using VIM terminology [1], “trueness” is related to

error τ (i.e. measured quantity value minus a reference quantity value) and “precision” as defined in the Directive is twice the repeatability or intermediate precision standard deviation.

For Cd in drinking water, the parametric value (that is, the upper limit) is $5 \mu\text{g L}^{-1}$, and τ and φ are $0.5 \mu\text{g L}^{-1}$ ($\tau = \varphi = 10\% \cdot 5 \mu\text{g L}^{-1}$).

According to Eq.(5):

$$\begin{aligned} u_c^{tg} &= \sqrt{(u_{ra}^{tg})^2 + (u_{sy}^{tg})^2} = \\ &= \sqrt{\left(\frac{\tau}{\sqrt{6}}\right)^2 + \left(\frac{\varphi}{2}\right)^2} = \quad (13) \\ &= 0.32 \mu\text{g L}^{-1} \end{aligned}$$

If, for example, the standard uncertainty of the measurement, u , is $0.39 \mu\text{g L}^{-1}$, the measurement does not meet this requirement, which is in addition to the mandatory performance requirement set by the Directive. In fact, if u is larger than u_c^{tg} , at least one of the performance requirements of the legislation has not been achieved. However, if the quantitative Cd results are taken as the mean of two duplicates performed by two analysts, the $u_{(mean)}$ becomes smaller than u_c^{tg} ($u_{(mean)} = 0.31 \mu\text{g L}^{-1}$) (see section 8). The reporting of duplicate measurement results from two analysts makes the precision of the final result adequate in relation to the performance criterion specified in the Directive. In this case it can be decided that non-compliance of cadmium content in drinking water, according to Directive 98/83/EC, is based on the mean of duplicate measurements performed by two analysts.

10.3 Defined decision risk

Good manufacturing practices of gold/silver/copper alloys, to be used in gold artefacts, are known to produce gold contents with deviation from the target composition of not larger than 5‰ [28] due to the uncertainty of known purity and weighing of pure metals. Therefore, deviations in gold

content of these alloys larger than 5 ‰ are only expected if poor manufacturing practice is followed or in fraud situations. Artefacts can be marked for 19.2 karat (e.g. 800 ‰ gold) if the gold content is proved to be above this limit, compliance assessment being performed without allowance for the uncertainty. Only if the measured gold content is above 800 ‰, is the product compliant for 19.2 karat. To make sure there is a chance of at least 99 % of deciding a product with a gold content at least 5 ‰ above 800 ‰ (i.e. 805 ‰) is compliant, the determination should be performed with a standard uncertainty not larger than 2.1 ‰ [$u^g=5 \text{ ‰}/t_f=5 \text{ ‰}/2.33=2.1 \text{ ‰}$] (section 5.1.4), where $t_f=2.33$ is the one-tailed critical value of Student's t for a high number of degrees of freedom and a confidence level of 99 %.

10.4 Proficiency tests

The adulteration of vegetable oil with mineral oil has been detected in products commercialised in Europe. This situation triggered the setting up of a proficiency test for the determination of mineral oil content in sunflower oil [29], by the Institute for Reference Materials and Measurements (IRMM) of the European Commission, in order to assess the quality of measurements performed in Europe. The provider of this proficiency test evaluated laboratory proficiency through the calculation of a z-score determined using the median of participants' results and an assigned standard deviation of 25 % of the median. This reference standard deviation was defined in an international workshop and, therefore, is expected to reflect the position of a representative number of experts.

For these measurements, the target relative standard uncertainty, u'^g , is 25 %.

10.5 Measurement reproducibility

The use of pentachlorophenol (PCP) for the preservation of leather was banned or restricted in several European countries due to its high toxicity and persistence. The ISO 17070 standard [30] describes a procedure for the measurement of PCP in leather. This standard gives values for the reproducibility in various mass fractions, estimated from a collaborative test. For example, at 5 mg kg⁻¹,

the stated reproducibility standard deviation is 0.6 mg kg⁻¹. Therefore, for measurement results in the range 1 to 25 mg kg⁻¹, the target standard uncertainty can be taken as 0.6 mg kg⁻¹.

10.6 Magnitude of studied trends

The optimisation of a wastewater treatment scheme, by changing conditions in a pilot plant, is controlled by the percentage reduction of the chemical oxygen demand (COD) with the treatment. If COD reductions of 5 % are considered relevant, the determination of the COD reduction should be carried out with a standard uncertainty not larger than 1.2 % (i.e. 1.2 ‰=5 ‰/4.2) (see section 5.4). The uncertainty of COD reduction determinations, to be considered in comparing different treatment schemes, should only take into account the uncertainty components responsible for deviations of compared COD reductions. For instance, if portions of the same wastewater are treated in competing treatment schemes, the uncertainty of the determination of the input COD value should be excluded from these calculations. Similarly, if the same reference is used in both COD determinations, the uncertainty associated with this reference will not affect the ratio.

10.7 Information from a different scope

EU Directive 2008/50/EC [7] on ambient air quality defines maximum limits for several contaminants in air, and target uncertainties for their measurements. Air quality measurements are divided into "fixed" and "indicative", where the quality requirements for indicative measurements are less strict than for fixed ones.

This directive suggests complementing the quantification of contaminants with the determination of the anthropogenic or natural origin of aerosols. The mass fractions of some ions in the water soluble portion of the aerosols are key parameters to identifying their origin. However, no specification limits or target measurement uncertainties are defined for these parameters in the Directive.

Since the mass fraction of a specific ion in the water soluble portion of aerosol is not being compared with any specification limits, quality requirements for indicative measurements of contaminants would seem to be an adequate reference for measurements of these low toxicity agents.

The indicative measurements of the various parameters have a target relative expanded uncertainty ranging between 25-50 %. Therefore, a target relative expanded uncertainty of 40 % seems to be adequate to determine the mass fraction of the water soluble chloride, nitrate and sulphate in aerosols [22].

If the variability of the uncertainty estimation process is considered, it can be decided that u' can be smaller than 48 % ($u'^{\max}=1.2\cdot 40=48\%$).

10.8 Variation of target uncertainty with the quantity value

The identification and quantification of pentachlorophenol (PCP) in leather can be performed by following the ISO 17070 standard [30]. In this document, the repeatability and reproducibility, estimated in a collaborative study, are reported for three PCP mass fractions. Table 2 presents the reproducibility observed at these mass fractions³.

Measurements described in Table 2 are considered fit for the intended use, and the respective performance data adequate to define the target uncertainty as described in section 5.2.2.

Table 2: Standard deviation, s_R , and relative standard deviation, s'_R , of the reproducibility of measurements of PCP mass fraction, w_{PCP} , in leather following the ISO 17070 standard [30].

w_{PCP} (mg kg ⁻¹)	s_R (mg kg ⁻¹)	s'_R (%)
5.0	0.6	12.0
6.7	0.8	11.9
16.8	2.1	12.5

Since the relative uncertainty tends to decrease with the quantity value and the uncertainty tends to be constant over a short quantity interval, the following model of the variation of the target uncertainty can be used (Table 3).

³ Example 10.5 discusses the use of reproducibility data observed at one level to define the target uncertainty.

Table 3: Model of the variation of the target standard uncertainty, u^{tg} , or relative target standard uncertainty, u^{tg} , with the mass fraction of PCP, w_{PCP} .

w_{PCP} (mg kg ⁻¹)	u^{tg} (mg kg ⁻¹)	u^{tg} (%)
1 – 5.0	0.6	-
5.0 – 16.8	-	12.5§
16.8 – (...)	-	12.5

§ - Maximum value of s'_R (Table 2).

Since the estimation of the uncertainty is variable, the maximum permissible estimated standard uncertainty, u^{max} , is 1.2 times larger than the target uncertainty, u^{tg} . Table 4 presents the u^{max} in a wide mass fraction interval.

Table 4: Model of the variation of the maximum permissible estimated standard uncertainty, u^{max} , or relative standard uncertainty, u^{max} , with the mass fraction of PCP, w_{PCP} .

w_{PCP} (mg kg ⁻¹)	u^{max} (mg kg ⁻¹)	u^{max} (%)
1 – 5.0	0.72	-
5.0 – 16.8	-	15
16.8 – (...)	-	15

The target uncertainty estimated using the reproducibility standard deviation at three mass fractions is more accurate than the target value estimated using information at one level (see section 10.5).

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