

	Standard Operating Procedure		SOP Number D-108	Revision 0
	Estimation of Measurement Uncertainty		Effective Date 11/02/21	Page Page 1 of 11
Written by/ Date Jm 10/13/21		Reviewed by/ Date SSS 10/15/21		Approved by/ Date [Signature] 10-13-21
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1.0 Purpose

The objective of the measurement uncertainty process is to determine the overall uncertainty of the measuring system. Guidance is provided for estimating uncertainty from all contributors affecting a measurement. Process requirements are described, including responsibilities and controls for estimation of uncertainty budgets. It is recognized that this estimation may be performed in various ways as long as the results are statistically justifiable.

2.0 Scope

This procedure applies to all internally performed, quantitative measurements derived from methods where known variability is inherent with equipment used. These uncertainty measurements will be calculated for all methods that are ISO.17025 accredited.

3.0 Responsibility

- 3.1 QC Laboratory Management is responsible for calculating expanded uncertainty for measurement systems used in testing and for documenting the results of such calculations in an Uncertainty Budget
- 3.2 QC Laboratory Management is responsible for reporting changes in measurement uncertainty and/or capability to the ISO 17025 accreditation agency.
- 3.3 QC Laboratory Management is responsible for ensuring that this procedure is accurate, understood and implemented effectively. No changes may be made to this procedure without the authorization of Laboratory Management.

4.0 Definitions

- 4.1 **Uncertainty**- a parameter associated with the result of a measurement that characterizes the dispersion of values that could reasonably be attributed to the measurand. Sources of uncertainty include incomplete definition of the measurand, sampling, matrix effects and interferences, environmental conditions, uncertainties of masses and volumetric equipment, reference values, approximations and assumptions incorporated in the measurement procedure, and random variation.
- 4.2 **Accuracy**- the closeness of the agreement between a measured quantity value and a true quantity value of a measurand.
- 4.3 **Dispersion** – the amount by which we can normally expect the measured values to spread or be different from one another.

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- 4.4 **Measurand-** a quantity intended to be measured.
- 4.5 **Measurement-** the process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity.
- 4.6 **Measurement Uncertainty-** a non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used. This is a quantitative value. The dispersion relates to how well the measurement is made and the accuracy and capability of the equipment in the measurement system.
- 4.7 **Standard Uncertainty-** uncertainty of the result of a measurement expressed as a standard deviation.
- 4.8 **Combined Standard Uncertainty-** the standard uncertainty of the result of a measurement when that result is obtained from the values of a number of other quantities.
- 4.9 **Expanded Uncertainty-** a quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand.
- 4.10 **Coverage Factor-** Numerical factor used as a multiplier of the combined standard uncertainty in order to obtain an expanded uncertainty.
- 4.11 **Uncertainty Budget** – a list of evaluated sources of uncertainty. It lists the sources and their values. An uncertainty budget may also list items that have been assessed and determined to have no impact on uncertainty.
- 4.12 **Sensitivity Coefficient-** a multiplier used to relate how the value of a measurement variable (e.g. the concentration of a reference standard, the temperature in the laboratory, or the tolerance of a pipet) is related to the final test result.
- 4.13 **Repeatability-** measurement precision under a set of repeatability conditions of measurement. The repeatability conditions of measurement are those creating a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time. The repeatability is the variation in measurements obtained.
- 4.14 **Reproducibility-** measurement precision under reproducibility conditions of measurement. The reproducibility conditions of measurement are those creating a set of conditions that includes different locations, operators, measuring systems, and the same measurements on the same or similar object.
- 4.15 **Bias-** systematic error in the measurement process.
- 4.16 **Drift-** systematic change in the measurement process over time.
- 4.17 **Resolution-** an evaluation of the smallest incremental change observed in your measurement process of system.

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5.0 References

- 5.1 JCGM 100:2008 Free version of ISO/IEC Guide 98-32008- Guide to expression of Uncertainty in Measurement (GUM).
- 5.2 ISO 17025 requirements for measurement uncertainty

6.0 Process Activities

- 6.1 Laboratory Management ensures that all types of accredited tests provided to customers have a current uncertainty of measurement calculated on an Uncertainty Budget. Laboratory Management also ensures that all uncertainty components which are of significance in the given situation are considered using appropriate methods of analysis.
 - 6.1.1 When using a well-recognized test method that specifies limits to the values of the major sources of measurement uncertainty and specifies the form of presentation of the calculated results, the laboratory is considered to have satisfied the evaluation of measurement uncertainty by following the test method and reporting instructions.
 - 6.1.2 When the measurement uncertainty of a method has been established and verified, there is no need to evaluate measurement uncertainty for each result if the laboratory can demonstrate that the identified critical influencing factors are under control.
- 6.2 Examples of uncertainty considerations are the environment, metrologist or technician, measuring equipment, properties and condition of item being tested, software, calculations, and physical characteristics of the material being tested.
- 6.3 When evaluating uncertainty for an instrument that has more than one parameter (e.g., voltage, current, resistance, etc.) and one or more ranges, the uncertainty must be evaluated for each range and parameter that will be reported to a customer.
- 6.4 Laboratory Management determines the uncertainty requirements for each test within the scope of accreditation.
- 6.5 There are several types of measurement uncertainty sources that can be calculated by Type A methods including but not limited to:
 - 6.5.1 The results of measurement assurance processes (control charts, etc.),
 - 6.5.2 Results of Gage Repeatability and Reproducibility (Gage R & R) studies,
 - 6.5.3 Data from experiments that were designed to evaluate a particular parameter or condition (e.g. an HPLC assay evaluated at several different temperatures).
- 6.6 Type B method of evaluation includes any reasonable method *except* statistical evaluation of your own measurements. The Type B evaluation is a standard uncertainty. An example of an uncertainty source that is evaluated using a Type B method is the

uncertainty of the purity of a standard used in the calibration of an instrument, which is obtained from the standard's certificate of analysis.

6.7 The following is an example demonstrating the use of the different methods:

6.7.1 If determining the uncertainty of the result of a length measurement, (which is affected by temperature changes), using Type B methods, one would look up the expansion coefficient of the material and multiply by the expected range of temperatures. Using Type A methods, the technician would repeat actual measurements at various temperatures. Both methods would then use those values in the measurement uncertainty calculation.

6.8 When an instrument manufacturer identifies a factor in a specification as being a contributor evaluated by Type A methods, this information is **NOT** a Type A contributor for Ion Labs' purposes, it is treated as a Type B contributor. This is a Type B contributor because the relevant measurements have not been performed by Ion Labs' personnel.

6.9 Uncertainty Budgets

6.9.1 An Uncertainty Budget is a listing of all known sources of uncertainty, their magnitudes, how they were obtained and whether they were evaluated by Type A methods or Type B methods. The goal of an uncertainty budget is to calculate measurement uncertainty for a specific measurand using a specific measurement system by a well-organized, structured approach.

6.9.2 There is no rule specifying how many contributors to uncertainty must be considered, except that all known, significant contributors must be evaluated. If a contributor was determined to have little significance, it may be omitted. Any contributors that have been omitted will be documented with a justification in the appropriate Uncertainty Budget.

6.9.3 Laboratory Management determines or creates the appropriate template for the Uncertainty Budget. A review of the contributors listed on the Uncertainty Budget is conducted by Laboratory Management to ensure that all significant contributors are listed.

6.9.4 For each uncertainty contributor, Laboratory Management will determine whether the Type A or Type B evaluation method will be used.

6.9.5 Laboratory Management or designated personnel performs Type A or Type B evaluations and documents all measurements on the designated template. Other resources (including external resources) may review the data at the discretion of Laboratory Management.

6.9.6 Laboratory Management calculates the Expanded Uncertainty and updates the associated documentation and/or template to ensure the Expanded Measurement

Uncertainty is available for accredited test reports. Laboratory Management reviews and approves the results of completed Uncertainty Budgets.

6.9.7 Uncertainty Budgets are updated when components contributing to the uncertainty of measurement change, and Laboratory Management determines the change is significant enough to warrant revising the budget. Examples of changes that may require reevaluation include replaced standards or new equipment. The revised Uncertainty Budget is reviewed and approved in the same manner as the original.

6.9.8 Uncertainty Budgets are retained in accordance with the Record Retention Matrix.

7.0 Process Outputs

7.1 Outputs from the process include but are not limited to:

7.1.1 Completed and current Uncertainty budgets for each test in the scope of accreditation.

7.1.2 A list of known and current calculated measurement capability.

8.0 Procedure

8.1 Specify the measurement process and equation.

8.1.1 Write down a clear statement of what is being measured, including the relationship between the measureand and the input quantities (e.g. volumes, reference standard concentrations, constants, etc.). A cause and effect diagram is often useful to help clarify uncertainty sources and their interdependence.

8.1.2 For the measurement procedure under consideration, evaluate each step of the test method to identify sources of uncertainty.

8.1.3 Identify the equipment, reagents, and standards that will be used.

8.1.4 Assess the desired range of measurement.

8.1.5 Evaluate any equations used to calculate the final result.

8.2 Identify which components of the measurement process may contribute to the uncertainty of the test result (uncertainty budget).

8.2.1 It is usually convenient to start with the expression used to calculate the final result from intermediate values. All the parameters in this expression may have an uncertainty associated with their value.

8.2.2 It is often useful to consider a measurement procedure as a series of discrete operations (or unit operations), each of which may be assessed separately to obtain estimates of uncertainty associated with them. This is particularly useful where similar measurement procedures share common unit operations.

- 8.2.3 Elements of overall method performance, such as precision and bias measured with respect to reference materials generally form the dominant contributions to the uncertainty estimate. It is then necessary to evaluate other possible contributions to check their significance, quantifying only those that are significant.
- 8.2.4 Typical sources of uncertainty to consider are:
- 8.2.4.1 **Sampling-** effects such as random variations between samples and any potential for bias in the sampling procedure form components of uncertainty affecting the final result.
 - 8.2.4.2 **Sample Storage-** The duration of storage as well as storage conditions should be considered as these can affect the final result.
 - 8.2.4.3 **Instrument effects-** may include, for example, a temperature controller that may maintain a mean temperature which differs (within specification) from its indicated set-point or an autosampler that is subject to carryover effects.
 - 8.2.4.4 **Reagent purity-** uncertainty in the purity of reagents and reference standards should be considered.
 - 8.2.4.5 **Measurement conditions-** for example, volumetric glassware may be used at an ambient temperature different from that at which it was calibrated.
 - 8.2.4.6 **Sample effects-** the recovery of an analyte from a complex matrix, or an instrument response, may be affected by the composition of the matrix.
 - 8.2.4.7 **Computational effects-** selection of the calibration model (e.g. using a straight line calibration on a non-linear response, leads to higher uncertainty. Truncation or rounding can lead to inaccuracies in the final result. Since these are rarely predictable, an uncertainty allowance may be appropriate.
 - 8.2.4.8 **Blank correction-** there will be an uncertainty on the value of the blank correction. This is particularly important in trace analysis (e.g. heavy metals testing).
 - 8.2.4.9 **Operator effects-** effects such as an operator reading a meter or scale consistently high or low should be considered.
 - 8.2.4.10 **Random effects-** random effects contribute to the uncertainty of all determinations.

- 8.3 Characterize sources of uncertainty (Type A or Type B).

- 8.3.1 **Type A** standard uncertainty is determined by performing statistical analysis of repeated measurements obtained under defined measurement conditions.
- 8.3.1.1 The value used to quantify uncertainty for a Type A contributor is typically the standard deviation of repeat measurements, which is expressed in the same units as the quantity being measured.
- 8.3.1.2 The degrees of freedom, equal to $n-1$ where standard deviation is calculated from n independent observations, should always be given when Type A evaluation of uncertainty components are documented.
- 8.3.2 **Type B** standard uncertainty is that which has been determined using any method other than statistical analysis. (e.g., using available information such as a calibration report or manufacturer's certificate of analysis).
- 8.4 Assign a probability distribution to each uncertainty component.
- 8.4.1 Potential probability distributions include:
- 8.4.1.1 Normal (Gaussian) – often used for Type A uncertainty components, calibration results, and accuracy specifications.
- 8.4.1.2 Uniform (rectangular) – often used for resolution components and environmental or physical influences.
- 8.4.1.3 Triangle
- 8.4.1.4 Log normal
- 8.4.1.5 Quadratic
- 8.4.1.6 U-shaped
- 8.5 Quantify the magnitude of uncertainty components. Various sources of information may be used, including but not limited to, precision studies, the test method itself, experimental results, manufacturer's manuals and specifications, technical documents and guides, published journal articles or studies.
- 8.6 Convert uncertainty components to standard uncertainty (u) corresponding to one standard deviation. The method of conversion depends on the source and format of the component.
- 8.6.1.1 Type A components are typically expressed in terms of one standard deviation and do not require conversion.
- 8.6.1.2 Type B component with standard deviation or standard uncertainty listed, but no coverage factor or confidence interval. In this case, the standard deviation should be assumed to be one standard deviation. No conversion is required.

- 8.6.1.3 Type B component with normal distribution and confidence interval and coverage factor given (e.g. “coverage factor $k=2$ at the 95% confidence interval”). Divide the stated uncertainty by the listed coverage factor to obtain the standard uncertainty.
- 8.6.1.4 Type B component with normal distribution and only confidence interval given. Divide the stated uncertainty by a coverage factor corresponding to the stated confidence interval.
- 8.6.1.4.1 68.27% confidence interval → no conversion required
- 8.6.1.4.2 90% confidence interval → divide by 1.645
- 8.6.1.4.3 95% confidence interval → divide by 1.960
- 8.6.1.4.4 95.45% confidence interval → divide by 2.000
- 8.6.1.4.5 99% confidence interval → divide by 2.576
- 8.6.1.5 Type B component stated in tolerance with unknown distribution.
- 8.6.1.5.1 Assume a uniform distribution and divide the tolerance by $\sqrt{3}$.
- 8.6.1.5.2 This method allows quick and easy calculations that can be used without having much knowledge on the source. It uses good engineering principles to perform this method with confidence. The downside of this method is that the resulting uncertainty is typically large compared to what it might be for full analysis and characterization of the instrument and determination of the real standard deviation.
- 8.6.1.6 Type B component stated in tolerance with known distribution.
- 8.6.1.6.1 Divide the stated tolerance by a value corresponding to the stated probability distribution.
- Normal distribution → divide by a value corresponding to the stated confidence interval as listed in 8.6.1.4.
 - Uniform distribution → divide by $\sqrt{3}$.
 - U-shaped distribution → divide by $\sqrt{2}$.
 - Triangular distribution → divide by $\sqrt{6}$. Instruments that drift must not be characterized by the triangular distribution.
 - Quadratic distribution → divide by $\sqrt{5}$.
 - Log-normal distribution → divide by 2.375.

- 8.7 Convert Standard Uncertainties (u) to units that match the measurement result.
- 8.7.1 Sensitivity coefficients (c) are used to convert standard uncertainties into units that match the measurement result.
- 8.7.2 Sensitivity coefficients show how the variables in an equation or function are related to the calculated result.
- 8.7.3 In many cases, the sensitivity coefficient will be equal to one. However, this should always be confirmed to ensure an accurate assessment of uncertainty.
- 8.7.4 Sensitivity coefficients are calculated using the following steps:
- 8.7.4.1 Identify the measurement function or equation.
- 8.7.4.2 Identify the variable of interest.
- 8.7.4.3 The sensitivity coefficient can be determined experimentally if the measurement equation is unknown or by calculation if the measurement equation is known.
- 8.7.4.4 Choose two values for your selected variable, and perform an experiment or calculation to determine the result under both conditions with all other variables constant.
- 8.7.4.5 Calculate the difference in the two results.
- 8.7.4.6 Calculate the difference in the two values of your selected variable.
- 8.7.4.7 Divide the difference in the results by the difference in the two values of your selected variable. This is the selectivity coefficient.
- 8.7.5 An example of sensitivity coefficient calculation for gage block calibration is given below:
- 8.7.5.1 The gage block is made of unknown material; therefore, its coefficient of linear thermal expansion is unknown and we do not know the measurement equation. The sensitivity coefficient must be determined experimentally.
- 8.7.5.2 The variable of interest is temperature, and the result is the length of the gage block.
- 8.7.5.3 At 20°C, the gage block measures 1.0 inches.
- 8.7.5.4 At 25°C, the gage block measures 1.0001 inches.
- 8.7.5.5 The difference in temperature is 5°C.
- 8.7.5.6 The difference in length is 0.0001 inches.
- 8.7.5.7 The sensitivity coefficient for temperature is:

$$c = \frac{0.0001in}{5^{\circ}C} = 2 \times 10^{-5} in/^{\circ}C$$

8.7.6 After the sensitivity coefficient has been calculated, multiply the standard uncertainty by the sensitivity coefficient to obtain the standard uncertainty in units that match the result of the test method.

8.8 Combined Standard Uncertainty (u_c)

8.8.1 Once the individual standard uncertainties (u) are determined, the values are combined to yield the Combined Standard Uncertainty (u_c). Uncertainty components should be combined using the root-sum-square (RSS) method. It is found by squaring each standard deviation, adding up the squares and taking the square root of the result. The following equation is an example of Combined Standard Uncertainty, if you had three uncertainties (u_1 , u_2 , and u_3).

$$u_c = \sqrt{u_1^2 + u_2^2 + u_3^2}$$

8.9 Expanded Uncertainty

8.9.1 When reporting a measurement in a test report or a specification, it is the expanded uncertainty (U) that should be reported.

8.9.2 The expanded uncertainty is the combined standard uncertainty (u_c) multiplied by the coverage factor (k) to provide an uncertainty range that is believed to include the true value of the measurand within a specific confidence interval. A coverage factor of $k=2$ or $k=1.960$ is recommended.

8.9.3 The value of k is chosen to match the desired confidence interval.

8.9.3.1 68.27% confidence interval \rightarrow no conversion required

8.9.3.2 90% confidence interval \rightarrow multiply u_c by 1.645

8.9.3.3 95% confidence interval \rightarrow multiply u_c by 1.960

8.9.3.4 95.45% confidence interval \rightarrow multiply u_c by 2.000

8.9.3.5 99% confidence interval \rightarrow multiply u_c by 2.576

8.9.4 Then the expanded uncertainty can be calculated:

$$U = k \times u_c$$

8.9.5 When reporting the expanded measurement uncertainty, the report will provide measurements along with the expanded uncertainty and indicate the coverage factor and/or confidence interval.

8.9.6 The following is an example of reporting of expanded uncertainty following GUM methods:

Caffeine = 100 mg/tablet ($U = \pm 0.5\text{mg/tablet } k=2$)

8.10 Evaluating Estimates of Uncertainty

8.10.1 The predicted standard deviation of an experimental measurement, which has been obtained by combining the various uncertainty components that characterize the measurement, can be compared to the experimentally observed variability of measurements to provide further confirmation of uncertainty estimates.

8.11 Reporting Measurement Uncertainty

8.11.1 Uncertainty Budgets are reported to the accreditation agency at the time of test accreditation application.

8.11.2 Revised Uncertainty Budgets are reported to the accreditation agency after review and approval by Laboratory Management.

8.11.3 Laboratory Management will ensure that revised testing measurement capability information is communicated to customers as appropriate.

9.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	10/12/21	New procedure.	N/A	J. Maignan