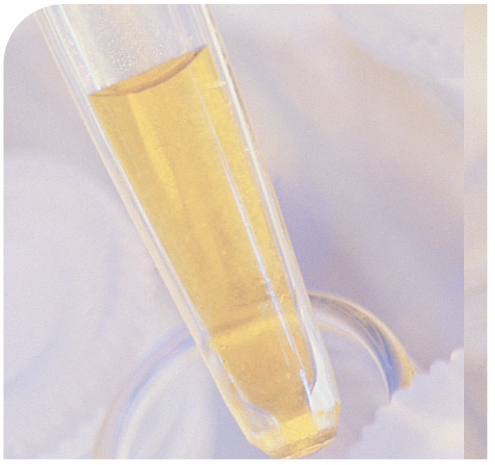
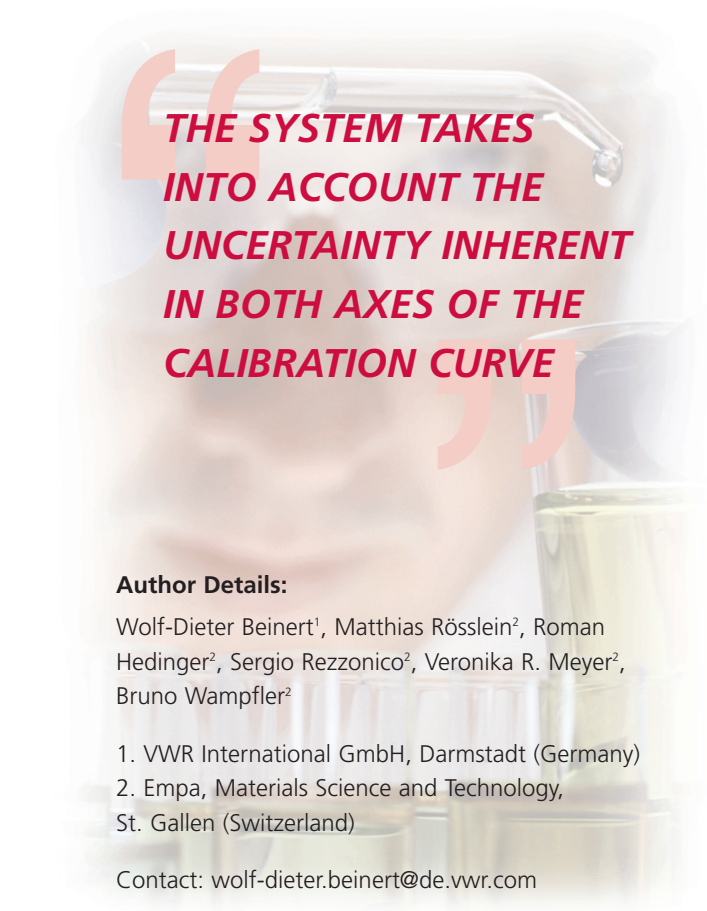


Laboratory Products Focus

RAPID DETERMINATION OF MEASUREMENT UNCERTAINTY IN ANALYTICAL CHEMISTRY

Wolf-Dieter Beinert[1], Matthias Rösslein[2], Roman Hedinger[2], Sergio Rezzonico[2], Veronika R. Meyer[2], Bruno Wampfler[2]

In order to be able to evaluate analytical results properly, one has to know the degree of uncertainty involved with the methods employed. Determination of measurement uncertainty is now being demanded by international standards authorities (e.g. ISO/IEC/EC 17025 (2005)). The UncertaintyManager® is a new software tool for the rapid determination of the measurement uncertainty of analytical results according to international standards Eurachem / CITAC Guide "Quantifying Uncertainty in Analytical Measurement" (2nd edition) and "ISO Guide to the Expression of Uncertainty in Measurement" (GUM). The software, based on a substantial database, comprises numerous functions that facilitate data entry, enable critical parameters to be visualized, calculate the measurement uncertainty and the compilation of reports. It also displays information on the contribution to uncertainty of the various parameters involved; this helps to minimize the measurement uncertainty of both existent and new analytical methods. Using the Uncertainty Manager software, the measurement uncertainty of a particular set of analytical results can be completely evaluated in short time.



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WHY SHOULD MEASUREMENT UNCERTAINTY BE INDICATED?

Knowledge of measurement uncertainty is a precondition for correct evaluation of analytical results. As to whether a particular limit is exceeded or whether a product fulfils its specifications can only be established if the measurement uncertainty is taken into account (*Figure. 1*). This is particularly important if the analytical results involved are relevant to safety, quality or if they are to be used in a court of law. In addition, reliable product specifications are indispensable in international trade. If the measurement uncertainty is taken into account, the apparent different analytical results as obtained by different analytical laboratories may well be found in fact to be identical. In this way, cases of conflict can be reduced and fewer repeat analyses become necessary; this in turn reduces costs considerably. Determination of measurement uncertainty is thus being demanded by international standards authorities (e.g. ISO/IEC/EC 17025 (2005)). However, determination of measurement uncertainty according to the Eurachem/CITAC Guide "Quantifying Uncertainty in Analytical Measurement" (2nd edition) (1), that is based on the "ISO Guide to the Expression of Uncertainty in Measurement" (2), is somewhat complex and very time-consuming.

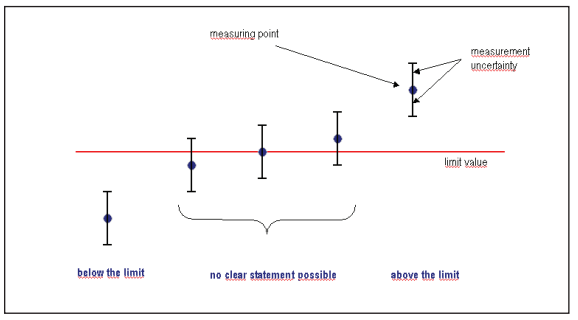

Figure 1. As to whether a particular limit is exceeded or whether a product fulfils its specifications can only be established if the measurement uncertainty is taken into account. The uncertainty bar indicates that the true measurement result is located inside of this measurement uncertainty interval with a certain probability to be defined.

WHEN DOES THE MEASUREMENT UNCERTAINTY OF ANALYTICAL RESULTS HAVE TO BE INDICATED CURRENTLY?

National accreditation authorities currently prescribe that their accredited laboratories must indicate how reliable their analytical measurements are. The determination of measurement uncertainty is particularly important for analytical laboratories in the following areas:

- All testing and calibration laboratories accredited according to ISO/IEC/EC 17025 (2005).
- Development of standard procedures (national, international, methods for pharmacopoeias).
- Characterisation of reference materials.
- Forensic and doping control laboratories.
- Food analyses (e.g. threshold values for pesticides, antibiotics, dioxin etc.).
- Environmental analyses (e.g. threshold values for environmental pollutants).
- Clinical analyses (decisions as to whether values are normal or pathological).
- Pharmaceutical analytics (e.g. threshold values for by-products and contaminants; this will presumably be required in the near future).

A NEW TOOL FOR THE RAPID DETERMINATION OF MEASUREMENT UNCERTAINTY

The UncertaintyManager® program calculates measurement uncertainty according to international standards Eurachem/CITAC Guide "Quantifying Uncertainty in Analytical Measurement" (2nd edition) and "ISO Guide to the Expression of Uncertainty in Measurement" (GUM). The UncertaintyManager® program can substantially reduce the expense and time required to determine measurement uncertainty.

The program was developed jointly in a cooperation project by experts in chemical metrology, users in analytical laboratories, software engineers and instrument manufacturers. The project is headed by Empa Materials Science and Technology, St. Gallen, Switzerland.

CALCULATING MEASUREMENT UNCERTAINTY

The user-friendly system UncertaintyManager® leads the user step-by-step through the entire evaluation process. In accordance with the Eurachem/CITAC Guide (1), it comprises the following elements:

- Specification of the measurand (establishment of measurement equation),
- Identification of all uncertainty sources,
- Quantification of all uncertainty influences,
- Calculation of overall uncertainty and
- Compilation of the report.

Working with the program is explained below using the example of HPLC analysis. The analyte in question is the plasticiser di-n-butyl-phthalate that is to be determined quantitatively in plastic using a single-point calibration.

Data entry

The user first describes the analytical procedure to be used in evaluation by entering the measurement equation. A programming wizard of UncertaintyManager® offers a comprehensive choice of templates. In this case the measurement equation is displayed in Figure 2:

*where A = peak area, m = mass (weighed quantity), V = volume of the graduated flask used to prepare the solutions, s is the sample and r the reference substance (Figure 2).*The analytical instruments, reagents and reference substances used can be entered from a comprehensive database containing the relevant uncertainty data (*Figure 3*).

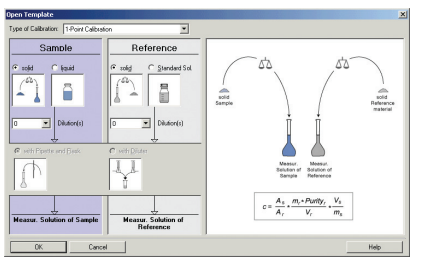

Figure 2. Input of measurement equation using the programming wizard of UncertaintyManager®. On the left side the user specifies how sample and reference are prepared. The right side illustrates the procedure and indicates the resulting measurement equation.

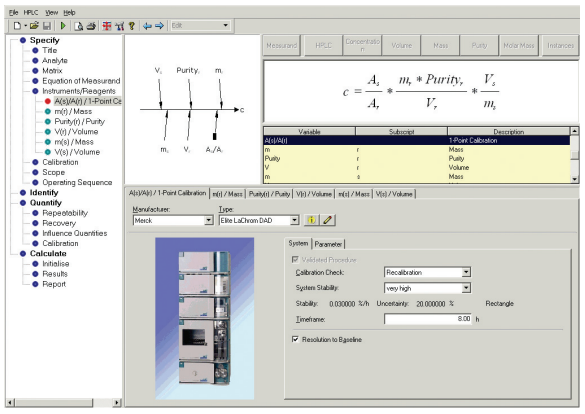

Figure 3. Input screen of UncertaintyManager®. On the left the clear user guidance: successively each item requires inputs or selections by the user. On the upper right the formula editor indicating the measurement equation (here shown: equation for HPLC method with one-point calibration). From the parameters of the measurement equation result the analytical instruments and reference substances (see menu in the lower part). The analytical instruments (here e.g.: HPLC system, balance, volumetric flasks) and reference substances used and their known uncertainties are selected and input from a comprehensive database.

In the module Sample Preparation, the analytical procedure to be used can be selected from a wide range of methods. In our case, a Soxhlet extraction is required while the reference substance need only be weighed and dissolved. The program has an entry window for recovery and its uncertainty, i.e. its repeatability (*Figure 4*). To facilitate data entry, most parameters and other factors that influence the measurement uncertainty can be selected and entered either from the suggestions presented automatically by the system or from the database itself. The database of UncertaintyManager® contains well-known uncertainty parameters and influences originating from the analytical instruments, reagents and reference substances supplied by various manufacturers. These are continuously updated. Data obtained from method validation can also be used for calculating measurement uncertainty. For overlapping peaks in chromatography there is also a Peak Simulation Module; this enables the measurement uncertainty of integration to be estimated.

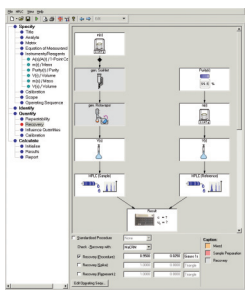

Figure 4. Illustration of the analytical procedure including sample preparation for the sample (left) and for the reference (right). The program requires the input of recovery and its repeatability.

Identification and quantification of uncertainty factors

Based on the available data, UncertaintyManager® generates all the parameters that can influence the measurement uncertainty and displays these together with their interaction capabilities in a cause-and-effect diagram (*Figure 5*).

As already mentioned, certain uncertainty factors (e.g. dilution in a graduated flask) are pre-logged in the program; the user need not thus bother about this. However, if so desired, all individual values can be specifically adapted to the analytical problem being tackled.

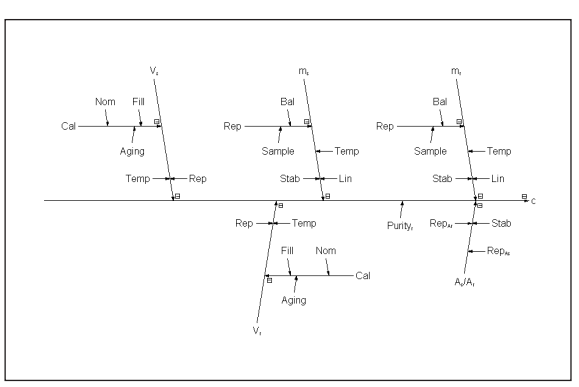

Figure 5. Cause-and-effect diagram for the measurement uncertainty of an HPLC method with one-point calibration.

Before the measurement uncertainty can be determined, the program requests concrete data for the analysis being performed – in the case above, the weighed quantity of reference the actual peak area measured as well as some data from the validation procedure.

Calculation

The measuring uncertainty of analytical results can be determined using either the classical uncertainty propagation (the more rapid method) or the Monte Carlo Simulation method, which provides more information and therefore is today preferred.

In the Monte Carlo Simulation, all the identified uncertainty factors are simulated in accordance with their distributions using random numbers and their effect on the overall measurement calculated. A further result provided by the Monte Carlo Simulation is the uncertainty distribution of the analytical results.

The system takes into account the uncertainty inherent in both axes of the calibration curve. This also means that the uncertainty of the calibration samples (e.g. purity of the reference substances, weighing and dilution) are included in the measurement uncertainty determined.

Report

The report documents all data entries, individual uncertainty factors with the formulae used for the calculation, a cause-and-effect diagram and the final result. The final result comprises the absolute and relative standard measurement uncertainties for the analytical result in question. In the case in point, a plasticiser content of 0.155 g/g with an uncertainty of ± 3.05 mg/g was determined.

This corresponds to a relative measurement uncertainty of 1.97 %. In addition, the individual uncertainties of the factors influencing the system are displayed in a histogram (*Figure 6*).

In our example, the influence of factor recovery is greatest, followed by the uncertainty of the peak areas, the repeatability and the purity of the reference substance. The Monte Carlo histogram illustrates the distribution of measurement uncertainty (*Figure. 7*). It is not always a Gaussian curve.

For documentation purposes, three different report formats with different contents are available.

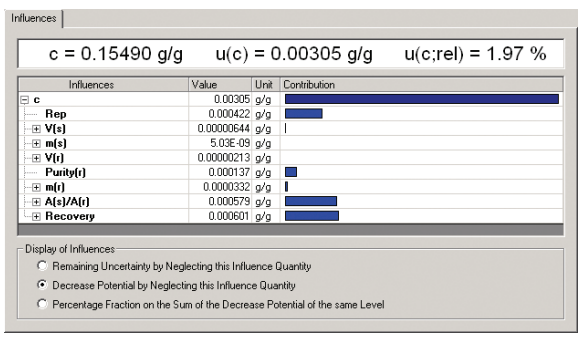

Figure 6. Result: Analytical measurement result with its absolute and relative standard measurement uncertainty. The histogram below shows the individual uncertainty contributions and their minimisation potentials.

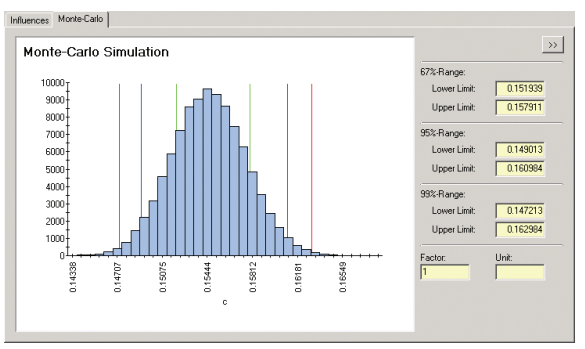

Figure 7. Uncertainty distribution of the analytical result after uncertainty calculation using the Monte Carlo Simulation method. Dependent on the analytical procedure in question and its working range different and often non-Gaussian uncertainty distributions result.

SPECIAL PROPERTIES

Use with existing methods and in method development

The software can be used for determining the measurement uncertainty of analytical results generated by existing methods and for the simulation and minimizing of measurement uncertainty when developing new methods. The minimizing potential of each individual influencing factor on uncertainty can be displayed; this is an important aid in method development. In addition, the system can simulate the robustness with respect to each influencing parameter.

Time saving

Compared to the manual calculation of overall measurement uncertainty, which is extremely time-consuming, the program performs the calculations in very short time.

FOR WHICH ANALYTICAL METHODS CAN MEASUREMENT UNCERTAINTY BE CALCULATED?

UncertaintyManager® version 2.0 contains the calculating modules and the database for the analytical techniques HPLC, GC / GC-MS, ICP-OES and titration.

Numerous modules for organic and inorganic sample preparation techniques are also included. Modules for further analytical techniques are under development.

CONCLUSION

Determination of measurement uncertainty according to ISO/IEC/EC guidelines is both complex and time-consuming if carried out manually. UncertaintyManager® is a new software tool for the determination of measurement uncertainty in the analytical laboratory. Numerous software functions enable the user to determine the measurement uncertainty of his analytical results with the minimum of effort and time.

Literature references

1. S.L.R. Ellison, M. Rösslein. A. Williams, Eurachem/Citac Guide „Quantifying Uncertainty in Analytical Measurement", 2nd edition (2000). Free of charge Download: http://www.measurementuncertainty.org/mu/guide.

2. "Guide to the Expression of Uncertainty in Measurement" ISO, Geneva (1993) ISBN 92-67-10188-9. www.uncertaintymanager.com