**APPENDIX I**

**DRAFT INFORMATION DOCUMENT**

**PROCEDURES FOR THE ESTIMATION OF MEASUREMENT UNCERTAINTY**

(For comment through CL 2023/14/OCS-MAS)

## 1 Introduction

A measurement result should always be accompanied by information regarding its uncertainty. Such information provides an indication of the quality of the measurement result and allows meaningful comparison to other measurement results or reference values. Without a statement of measurement uncertainty, a measurement result is essentially incomplete and cannot be properly interpreted.

This document provides guidance regarding those sources of uncertainty which originate in the laboratory itself, i.e. in connection with the procedures and conditions starting with the laboratory sample and ending with the measurement result. In particular: the question of sampling uncertainty and the extent to which laboratory samples are representative of the content in the container will not be addressed. Such questions are addressed in CXG 50-2004 [13].

Measurement uncertainty is defined as a parameter "…that characterizes the dispersion of the values that could reasonably be attributed to the measurand", see 2.2.3 in GUM [1]. This document aims to clarify what is meant in this definition and to provide the information which is necessary to understand how different approaches for the evaluation of measurement uncertainty relate to one another. This should allow the reader to make informed decisions regarding the best procedure to adopt in any given case.

Accordingly, the present document provides background information and clarifies basic notions which are central to a correct evaluation and interpretation of measurement uncertainty. First, the top-down and bottom-up approaches are described and compared. Then, the basic model for the top-down approach is presented. This constitutes a convenient framework within which to elucidate some of the basic conceptual aspects of measurement uncertainty. In the course of the discussion, the term *measurand* will be explained and the relationship between the top-down and bottom-up approaches will be further clarified on the basis of a more general classification of uncertainty sources. The question of the statistical uncertainty in estimating dispersion parameters – such as standard deviation values – will be addressed; and the effect of the number of observations on this statistical uncertainty will be examined. Specific designs for the evaluation of the different components of the top-down approach will then be provided, including designs for the evaluation of subsampling and matrix effects. Finally, examples will illustrate how measurement uncertainty influences sampling plans.

## 2 Top-down versus bottom-up approaches

The term "bottom-up approach" is used to denote any approach in which the measurement uncertainty is calculated on the basis of an equation expressing the relationship between input variables and the measurement result. In the phrasing from Section 4.1.1 of the *Guide to the expression of uncertainty in measurement* (GUM) [1]: In most cases, a measurand $Y$ is not measured directly, but is determined from $N$ other quantities $X_1, X_2, \dots, X_N$ through a functional relationship (model) $f$:

$$Y = f(X_1, X_2, \dots, X_N)$$

It must be emphasized that, in this approach, the measurement result $Y$ is *calculated* from the input variables $X_1, X_2, \dots, X_N$. Analyte concentration is an example of a measurement result; optical density, peak area and signal height are examples of input variables.

An alternative approach – described e.g. in EURACHEM/CITAC Guide CG4 [2] and in ISO 21748 [4] – consists in making use of available *method validation* data. In the words of Section 7.6.1 in the EURACHEM Guide [2]: "A collaborative study carried out to validate a published method […] is a valuable source of data to support an uncertainty estimate." In this approach, there is no "functional relationship" between input variables and the measurement result. Rather, results are obtained under different measurement conditions, and total observed variation is partitioned into individual components. This approach is often referred to as the *top-down* approach.

In order to obtain measures of precision which can subsequently be used to "support an uncertainty estimate" following the top-down approach, two main types of experiments can be conducted: single-lab (in-house) and multi-lab (collaborative) studies. It must be emphasized that precision measures obtained in these two types of studies are not always comparable. Nonetheless, if relevant uncertainty sources have not been taken into account, it is often expedient to complement the information from a multi-lab study by subsequent single-lab experiments.

The main distinction between the two approaches is that whereas the bottom-up approach starts from a physico-chemical consideration of the actual measurement mechanism, the top-down approach starts from a data set in which the variation between different measurement results is directly observable. In this sense, it can be said that the bottom-up approach is *theoretical* whereas the top-down approach is *empirical*.

A related distinction is that, in the bottom-up approach, the starting point is the relationship between the measurement result and input variables, whereas, in the top-down approach, the starting point is the relationship between total variation and individual components of variation.

Finally, another distinction between both approaches is that while the number of components in the top-down approach is usually low[4], the number of input variables in the bottom-up approach can be quite high. For this reason, in the bottom-up approach, it will often be impractical to conduct an experiment in which estimates for the uncertainties associated with all the input variables can be reliably obtained. Indeed, the bottom-up approach explicitly allows the inclusion of *prior information* regarding the size of the errors which can be expected to arise in connection with each source (Type B evaluation).

In the case of the bottom-up approach, there are two options for the calculation of the combined (i.e. total) measurement uncertainty. The first option consists in performing a linear approximation. This option is often referred to as the law of propagation of uncertainty. In the case that there are no correlations between the different input variables, the combined measurement uncertainty – expressed as a standard deviation – is obtained as follows:

$$u_c = \sqrt{\sum_{i=1}^{N} c_i \cdot u_i^2}$$

where $u_c$ denotes the combined uncertainty, $u_i$ denotes the uncertainty associated with input variable $i$ and $c_i$ denotes the corresponding sensitivity coefficient, usually obtained via partial differentiation $\left(c_i = \left(\frac{\partial f}{\partial X_i}\right)^2\right)$, see 5.1.2 and 5.1.3 in GUM [1].

The second option consists in applying a Monte Carlo method (MCM). This can briefly described as “repeated sampling from the PDFs of the $X_i$ and the evaluation of the model in each case,” see 5.9.1 in [3]. This option is also referred to as the propagation of distributions. In practice, the implementation of this option requires software, since the number of simulation runs (i.e. the number of times each input variable is sampled) is typically on the order of $10^6$. If the model $f$ is highly nonlinear, the MCM is recommended. For instance, in the case of standard addition, the model is

$$Y = \frac{a}{b}.$$

In this model, $b$ denotes the slope parameter, calculated as

$$b = \frac{\sum_{i=1}^{n}(x_i - \bar{x}) \cdot (y_i - \bar{y})}{\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

where the $x_i$ denote the added standard concentrations (with mean value $\bar{x}$) and the $y_i$ denote the corresponding response values (with mean value $\bar{y}$); and $a$ denotes the intercept, calculated as

$$a = \bar{y} - b \cdot \bar{x}.$$

The uncertainty values of the individual $x_i$ variables are taken from the certificates of the reference standard substances of materials, while the uncertainty values for the $y_i$ variables are obtained from the regression analysis (residual standard deviation).

For such a model, the results obtained via linear approximation and via MCM can differ considerably. The MCM calculation will also show whether the distribution of the measurand is asymmetric. For instance, in the case of standard addition, the distribution for the measurand $\mathrm{Y} = \frac{\mathrm{a}}{\mathrm{b}}$ is typically right-skewed:

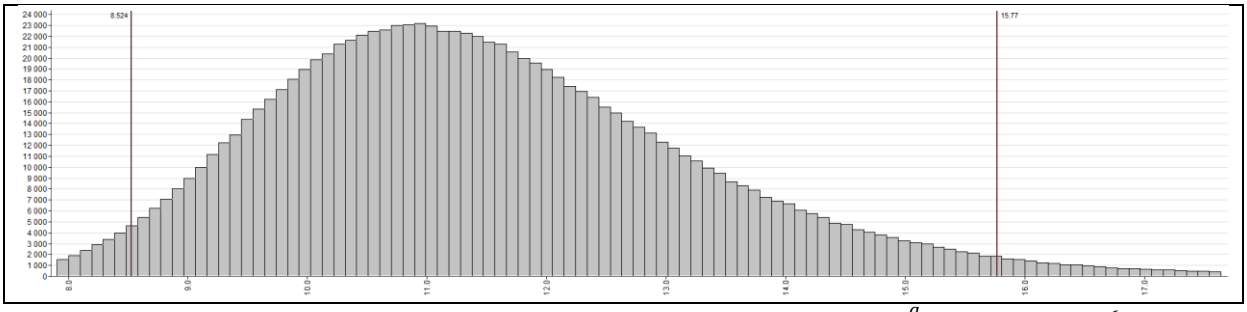


Figure 1: Right-sk*ewed distribution for the* standard addition measurand $Y = \frac{a}{b}$ obtained via $10^6$ MCM simulation runs.

In the case of the top-down approach, the total measurement uncertainty is obtained by summing different variance components, such as between-laboratory variance and repeatability variance. The number of replicate measurements should be taken into consideration. For instance, in the simplest case, the total standard uncertainty is obtained as

[4] The number of components follows directly from the experimental design of the method validation study.

$$u = \sqrt{s_L^2 + \frac{s_r^2}{n_r}}$$

where $s_L$ denotes the between-laboratory standard deviation, $s_r$ denotes the repeatability standard deviation and $n_r$ denotes the number of replicates whose mean value is taken as the final measurement result. For further information, the reader is referred to ISO 21748 [4].

## 3 Basic model for the top-down approach

In this section, the basic model for the top-down approach is discussed. The model is premised on the assumption that data from an interlaboratory validation study (also known as a collaborative study) are available. Such a study is conducted in order to characterize the performance of an analytical method. In particular, the characterization of the *precision*[5] of an analytical method can be used "to support an uncertainty estimate". The reader is referred to the ISO 5725 series – in particular to Part 2 [5] – for background information.

The basic model is as follows:

$$\text{Measurement value } Y = \textit{true value} + \textit{method bias}\ (\textit{average across labs and matrices}) + \textit{matrix-specific bias} + \textit{laboratory bias} + \textit{repeatability error}$$

For further details, the reader is referred to [6] and [7].

In the following, the individual terms of the basic model are discussed.

*True value*

In general, the true value is not known. It can be estimated by averaging e.g. across methods, samples and laboratories. However, it is crucial to note that in the GUM [1], measurement uncertainty is defined *without any reference to a true value*; rather, it is defined as a parameter "… that characterizes the dispersion of the values which could reasonably be attributed to the measurand", see 2.2.3 in GUM [1]. This definition has since been adopted in all other relevant standards and guidance documents (EURACHEM [2], VIM [8]). This does not mean that the true value no longer plays a role in the evaluation of measurement uncertainty. However, it is not the (unavailable) difference between true value and measurement result, but *the uncertainty of bias correction* which must be taken into account in the evaluation of measurement uncertainty. In other words, the focus shifts from the (unavailable) true value itself to the uncertainty in the estimation of the bias. Note that if a certified reference value is available along with a reference uncertainty value, the latter can be included in the uncertainty of bias correction.

*Method bias (average across labs and matrices)*

The method bias across both labs and matrices can be estimated by averaging across laboratories and matrices. As explained in the discussion of the true value, the corresponding contribution to the calculation of measurement uncertainty will consist in the uncertainty in the estimate of this bias.

*Matrix-specific bias (matrix mismatch)*

In many cases, a method's bias depends on the matrix being examined. In other words: bias varies from one matrix to another. Such effects occur when the extraction of analyte is affected by the matrix, so that a part of the analyte is not recovered; or when a part of the matrix is extracted along with the analyte and interacts with the measurement's physico-chemical mechanism, resulting in a bias. The corresponding component of total variability is referred to as the matrix mismatch component. It is important to note that all the uncertainty sources listed in Section 7 contribute to this term of the basic model. See Uhlig (2023) [24] for further information.

*Laboratory bias*

In many cases, a method's bias depends on the laboratory which is performing the measurement. In other words, the bias varies from laboratory to laboratory. The corresponding component of total variability is called the laboratory standard deviation.

*Repeatability error*

This term represents variation across replicate measurements (i.e. independent measurements performed under near-identical test conditions).

**Note regarding the case that the precision depends on the concentration level:**

[5] Precision is defined (paraphrasing 2.15 in [8]) as the degree of agreement between independent measurement results obtained under specified conditions. For instance, reproducibility precision characterizes the agreement between results from different laboratories, while repeatability precision characterizes the agreement between results obtained under near-identical conditions in the same laboratory. Precision can be used to derive a measurement uncertainty estimate – but it must not be confused with measurement uncertainty.

When there is a known relationship between precision (e.g. in-house reproducibility) and concentration, it is possible to apply an approach based on a clear distinction between, on the one hand, random variation between test results at a given concentration level, and, on the other, the range of values which can "reasonably be attributed to the measurand," i.e. the measurement uncertainty. This approach is described in Uhlig (2023) [25] and gives rise quite naturally to asymmetrical measurement uncertainty intervals in cases of relatively high precision (say, greater than 10 %) and heteroscedasticity (e.g. constant *relative* in-house reproducibility). This approach is also described in Annex E of ISO TS 23471 [20].

## 4 Specifying the measurand

The concept "measurand" clearly plays a central role in the definition of measurement uncertainty and will shed further light on the connection between validation data and measurement uncertainty.

Leaving aside the technicalities of the definition of a measurand[6], it is sufficient to note that the specification of a measurand has three separate components:

- specification of a property, e.g. *mean arsenic concentration.* Note that the concept "analyte" corresponds to this part of the specification of the measurand
- specification of a phenomenon, body or substance which the property is associated with, e.g. *a given batch of apple juice*. Note that the concept "matrix", used in the previous section, corresponds to this part of the specification of the measurand
- and specification of a reference framework regarding the manner in which the property is characterized, e.g. [ng/ml]

Loosely phrased, specifying a measurand thus involves stating (1) *what* is to be measured, (2) what is it to be measured *in*, and (3) *how* should the measurement result be expressed in order to ensure comparability to other measurement results or relevant values?

In particular, the specification of the measurand should include information as to whether analyte concentration is to be measured in a laboratory sample or in a "larger sample" or a batch of products in a container. Only in the latter case is *sampling* uncertainty relevant (see Section 7 for an overview of the different sources of uncertainty). Similarly, if measurement results from several laboratory samples are used to assess the conformity of bulk material from a container, it is the measurement uncertainty of the mean value across the results corresponding to the individual laboratory samples which is relevant.

More generally, while measurement uncertainty is always determined on the basis of the laboratory sample, it is nevertheless important to include all available information about the laboratory sample in the evaluation of measurement uncertainty, e.g.

- Where does the material come from (e.g. container)?
- Have other samples from the same origin been tested?
- What is the intended use of the measurement result (e.g. conformity assessment for the individual laboratory sample or for the container)?

For example, determining the contribution to uncertainty which arises from the material's heterogeneity (e.g. fundamental variability, see Section 9.4) may require a considerable amount of work, depending on the analyte, concentration and grain/particle size. If the origin of the material is known, it may be possible to use previously obtained results regarding the heterogeneity contribution to uncertainty instead of obtaining a new estimate from scratch.

The specification of the measurand should also make it possible to determine whether bias/recovery correction is required, and what form this correction should take. For example, if the measurand is specified in terms of the amount of analyte recovered, then recovery correction may not be appropriate. On the other hand, if the measurand is specified in terms of the total amount of analyte present in a test sample, then recovery correction may be necessary.

Finally, it may be impractical or impossible to provide an exhaustive specification of the measurand. For this reason, it may be necessary to include an extra component of measurement uncertainty, called "definitional uncertainty" (see definition 2.27 in VIM [8]), in order to account for any ambiguity ("finite amount of detail") in the specification of the measurand. However, in most cases, the definitional uncertainty can be considered negligible.

[6] In the VIM [8], measurand is defined (definition 2.3) as "quantity intended to be measured". Quantity, in turn, is defined (definition 1.1) as "property of a phenomenon, body, substance, where the property has a magnitude that can be expressed as a number and a reference". An example given directly under this definition is "amount-of-substance concentration of ethanol in wine sample $i$". The term "reference" in this definition is explained in NOTE 2 as: "A reference can be a measurement unit, a measurement procedure, a reference material, or a combination of such."

## 5 Relation between measurand and validation data

If the results of a validation study are to be used to determine measurement uncertainty, it must be ensured that the study refers to the same measurand.

Example 1: Measurement uncertainty is being evaluated in a given laboratory for a measurand specified in terms of analyte concentration in test samples. The analytical method used has been validated for the same analyte, but on the basis of extracts rather than test samples. In other words, the measurand for the validation study is analyte concentration in extracts. It follows that the measurand for which measurement uncertainty must be evaluated is different from the measurand from the validation study. Accordingly, the measurement uncertainty cannot be evaluated on the basis of the characterization of the dispersion of measurement results from the validation study.

Example 2: Measurement uncertainty is being evaluated in a given laboratory for a measurand which is specified in terms of a range of matrices. The analytical method used has been validated for the same analyte, but for only one of the matrices. It follows that the measurand for which measurement uncertainty must be evaluated is different from the measurand from the validation study. Accordingly, the measurement uncertainty cannot be evaluated on the basis of the characterization of the dispersion of measurement results from the validation study (the matrix bias term is missing).

The conditions under which validation data can be used to support a measurement uncertainty estimate can be stated as follows:

| | |
|---|---|
| | **If…** |
| | the measurement result is obtained using a validated method |
| | **and the *measurand* is included in the scope of the validation** |
| | and precision within the laboratory which is evaluating measurement uncertainty is comparable to the method's precision as characterized in the validation study |
| | **then…** |
| → | the precision estimates from the validation study can be used in the calculation of measurement uncertainty. |

In order to check and provide evidence of competence in the application of the method and to ensure adequate precision in the laboratory which is evaluating measurement uncertainty, it may be necessary to perform a verification study.

The reader is referred to Section 7 in EURACHEM [2] for further guidance regarding using validation data in the evaluation of measurement uncertainty.

## 6 Empirical versus rational methods

In the definition of the measurand, the specification of the property must include sufficient information to allow an appropriate reference (see 1.1 in the VIM [8]) to be selected. In particular, it is important to distinguish between

- Empirical method (type I methods in the Codex system)
- Rational method (type II-IV methods in the Codex system)

In Section 5.4 of EURACHEM [2], the following explanation is provided: *"In analytical measurement, it is particularly important to distinguish between measurements intended to produce results which are independent of the method used, and those which are not so intended. The latter are often referred to as empirical methods or operationally defined methods."*

In Section 5.5 of the same document, it is explained that non-empirical methods are sometimes called rational methods. This distinction is closely related to that between *operationally defined* and *non-operationally defined* measurands found in Section 9.2.3 of ISO Guide 35 [9]. The reader is also referred to Section 3.1 in the EURACHEM Guide to Metrological Traceability in Chemical Measurement [21].

As far as the evaluation of measurement uncertainty is concerned, this distinction has the following important implication: for *empirical* methods (*operationally defined* measurands), there is no method bias term in the basic model for the top-down approach described in Section 3. (Please note that the bottom-up approach does not allow the distinction *method* versus *other* bias components).

## 7 Uncertainty sources in the top-down and bottom-up approaches

In the *top-down* approach, total variation observed in a data set is partitioned into different components. In the *bottom-up* approach, the total uncertainty is obtained from uncertainty values associated with individual input variables. The following question arises: what is the *relationship* between the components from a top-down model and the uncertainty sources included in a bottom-up model?

In order to answer this question, an overview of different types of uncertainty sources – *independently of the approach* – is now provided. The intention is to distinguish broad categories of uncertainty sources. Apart from shedding further light on the relationship between the top-down and bottom-up approaches, this overview may prove useful for determining which sources may be relevant in any given case, and whether all relevant sources have been included in the evaluation of measurement uncertainty.

Sources of uncertainty are conveniently classified under six main headings:

- Sampling (The question of sampling uncertainty is not addressed in the present document. The reader is referred to CXG 50-2004 [13])
- Storage/transportation
- Subsampling
- Measurement conditions
- Measurement procedure
- Computational effects

| Source of uncertainty | Role in measurement uncertainty |
|---|---|
| *Sampling* | If the measurand is defined in terms of e.g. analyte concentration in a container or in a batch of products, then sampling is required, and its contribution to measurement uncertainty must be assessed, see Section 7.6 in ISO 17025 [10].<br><br>If the measurand is defined in terms of a single test material (laboratory sample), then there is no contribution to uncertainty due to sampling. There may be a contribution from subsampling, however (i.e. obtaining test portions from the laboratory sample).<br><br>*Fundamental variability* is one of the “subcomponents” of sampling uncertainty, see the discussion in Section 9.4. |
| *Storage/transportation* | If different storage or shipping conditions have an effect on measurement results, then the corresponding contribution to the total uncertainty must be taken into account. |
| *Subsampling* | This term denotes taking test portions from the laboratory sample. If the latter is not homogeneous (finely ground in case of solid matter, mixed or agitated in case of liquids and semi-solids), then it cannot be ensured that the subsampling uncertainty is negligible. Accordingly, appropriate homogenisation is required before subsampling in order to reduce this uncertainty source.<br><br>*Fundamental variability* is one of the “subcomponents” of subsampling uncertainty, see the discussion in Section 9.4. |
| *Measurement conditions* | It must be emphasized that the term measurement as used here includes any sample preparation and clean-up procedures.<br><br>If different measurement conditions (e.g. different time of year, different technician, different reagents, different equipment) contribute to measurement uncertainty, this source must be taken into consideration. |
| *Measurement procedure* | This term denotes the intrinsic or irreducible uncertainty component associated with the physical/chemical/biochemical mechanisms involved in the measurement procedure (including sample preparation and clean-up procedures), e.g. extraction efficiency. The input variables in the bottom-up approach can be considered to belong under this heading. |
| *Computational effects* | Inaccurate calibration model and calculation methods, peak integration procedures and rounding will also contribute to measurement uncertainty. |

**Note regarding subsampling:**

In the top-down approach, any estimate of measurement uncertainty must take into consideration at least the following two components: laboratory bias and repeatability. For non-destructive methods, any sub-sampling variation contributes to the repeatability component. In order to reflect sub-sampling variation found in routine samples, “real" samples must be used in the validation study. If this is not practicable (e.g. because the samples differ too much from lab to lab), and homogenous test material is used, then the sub-sampling component of repeatability must be estimated in a separate experiment. The sub-sampling component must not be confused with the matrix bias (matrix-mismatch) component, which may vary considerably from lab to lab, thus inflating the between-laboratory component.

## 8 Requirements regarding data size

If a standard deviation is calculated on the basis of a series of measurement results, how well does it characterize the actual dispersion of the values? Indeed, if several measurement series are performed and a separate standard deviation value is calculated for each, these standard deviation values will differ. In other words, a given standard deviation, obtained on the basis of empirical data, only represents an *estimate* of the "true" standard deviation.[7]

The confidence interval for a standard deviation can be obtained by means of the following Excel formula: SQRT((N-1)/CHISQ.INV(p,N − 1)), where p is the probability value (e.g. 0.025 or 0.975) and N is the number of laboratories or the number of tests inside the single laboratory. This Excel formula corresponds to the following mathematical formulas for the lower and upper limits (LCL and UCL) of a 95 % confidence interval given a standard deviation estimate $s$: LCL = $\sqrt{\frac{\mathrm{N}-1}{\chi^2_{(\mathrm{N}-1,0.975)}}} \cdot s$ and UCL = $\sqrt{\frac{\mathrm{N}-1}{\chi^2_{(\mathrm{N}-1,0.025)}}} \cdot s$, where $\chi^2_{(\nu,\mathrm{p})}$ denotes the p-quantile of a chi-squared distribution with ν degrees of freedom.

It is recommended that standard deviations be computed on the basis of a minimum of $N = 12$ values (corresponding to $\nu = 11$ degrees of freedom for the estimation of the standard deviation), in which case $\chi^2_{(\mathrm{N}-1,0.975)} = \chi^2_{(11,0.975)} = 21.92$ and $\chi^2_{(\mathrm{N}-1,0.025)} = \chi^2_{(11,0.025)} = 3.82$, and the confidence interval for the standard deviation is $[0.71 \cdot s, 1.70 \cdot s]$.

As far as the simultaneous estimation of e.g. between-laboratory (or between-matrix) standard deviation and repeatability standard deviation is concerned, this recommendation means that measurement results from at least 12 laboratories (or matrices) should be available, each with at least two replicates per laboratory (or matrix).

It is required that data from at least 8 laboratories must be available (see Section 6.3.4 in ISO 5725-1 [18] where 8-15 laboratories is proposed as a "common" figure).

In the case that different uncertainty sources are *simultaneously* taken into consideration, say in the bottom-up approach, the requirement regarding data size can be applied via the Satterthwaite formula. More specifically: take the case that 2 different uncertainty sources are included in the calculation of the combined uncertainty, $u_1$ and $u_2$. Say that each was obtained by applying the formula for the sample standard deviation on the basis of $n_1$ and $n_2$ measurement results, respectively. The number of degrees of freedom for the combined uncertainty can then be computed as

$$\text{Degrees of freedom for combined uncertainty} = \frac{(u_1^2/n_1 + u_2^2/n_2)^2}{\frac{(u_1^2/n_1)^2}{n_1 - 1} + \frac{(u_2^2/n_2)^2}{n_2 - 1}}$$

The recommendation is to ensure a minimum of 11 degrees of freedom for the combined uncertainty.

In the case that prior information is used for an individual $u_i$ value (Type B variable) and that no information regarding data size is available, it is suggested to use $n_i = 7$; the uncertainty which corresponds to this data size is intended to reflect the fact that, in the case of Type B variables, distributional assumptions are often based on "educated guesses."

Example of the application of the Satterthwaite formula

Take the case that measurement uncertainty must be evaluated on the basis of the following functional relationship, where the measurement result $Y$ is expressed as a function of 4 input variables:

$$Y = f(X_1, X_2, X_3, X_4) = X_1 + X_2 + X_3 + X_4$$

**Table 1: Data size and uncertainty values for the input variables**

| Input variable | Type | $n$ | $u^2$ |
|---|---|---|---|
| $X_1$ | A | 3 | 4 |
| $X_2$ | B | 30 | 15 |
| $X_3$ | B | 30 | 15 |
| $X_4$ | B | Not available<br>Take $n_4 = 7$ | 5 |

[7] Table 3 in CXG 59 [11] provides expected ranges for standard deviation estimates calculated from empirical data for different values of $N$ (number of observations). Please note that expected ranges must not be confused with the confidence intervals.

The Satterthwaite formula can now be applied.

$$\text{Degrees of freedom for combined uncertainty} = \frac{(u_1^2/n_1 + u_2^2/n_2 + u_3^2/n_3 + u_4^2/n_4)^2}{\frac{(u_1^2/n_1)^2}{n_1 - 1} + \frac{(u_2^2/n_2)^2}{n_2 - 1} + \frac{(u_3^2/n_3)^2}{n_3 - 1} + \frac{(u_4^2/n_4)^2}{n_4 - 1}} = 9.4$$

## 9 Simple procedures for evaluating uncertainty components

If validation data are incomplete (i.e. some of the relevant sources of uncertainty have not been characterized), further experiments must be conducted before the top-down approach can be applied.

For instance, in a collaborative study, each participating laboratory should ideally receive samples representing different matrices and different analyte concentrations. However, due to restrictions in material availability, collaborative studies are often conducted on the basis of a single sample per participant. In such a case, almost no conclusions can be drawn regarding the impact of matrix effects. Accordingly, the characterization of the matrix-specific bias term from the basic model must often be performed in a separate experiment.

In the following, simple procedures are described for characterizing different components of variation – such as the matrix-specific bias.

More sophisticated procedures for simultaneously estimating several components of variation are provided in [12]. The reader is also referred to ISO TS 23471 [20], in which study designs are described for the evaluation of data obtained from several concentration levels in one laboratory; and to ISO 5725-3 [19], in which, mainly, alternative study designs are described for the evaluation of data from one concentration level in several laboratories.

### 9.1 PROCEDURE FOR CHARACTERIZING IN-HOUSE VARIATION

If the analytical method is an in-house method, then an in-house (single-lab) validation study is conducted. If validation data are incomplete or unavailable, in-house components of variation can be characterized on the basis of a further experiment (or QC data, as long as such data are available and have an appropriate structure).

Total in-house variation is called intermediate precision and should reflect all relevant uncertainty sources except matrix bias[8] – in particular, variation arising from different measurement conditions (i.e. operator, reagent batch, etc.) within the laboratory, along with repeatability.

The structure of the experimental or QC data must allow the distinction between in-house repeatability conditions and intermediate conditions (different day, different technician, different reagent batch, etc.). The uncertainty can then be calculated as follows:

$$u = \sqrt{s_I^2 - s_{r,inhouse}^2 + \frac{s_{r,inhouse}^2}{k}}$$

where $s_I$ denotes the intermediate standard deviation, $s_{r,inhouse}$ denotes the repeatability estimate and $k$ denotes the number of replicates whose mean value is taken as the final measurement result.

As explained in Section 0, it is recommended that, at a minimum, $N = 12$ different in-house measurement conditions (e.g. different days) be represented in the data set.

In the following example, we take the case that QC data are available for 20 different days. (If appropriate QC data are not available and a further experiment is required, $N = 12$ days are sufficient).

**Table 2: In-house QC data for the calculation of intermediate (in-house) and repeatability standard deviation values**

| | Result 1 | Result 2 |
|---|---|---|
| Day 1 | 10.72 | 12.29 |
| Day 2 | 4.56 | 0.90 |
| Day 3 | 8.79 | 9.75 |
| Day 4 | 10.08 | 6.51 |
| Day 5 | 12.29 | 11.32 |
| Day 6 | 7.95 | 6.79 |
| Day 7 | 13.06 | 14.54 |
| Day 8 | 11.23 | 12.09 |

[8] By definition, intermediate precision does not include matrix bias, see 2.22 in VIM [8]. If matrix bias is included, then the term in-house reproducibility is used.

| | | |
|---|---|---|
| Day 9 | 7.31 | 9.51 |
| Day 10 | 5.85 | 5.08 |
| Day 11 | 7.48 | 9.12 |
| Day 12 | 12.59 | 10.65 |
| Day 13 | 7.55 | 6.59 |
| Day 14 | 12.05 | 11.15 |
| Day 15 | 4.86 | 6.48 |
| Day 16 | 6.99 | 7.10 |
| Day 17 | 7.40 | 6.75 |
| Day 18 | 8.85 | 11.15 |
| Day 19 | 11.93 | 10.17 |
| Day 20 | 8.50 | 8.29 |

The between-day and repeatability standard deviation values are calculated as follows.

First we introduce the following notation: the days are indexed $i = 1, \ldots, m$ (in this example, $m = 20$); the replicates within each day are indexed $j = 1, n$ (in this example, $n = 2$); and the individual measurement results are denoted $x_{ij}$.

First, compute the overall mean value $\bar{x}$, and the day-specific mean values $\bar{x}_i$. Then compute the between-day sum of squares:

$$SSB = n \cdot \sum_{i=1}^{m} (\bar{x}_i - \bar{x})^2$$

and the within-day sum of squares:

$$SSW = \sum_{i=1}^{m} \sum_{j=1}^{n} \left(x_{ij} - \bar{x}_i\right)^2$$

The in-house repeatability standard deviation $s_{r,inhouse}$ is then obtained as

$$s_{r,inhouse} = \sqrt{\frac{SSW}{m \cdot (n-1)}}$$

and the between-day standard deviation $s_D$ is obtained as

$$s_D = \sqrt{\frac{1}{n}\left(\frac{SSB}{m-1} - s_{r,inhouse}^2\right)}.$$

(If the value under the square root sign is negative, then $s_D = 0$.)

Finally, the intermediate (in-house) standard deviation is calculated as:

$$s_I = \sqrt{s_D^2 + s_{r,inhouse}^2}.$$

For the data from Table 2, the calculation results are as follows:

**Table 3: Calculation of $SSB$ and $SSW$ on the basis of in-house QC data**

| Overall mean value $\bar{x}$ | Day-specific mean values $\bar{x}_i$ | Differences $\bar{x}_i - \bar{x}$ | $SSB$ | Differences $x_{ij} - \bar{x}_i$ | Differences $x_{ij} - \bar{x}_i$ | $SSW$ |
|---|---|---|---|---|---|---|
| 8.91 | 11.51 | 2.60 | 283.05 | -0.79 | 0.79 | 29.95 |
| | 2.73 | -6.18 | | 1.83 | -1.83 | |
| | 9.27 | 0.36 | | -0.48 | 0.48 | |
| | 8.29 | -0.61 | | 1.79 | -1.79 | |
| | 11.80 | 2.90 | | 0.49 | -0.49 | |
| | 7.37 | -1.54 | | 0.58 | -0.58 | |
| | 13.80 | 4.90 | | -0.74 | 0.74 | |
| | 11.66 | 2.75 | | -0.43 | 0.43 | |
| | 8.41 | -0.50 | | -1.10 | 1.10 | |

| | | | |
|---|---|---|---|
| 5.46 | -3.44 | 0.39 | -0.39 |
| 8.30 | -0.61 | -0.82 | 0.82 |
| 11.62 | 2.72 | 0.97 | -0.97 |
| 7.07 | -1.83 | 0.48 | -0.48 |
| 11.60 | 2.69 | 0.45 | -0.45 |
| 5.67 | -3.24 | -0.81 | 0.81 |
| 7.05 | -1.86 | -0.06 | 0.06 |
| 7.08 | -1.83 | 0.32 | -0.32 |
| 10.00 | 1.09 | -1.15 | 1.15 |
| 11.05 | 2.14 | 0.88 | -0.88 |
| 8.40 | -0.51 | 0.10 | -0.10 |

The following precision estimates are obtained:

**Table 4: Precision estimates obtained from in-house QC data**

| $s_{r,inhouse}$ | $s_D$ | $s_I$ |
|---|---|---|
| 1.22 | 2.59 | 2.86 |

### 9.2 PROCEDURES FOR CHARACTERIZING VARIATION ACROSS MATRICES (MATRIX MISMATCH)

In this section it is assumed that heterogeneity between laboratory samples is negligible, and that the measurand is specified in terms of a number of matrices, from which $N$ matrices are selected[9]. Selection should be based on the method's intended use/scope. As explained in Section 0, it is recommended that, at a minimum, $N = 12$ matrices be included.

A simple approach for characterizing variation across matrices consists in spiking the $N$ matrices and obtaining duplicate measurement results in a single laboratory for each matrix. In this manner, variation between the matrices (matrix-specific bias) can be distinguished from variation within each matrix (repeatability error). In this procedure, the matrix is modelled as a random effect, and the result is a standard deviation characterizing variation across all the matrices included in the specification of the measurand.

Example

**Table 5: Data from an experiment for the calculation of the matrix bias**

| | MV1 | MV2 |
|---|---|---|
| Matrix 1 | 114.51 | 112.24 |
| Matrix 2 | 120.25 | 111.59 |
| Matrix 3 | 88.46 | 86.62 |
| Matrix 4 | 118.93 | 102.35 |
| Matrix 5 | 74.06 | 80.91 |
| Matrix 6 | 117.50 | 102.69 |
| Matrix 7 | 120.96 | 109.35 |
| Matrix 8 | 96.05 | 92.92 |
| Matrix 9 | 98.43 | 87.09 |
| Matrix 10 | 107.99 | 117.42 |
| Matrix 11 | 117.34 | 126.87 |
| Matrix 12 | 76.56 | 109.79 |

Applying the same calculation procedure as in Section 9.1, the following precision estimates are obtained:

**Table 6: Precision estimates for the calculation of matrix bias**

| $s_r$ | $s_{matrix}$ |
|---|---|
| 9.53 | 12.24 |

For further information on matrix bias, see Uhlig (2023) [24]

[9] For instance, a number of different apple types, or a number of different cattle breeds.

### 9.3 PROCEDURES FOR CHARACTERIZING BETWEEN-LABORATORY VARIATION

Procedure 1: Conduct an interlaboratory validation study with a minimum of $N = 12$ laboratories and with duplicate measurement results within each laboratory. It is necessary to ensure that heterogeneity between laboratory samples is negligible. In this manner, variation between the laboratories (lab bias) can be distinguished from variation within the laboratories (repeatability error). In this procedure, the laboratory is modelled as a random effect, and the result is a standard deviation characterizing variation across laboratories.

Example

**Table 7: Data from an experiment for the calculation of the lab bias**

| | MV1 | MV2 |
|---|---|---|
| Lab 1 | 0.981 | 1.238 |
| Lab 2 | 0.182 | 0.601 |
| Lab 3 | 1.107 | 0.994 |
| Lab 4 | 1.471 | 1.532 |
| Lab 5 | 1.169 | 0.674 |
| Lab 6 | 0.491 | 1.271 |
| Lab 7 | 1.717 | 0.970 |
| Lab 8 | 0.931 | 1.171 |
| Lab 9 | 1.017 | 1.248 |
| Lab 10 | 0.909 | 0.723 |
| Lab 11 | 0.812 | 1.312 |
| Lab 12 | 1.375 | 1.719 |

Applying the same calculation procedure as in Section 9.1, the following precision estimates are obtained:

**Table 8: Precision estimates for the calculation of lab bias**

| $s_r$ | $s_{lab}$ |
|---|---|
| 0.30 | 0.23 |

Procedure 2: If PT data are available, and a sufficient number of participants (ideally, at least 12) have used the same method – then these data can be used to characterize variation across laboratories. In order to ensure neutral data evaluation and avoid conflicts of interest, the data should come from PT schemes run by competent authorities.

### 9.4 PROCEDURES FOR CHARACTERIZING FUNDAMENTAL VARIABILITY

Fundamental variability is a subcomponent of the repeatability error term from the basic model in Section 3 and denotes the irreducible variation between samples which remains even under the highest achievable degree of homogeneity. Fundamental variability reflects heterogeneity at the level of the sample's constituent particles; it has an influence on the uncertainty of measurement results when the target analyte is located on sparsely distributed carrier particles. Fundamental variability appears twice: first, during sampling, and second, during subsampling in the laboratory, i.e. extraction of a test portion after homogenization of the laboratory sample. In practice, nonnegligible fundamental variability can be reduced by modifying the testing procedure in two respects: first, by finer grinding or comminuting or mixing of the test material, and second, by increasing the test portion size.

It should be noted that, while a correct partitioning of observed variability between sampling, subsampling and other uncertainty components is achievable in theory, doing so is difficult in practice *when the fundamental variability is significant*. Take the case that the number of carrier particles in the laboratory sample collected from the container or batch of products varies randomly between 0 and 10. The fundamental variability between subsamples (test portions) will thus depend on which laboratory sample they were collected from. In such a situation, a correct characterization of fundamental variability would be quite involved. It would be much more efficient to ensure variation regarding carrier particle numbers between laboratory samples were negligible – in other words, to ensure that every single laboratory sample were representative of the container or batch of products, thus eliminating the sampling fundamental variability from the equation. Often, this may be achieved by increasing laboratory sample size; but a more general point is that a correct evaluation of fundamental variability requires an appropriate inclusion of the sampling step, i.e. a consideration of the different steps from sampling to analysis as one single process[10].

[10] Consider the following example: a 5 t container contains one single carrier particle, translating to 1 µg/kg analyte concentration. A 5 kg laboratory sample is collected from the container. Thus, with 99.9 % probability, the laboratory sample will contain no carrier particle, and there will be no fundamental variability. However, with 0.1 % probability, the laboratory sample will contain the single carrier particle. In such a case, if a 500 g test portion is taken from the laboratory sample, then the analyte concentration in the test portion will be either 0 mg/kg (nine times out of ten) or 10 mg/kg (one time out of ten). This corresponds to a (Poisson) standard

The question thus arises: how can we decide whether fundamental variability is significant? Fundamental variability cannot be characterized by means of classical homogeneity studies such as the standard designs described in ISO 13528 [22] and Guide 35 [9]. Indeed, in these designs, it is not possible to distinguish fundamental variability from sample heterogeneity *per se*, so that the former may be mistaken for the latter.

The following procedure, originally proposed in Uhlig (2022) [23], allows a characterization of fundamental variability.

Step 1

Check whether one of the following criteria are met:

Criterion 1: The in-house repeatability standard deviation is larger than 3 times the expected value.

Criterion 2: The in-house repeatability standard deviation is larger than the Horwitz SD value.

Criterion 3: Conspicuous "upper" outliers are present in QC data. For instance, in the QC data provided in Table 2 (Section 9.1), the Day 7 value of 14.54 could be considered such an "upper" outlier. The presence of such outliers constitutes a further indication that the unexpectedly large observed variability may be due to fundamental variability.

If at least one of these criteria is met, proceed to Step 2.

Step 2

Conduct the following experiment:

1. Obtain 20 test results under repeatability conditions. Calculate the corresponding variance $s_1^2$.
2. Increase test portion size by a factor $k$ (e.g. triple test portion size, $k = 3$). If it is not possible or practical to increase test portion size, grinding and homogenizing a volume corresponding to a $k$-fold increase in test portion size prior to taking a test portion with the original size is another option.
3. Obtain 20 test results under repeatability conditions on the basis of the finely ground test material / increased test portion size. Calculate the corresponding variance $s_2^2$.
4. If the ratio $\frac{s_1^2}{s_2^2}$ is greater than 2.17, then calculate the SD characterizing fundamental variability as follows:

$$s_F = \sqrt{\frac{k}{(k-1)} \cdot (s_1^2 - s_2^2)}$$

Example

**Table 9: Test results from an experiment for the calculation of fundamental variability**

| | Experiment 1: Original test portion size | Experiment 2: Test portion size is tripled |
|---|---|---|
| Sample 1 | 14.0 | 15.1 |
| Sample 2 | 11.9 | 13.8 |
| Sample 3 | 10.5 | 11.8 |
| Sample 4 | 14.9 | 14.0 |
| Sample 5 | 13.1 | 11.4 |
| Sample 6 | 9.5 | 15.7 |
| Sample 7 | 15.6 | 12.4 |
| Sample 8 | 18.3 | 11.5 |
| Sample 9 | 12.5 | 12.1 |
| Sample 10 | 16.4 | 13.7 |
| Sample 11 | 18.0 | 15.8 |
| Sample 12 | 14.0 | 12.5 |
| Sample 13 | 13.0 | 12.8 |
| Sample 14 | 20.8 | 15.1 |
| Sample 15 | 10.2 | 11.8 |
| Sample 16 | 21.5 | 10.6 |
| Sample 17 | 13.9 | 11.1 |

deviation of 1 mg/kg – which clearly constitutes a disproportionate estimate in relation to the situation in the container. This example shows how restricting the calculation of fundamental variability to the subsampling step can lead to gross misestimation.

| | | |
|---|---|---|
| Sample 18 | 17.8 | 12.9 |
| Sample 19 | 7.7 | 11.4 |
| Sample 20 | 12.2 | 16.3 |

Note that, in Experiment 1, several conspicuously large values are obtained – an indication that fundamental variability is non-negligible.

The following variances and corresponding ratio are obtained:

**Table 10: Variances and their ratio**

| $s_1^2$ | $s_2^2$ | $s_1^2/s_2^2$ |
|---|---|---|
| 13.54 | 3.05 | 4.44 |

As can be seen, the ratio $s_1^2/s_2^2$ is greater than the value 2.17. Accordingly, the fundamental variability is calculated as

$$s_F = \sqrt{\frac{3}{2} \cdot (s_1^2 - s_2^2)} = 3.97.$$

## 10 Influence of measurement uncertainty on sampling plans: examples

In the *General guidelines on sampling* [13], it is stated that "Codex Methods of Sampling are designed to ensure that fair and valid sampling procedures are used when food is being tested for compliance with a particular Codex commodity standard". Sample size and acceptance number / acceptability constant for inspection by attributes / variables are determined on the basis of procedures and sampling plans described in ISO standards and/or Codex guidelines. While measurement uncertainty may be considered irrelevant for inspection by attributes, its impact on inspection by variables must be accounted for.

In the introduction to ISO 3951-1:2013, it is stated that "[i]t is assumed in the body of this part of ISO 3951 that measurement error is negligible […]". Nonetheless, procedures for increasing the sample size are provided in Annex B of ISO 3951-1 [14] and Annex P of ISO 3951-2 [15] for the case that measurement uncertainty is non-negligible. It is important to note that these procedures are only applicable if "the measurement method is unbiased, i.e. the expected value of the measurement error is zero" (see Annex P.1 in ISO 3951-2:2013 [15]). In such a case, total variability is expressed as

$$\sigma_{total} = \sqrt{\sigma^2 + \sigma_m^2}$$

where $\sigma$ denotes the process standard deviation and $\sigma_m$ denotes the measurement standard deviation.

If $\sigma_m$ is non-negligible (i.e. greater than one tenth of the sampling standard deviation $s$ or process standard deviation $\sigma$), the sample size $n$ must be increased to either $n^* = n \cdot (1 + \gamma^2)$ where $\gamma = \sigma_m/\sigma$ (the process standard deviation $\sigma$ is known) or $n^* = n \cdot (1 + \tilde{\gamma}^2)$ where $\tilde{\gamma}$ is an estimated upper bound of $\gamma = \sigma_m/\sigma$ (the process standard deviation $\sigma$ is unknown). The acceptability constant $k$ remains unchanged. For further details, see Annex P in ISO 3951-2:2013 [15].

Example

A lot of 500 items of pre-packaged mineral water is assessed for sodium content. If the measurement uncertainty is not taken into consideration, for an agreed AQL of 2.5 % (maximum concentration 200 mg/L), general inspection level II (default level) a sample of 30 items should be collected for assessment, (ISO 3951-2 [15], Annex A, Table A1 and Annex B, Table B1). The production is well under control and the control charts give a process standard deviation $\sigma$ of 2 mg/L. The measurement uncertainty standard deviation $\sigma_m$ is 1 mg/L and is thus non-negligible. With $\gamma = \sigma_m/\sigma = 0.5$ and $1 + \gamma^2 = 1.25$ the sample size must be increased to 38.

If there is a bias, the above procedure must be modified. One possibility would be to proceed as follows[11]. The standard deviation of $\bar{x}$, the mean across the $n$ measurement results, is expressed as

$$\sigma_{\bar{x}} = \sqrt{\frac{\sigma^2 + \sigma_0^2}{n} + \sigma_b^2}$$

where $\sigma$ denotes the process standard deviation, $\sigma_0$ denotes the repeatability component of measurement uncertainty (calculated on the basis of the $n$ items sampled from the lot), and $\sigma_b$ represents available information (e.g. the between-lab standard deviation from a method validation study) used to estimate the bias term.

The modified procedure is as follows:

1. Increase the sample size under the assumption that there is no measurement error
2. Calculate $d = \frac{1}{n} - \frac{\sigma_b^2}{\sigma^2}$

[11] This modified procedure is taken from current stage of development of Annex B of ISO/WD ISO 3951-6 [16].

3. If $d \leq 0$, inflated variability due to a bias cannot be compensated for via an increase in sample size.
4. If $d \leq \frac{1}{2n}$, bias compensation via an increase in sample size may not be appropriate due to the large number of samples required. It is then suggested to reduce bias or to use another measurement method.
5. If $d > \frac{1}{2n}$, calculate the new sample size as $n^* = \frac{1+\frac{\sigma_0^2}{\sigma^2}}{d} = \frac{\sigma^2+\sigma_0^2}{\frac{\sigma^2}{n}-\sigma_b^2}$

Example (continued from previous example)

It is now assumed that there is a method bias and that a $\sigma_b$ estimate of 0.2 mg/L is available. Accordingly, on the basis of the previously calculated value of $n = 38$, $d$ is calculated as $d = 0.016$. Since $d > \frac{1}{2n} = 0.013$, the new sample size is calculated as $n^* = 77$ (with $\sigma_0 = \sigma_m = 1$ mg/L).

Procedures for bulk sampling are provided in ISO 10725:2000 [17]. As in the case of sampling from packages, these procedures are only valid under the assumption that there is no method bias. Modified procedures for the case that there is a method bias are currently being developed. For now, the discussion is limited to the case that there is no bias.

A *dominant* measurement uncertainty has an effect on the number of test samples per composite sample $n_T$ as well as the number of measurements per test sample $n_M$. The measurement uncertainty is dominant when both the standard deviation of the sampling increment $\sigma_I$ and the standard deviation between test samples $\sigma_P$ are far less (one tenth or less) than the measurement standard deviation $\sigma_M$ (i.e. the measurement uncertainty), which must be known and stable, see Annex B in ISO 10725 [17]. The number of sample increments per composite sample $n_I$ remains unchanged, no matter whether the measurement uncertainty is dominant or not. The mass of the increments should be sufficiently large to offset the fundamental variability.

Example

A lot of wheat bulk material is to be assessed for cadmium content (maximum concentration e.g. $0.1$ mg/kg). In this example, it is assumed that cadmium concentrations in the lot are homogeneous, resulting in very low standard deviations $\sigma_I$ and $\sigma_P$, estimated as $0.0015$ mg/kg and $0.002$ mg/kg, respectively. Since the concentrations are very low, a relatively high measurement uncertainty $\sigma_M = 0.025$ mg/kg is obtained. The discrimination interval $D$ (difference between agreed risk-based acceptance and rejection levels) is $0.02$ mg/kg. The measurement standard deviation $\sigma_M = 0.025$ mg/kg is thus dominant ($d_I$ is calculated as 0.075). The number of increments per composite sample is $n_I = 6$, the number of test samples per composite sample is $n_T = 2$ and the number of measurements per test sample is $n_M = 2$ (yielding a product $n_T \cdot n_M = 4$, which can be interpreted as a measure of the analytical workload). The combined overall standard deviation $\sigma_0$ is calculated as $\sqrt{\frac{n_T \cdot n_M}{n_I}{\sigma_I}^2 + n_M{\sigma_P}^2 + {\sigma_M}^2} \approx 0.03$ mg/kg and divided by the discrimination interval $D$ in order to obtain the relative standard deviation $d_0 = \sigma_0/D \approx 1.26$. By means of Table B1 in Annex B of ISO 10725 [17], this relative standard deviation $d_0$ is used to determine the adjusted number of test samples per composite sample $n_T = 2$ (i.e. $n_T$ remains the same) as well as the adjusted number of measurements per test sample $n_M = 3$, yielding a product $n_T \cdot n_M = 6$.

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