

# Calculation of Measurement Uncertainty

## An Example for Titration

Measurement results must encompass statistic evaluation and uncertainty estimation to **comply with quality standards** and to be complete. Strictly speaking, the result of a chemical analysis is meaningless without an indication of the uncertainty involved in its measurement. A realistic estimate of measurement uncertainty is therefore crucial for achieving analytical quality in the laboratory.

This text explains how this parameter is estimated for a typical titration. The example chosen was the determination of the concentration of a freshly prepared solution of sodium hydroxide using potassium hydrogen phthalate as the primary standard.

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# 1. Introduction

Many important decisions are nowadays based on the results of chemical analyses. For example, the results are used to determine the yield in production processes, to check materials with regard to specifications (i.e. quality control QC), or to evaluate compliance with a statutory limit. Such decisions often involve large sums of money. This applies especially to **pharmaceutical, food & beverage, cosmetic and chemical** companies due to tight regulations. However, other industries are concerned as well.

For this reason, laboratories that supply such analytical chemical results must be able to ensure that they provide adequate quality assurance measures. These measures include validated analytical procedures, internal quality assurance procedures, participation in interlaboratory comparison, accreditation according to ISO/IEC/EN 17025 (2005), the medical technical field ISO 15189 (2007–2008) and the traceability of measurement results.

The aim of all these activities is to document the quality of the analytical results by providing a value for their trustworthiness and reliability. A very useful and widely accepted concept is the uncertainty of measurement (measurement uncertainty or simply uncertainty). This is defined as a parameter associated with the result of a measurement, which characterizes the range of values within which the quantity being measured (the measurand) is expected to lie with a stated level of confidence.

Although measurement uncertainty has long been recognized as a concept in analytical chemistry, it was the publication of the "Guide to the Expression of Uncertainty in Measurement (GUM)" [1] in 1993, which first formally established general rules for evaluating and expressing uncertainty in measurement.

Another seven years passed before the Eurachem/CITAC Guide entitled "Quantifying Uncertainty in Analytical Measurement (QUAM)" [2] appeared with procedures of a more practical nature and more suitable for analytical chemistry.



The following text describes how this concept is applied in practice using a commonly performed titration as an example.

## 2. The Four Main Steps

The procedure for calculating the measurement uncertainty of results determined in a chemical analysis consists of the following four steps:

- Step 1: Specifying the measurand
- Step 2: Identifying all the relevant sources of uncertainty
- Step 3: Quantifying the different uncertainty components
- Step 4: Calculating the combined measurement uncertainty

The implementation of these four steps in practice for a titration is shown for the determination of the concentration of a freshly prepared CO<sub>2</sub>-free solution of sodium hydroxide (NaOH) using potassium hydrogen phthalate (KHP) as the primary standard. The NaOH concentration is about 0.1 mol/L. This is calculated from the consumption up to the equivalence point of the potentiometric titration curve.

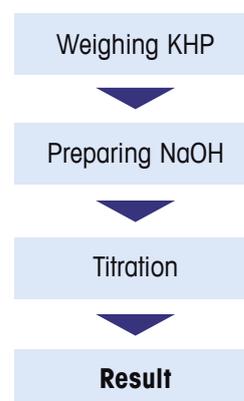
### 2.1 Step 1 – Specifying the Measurand

The aim of this first step is to describe the titration procedure as it is performed in the laboratory. This information is already available in part in standard operating procedures (SOPs). They describe the individual steps of the analytical procedures and the equation of the measurand with all variables and parameters from which it directly depends, such as the consumption of NaOH up to the equivalence point.

#### Titration procedure

The titration procedure consists of the following stages (Fig. 1):

1. The KHP is dried according to the instructions of the supplier and a sample weighed out on an analytical balance with a resolution of 0.1 mg.
2. A fresh solution of approximately 0.1 mol/L NaOH is prepared, taking all measures necessary to ensure that the solution is free of CO<sub>2</sub>.
3. The weighed sample of KHP is dissolved in about 50 mL deionized water and then titrated with the NaOH solution. The consumption of sodium hydroxide is determined up to the equivalence point of the potentiometric titration curve recorded by the titrator.



#### Equation of the measurand

The equation of the measurand corresponding to the concentration of a freshly prepared sodium hydroxide solution is as follows:

$$C_{\text{NaOH}} = 10 \cdot p_{\text{KHP}} \cdot m_{\text{KHP}} / \text{VEQ} \cdot M_{\text{KHP}}$$

$C_{\text{NaOH}}$ :	Measurand: concentration of the sodium hydroxide (NaOH)	→ mol/L
$p_{\text{KHP}}$ :	Purity of the KHP standard [3]	→ %
$m_{\text{KHP}}$ :	Sample mass of the KHP standard	→ g
VEQ:	Consumption of NaOH up to the equivalence point	→ mL
$M_{\text{KHP}}$ :	Molar mass of the KHP standard	→ g/mol

Figure 1: The different stages of the titration procedure.

## 2.2 Step 2 – Identifying all the Relevant Sources of Uncertainty

The aim of the second step is to identify all the major sources of uncertainty and to understand their effect on the uncertainty of measurement of the measurand. This has been shown to be one of the most difficult steps in evaluating the uncertainty of a measurement result. On the one hand, there is a risk of neglecting important sources of uncertainty and on the other hand of double-counting other influences. The use of a cause and effect diagram is a good way to avoid this. It has proven itself in practice. The first step in preparing the diagram is to draw the four parameters of the equation of the measurand as the main branches.

Afterward, each step of the analytical procedure is examined more closely and any further influence factors on a parameter or the measurand are entered in the diagram. This is carried out working outward along each branch until the influences are so unimportant that their effect on the result and its uncertainty are negligible<sup>[4]</sup> (Fig. 3).

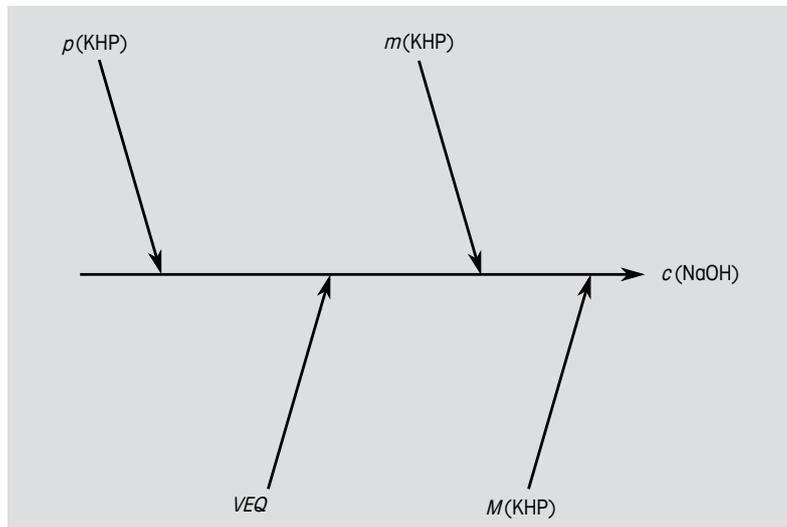


Figure 2: Cause and effect diagram with the four main branches: purity, sample mass and molar mass of the KHP standard, and the consumption of NaOH up to the equivalence point.

### Purity of the KHP primary standard ( $\rho_{\text{KHP}}$ )

The purity of the KHP primary standard is quoted in the supplier's catalog to be within the limits of 99.9% and 100.1%. There are no further sources of uncertainty if the primary standard is dried according to the supplier's specifications.

### Sample mass of the primary standard KHP ( $m_{\text{KHP}}$ )

The mass of the KHP standard is determined by difference weighing. The empty beaker is first placed on the balance to determine its tare weight. The primary standard is then added to the beaker and then the gross weight measured. For both these measurements, the possible difference between the mass recorded by the balance and the actual mass on the balance pan must be taken into account as a source of uncertainty.

This difference is called the linearity by the manufacturer. For the difference weighing only one repeatability can be determined. These three influence factors are entered as sources of uncertainty in the cause and effect diagram.

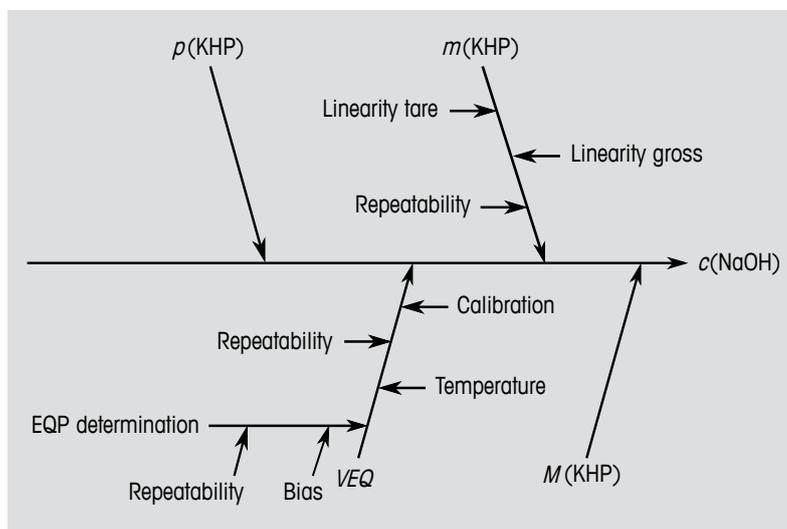


Figure 3: Cause and effect diagram showing all the relevant sources of uncertainty.

## Molar mass of the KHP primary standard ( $M_{\text{KHP}}$ )

The uncertainty in the molar mass of KHP can be determined by combining the uncertainty in the atomic masses of its constituent elements. This uncertainty contribution is negligible in comparison to all other sources of uncertainty and will not be further discussed.<sup>[5]</sup>

## Consumption of NaOH up to the equivalence point (VEQ)

The sources of uncertainty for the consumption of NaOH up to the equivalence point can be divided into two groups.

The first group comprises the influence factors that have to do with the volumetric addition of the NaOH solution. It includes the calibration of the piston burette, the repeatability of the delivered volume and the influence of the difference between the temperature in the laboratory and the temperature at which the piston burette was calibrated.

The second group has to do with the possibility of a systematic difference or bias in the determination of the equivalence point by the titrator and its repeatability.

## Combining the individual repeatability contributions

Finally, the cause and effect diagram is examined to identify influence factors that can be combined to a new source of uncertainty. In this example, there are only the repeatability contributions of the different parameters. The contributions are combined to one repeatability contribution for the overall titration and entered as a new main branch in the diagram (Fig. 4).

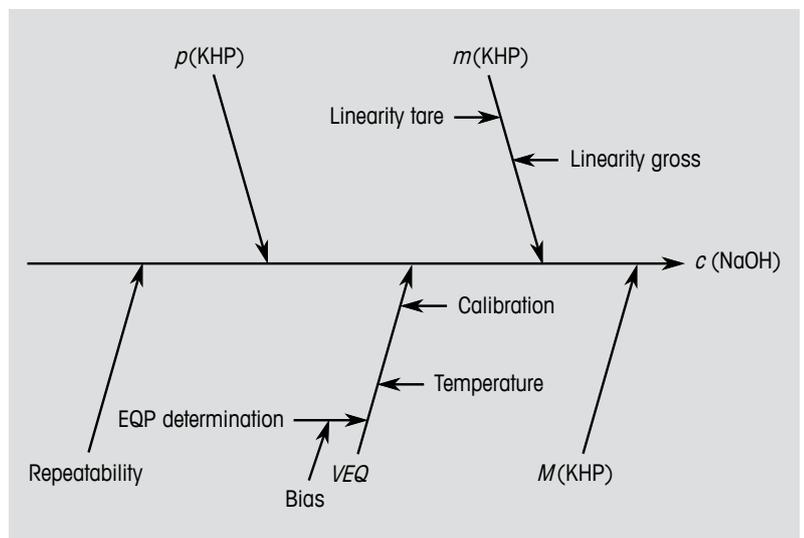


Figure 4: Cause and effect diagram after combining all the repeatability contributions to the variation of the overall titration procedure.

## 2.3 Step 3 – Quantifying the Different Sources of Uncertainty

In step 3 of the calculation of the measurement uncertainty, each individual source of uncertainty entered in the cause and error diagram is quantified and converted to a standard deviation.

### Repeatability of titration (rep)

The contribution for the repeatability of the titration is usually examined in detail when the analytical procedure is developed and is determined when the procedure is validated. In this example, it amounts to 0.12%.

$$\text{rep} = 0.12\%$$

### Purity of the KHP standard ( $p_{\text{KHP}}$ )

The supplier of the KHP quotes the purity of the standard after drying as  $100\% \pm 0.1\%$ . Since no further details are given by the supplier, the purity distribution is best described by a rectangular distribution. The standard deviation is given by:

$$\begin{aligned} u(p_{\text{KHP}}) &= 0.1\% / \sqrt{3} \\ &= 0.058\% \end{aligned}$$

### Sample mass of the KHP standard ( $m_{\text{KHP}}$ )

The calibration certificate of the XP205DR analytical balance used in these experiments quotes a linearity of 0.15 mg over the entire weighing range. This source of uncertainty is best modeled using a rectangular distribution function. The standard uncertainty contribution for the sample mass of the KHP is made up of the standard deviations for the linearity of the two weighing operations, one for the empty beaker (tare) and one for the beaker plus the standard (gross).

$$\begin{aligned} u(m_{\text{KHP}}) &= \sqrt{(0.15 \text{ mg} / \sqrt{3})^2 + (0.15 \text{ mg} / \sqrt{3})^2} \\ &= 0.012 \text{ mg} \end{aligned}$$

### Consumption of NaOH up to the equivalence point (VEQ)

The uncertainty of the consumption of NaOH is made up of the following contributions:

#### a) Calibration

The limits of accuracy for a delivered volume of water from a 20-mL burette is  $\pm 0.04$  mL over the entire working range. Since the accuracy of piston burettes is continuously monitored in production, a triangular distribution is recommended.

The standard deviation is then calculated as follows:

$$\begin{aligned} u(\text{VEQ}_{\text{cal}}) &= 0.04 \text{ mL} / \sqrt{6} \\ &= 0.016 \text{ mL} \end{aligned}$$

## b) Temperature

The international standard is to quote the calibration of volume measuring equipment at 20 °C. Since the temperature in the laboratory is usually not 20 °C when titration is performed, the uncertainty due to difference in temperature between that in the laboratory and the calibration temperature must be taken into account. The formula only takes the volume expansion of the liquid (aqueous solution) into account because this is much greater than the expansion of solids:

$$\begin{aligned}u(\text{VEQ}_{\text{Temp}}) &= 19 \text{ mL} \cdot 2.1 \cdot 10^{-4} \text{ }^{\circ}\text{C}^{-1} \cdot 3 \text{ }^{\circ}\text{C} / \sqrt{3} \\ &= 0.007 \text{ mL}\end{aligned}$$

## c) Bias

The titration is performed in the beaker under a layer of a protective gas such as argon in order to exclude any bias due to the absorption of CO<sub>2</sub> by solutions. The principle here is that it is better to prevent bias rather than to correct for a bias.

In addition, quality assurance measures such as regular maintenance and the checking of pH sensors ensure that the titration is performed according to the criteria specified in the validation and hence without bias.

Finally, the two standard uncertainties for the calibration and the temperature difference are combined according to the principles of uncertainty propagation.

$$\begin{aligned}u(\text{VEQ}) &= \sqrt{u(\text{VEQ}_{\text{Cal}})^2 + u(\text{VEQ}_{\text{Temp}})^2} = \sqrt{(0.016 \text{ mL})^2 + (0.007 \text{ mL})^2} \\ &= 0.017 \text{ mL}\end{aligned}$$

## 2.4 Step 4 – Calculating Measurement Uncertainty

For the final calculation of the measurement uncertainty, it is advisable to first summarize the different parameters of the equation of the measurand in a table (Table 1):

The concentration of NaOH (measurand) is calculated using the values from the table:

$$\begin{aligned} c_{\text{NaOH}} &= 10 \cdot p_{\text{KHP}} \cdot m_{\text{KHP}} / M_{\text{KHP}} \cdot \text{VEQ} \\ &= 10 \cdot 100 \cdot 0.3888 / 204.2122 \cdot 18.64 \\ &= 0.10214 \text{ mol/L} \end{aligned}$$

The combined uncertainty for this value is then calculated using the principles of uncertainty propagation (see Formula 1). The percentage contributions of the different parameters of the equation of the measurand to the combined uncertainty are shown in Figure 5. The diagram also shows which contributions are greatest and hence indicates where the titration procedure could be improved.

To compare the result of a titration with another result or to check the compliance against a limit, the expanded measurement uncertainty is usually calculated in addition to the combined standard uncertainty.

This is done by multiplying the combined uncertainty by a coverage factor of 2 ( $k=2$ ), in which case the confidence interval [6] is then 95.5 %.

$$\begin{aligned} u_c(c_{\text{NaOH}}) &= c_{\text{NaOH}} \cdot 1.61 \cdot 10^{-3} \\ &= 0.10214 \text{ mol/L} \cdot 1.61 \cdot 10^{-3} \\ &= 1.644 \cdot 10^{-4} \text{ mol/L} \end{aligned}$$

Parameter	Description	Value	u(x)	u(x)/x
rep	Repeatability	1.0	0.12%	0.0012
$p_{\text{KHP}}$	Purity KHP	100.0%	0.058%	0.00058
$m_{\text{KHP}}$	Sample mass KHP	0.3888 g	0.000012 g	0.000031
$M_{\text{KHP}}$	Molar mass KHP	204.2122 g/mol	0.0038 g/mol	0.000019
VEQ	Consumption NaOH	18.64 mL	0.017 mL	0.00091

Table 1: The parameters of the equation of the measurand.

### Combined uncertainty

Formula:

$$\frac{u(c_{\text{NaOH}})}{c_{\text{NaOH}}} = \sqrt{\text{rep}^2 + \left(\frac{u(p_{\text{KHP}})}{p_{\text{KHP}}}\right)^2 + \left(\frac{u(m_{\text{KHP}})}{m_{\text{KHP}}}\right)^2 + \left(\frac{u(M_{\text{KHP}})}{M_{\text{KHP}}}\right)^2 + \left(\frac{u(\text{VEQ})}{\text{VEQ}}\right)^2}$$

Result:

$$\begin{aligned} \frac{u(c_{\text{NaOH}})}{c_{\text{NaOH}}} &= \sqrt{0.0012^2 + 0.00058^2 + 0.000031^2 + 0.000019^2 + 0.00091^2} \\ &= 0.00161 = 1.61 \cdot 10^{-3} \end{aligned}$$

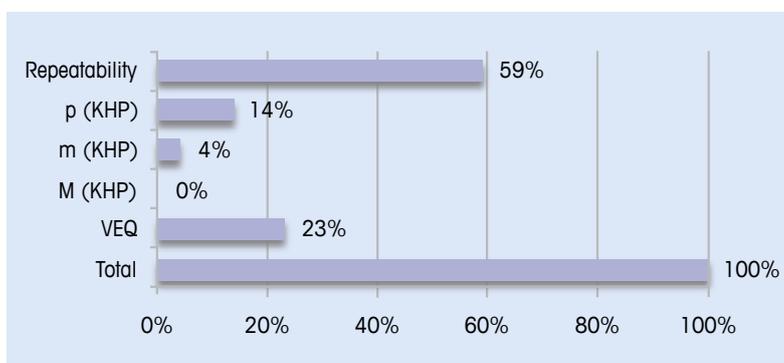


Figure 5: Percentage contributions of the individual parameters of the equation of the measurand to the combined measurement uncertainty.

### Expanded uncertainty

Valid for confidence interval of 95.5 %:

Formula:

$$U(c_{\text{NaOH}}) = k \cdot u_c$$

Result:

$$U(c_{\text{NaOH}}) = 2 \cdot 1.644 \cdot 10^{-4} \text{ mol/L}$$

$$= 3.29 \cdot 10^{-4} \text{ mol/L}$$

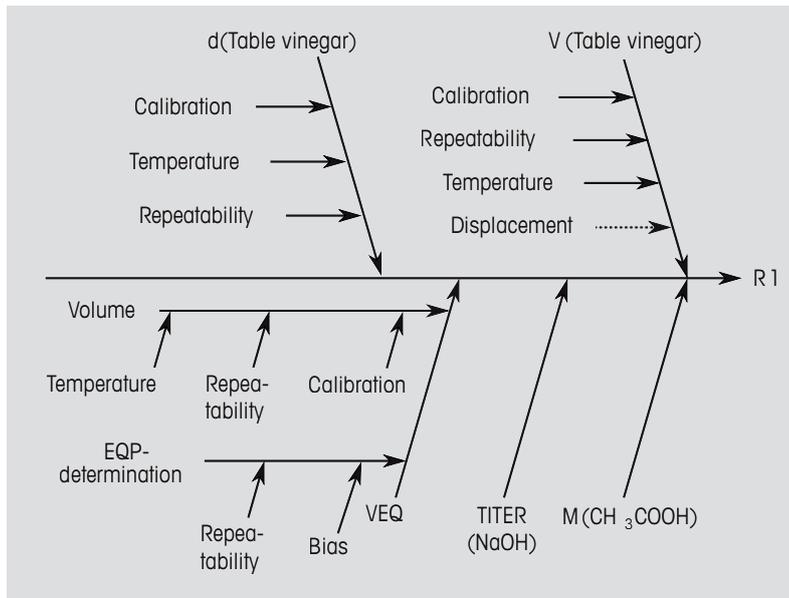


Figure 6: Cause and effect diagram of acidity determination in vinegar

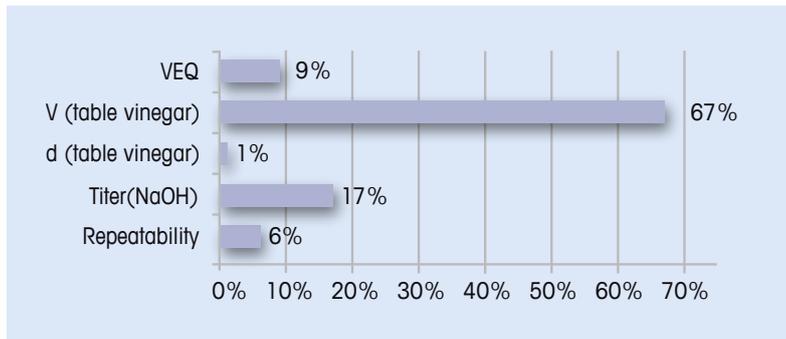


Figure 7: Acidity determination in vinegar: Assessment of all uncertainty factors

Figure 8: Example of a modern autotitrator with color touch screen, 3 burettes for titration and dispensing, overhead propeller stirrer and electrode: Titration Excellence T70



### 3. Conclusions

To evaluate the titration results, the measurement uncertainty and thus the confidence interval must be known. Only when this information is available can one decide whether the titration results obtained in another laboratory for the same samples lead to the same conclusions.

#### Evaluating the titration results

For this reason, calculation of measurement uncertainty is of the utmost importance in many widely different fields of analytical chemistry ranging from production control to forensic investigations:

- Laboratories in the food and beverage industry
- Laboratories in pharmaceutical chemistry
- Medical analytical laboratories
- Forensic laboratories
- Laboratories for doping analysis
- and many others

Furthermore, laboratories that are accredited according to ISO/IEC/EN/DIN 17025 (2005) must be able to estimate measurement uncertainties for all their analytical procedures.

This introductory example of a titration illustrates how the measurement uncertainty of a titration result is estimated. It serves as a simple introduction and by no means covers this extremely wide and dynamic topic. The aim was rather to present some basic concepts and explain important points using a practical titration procedure as an example. For this reason, the article makes no reference to important matters such as the influence of sampling or sample preparation, nor does it mention more complex titration methods such as back titration.

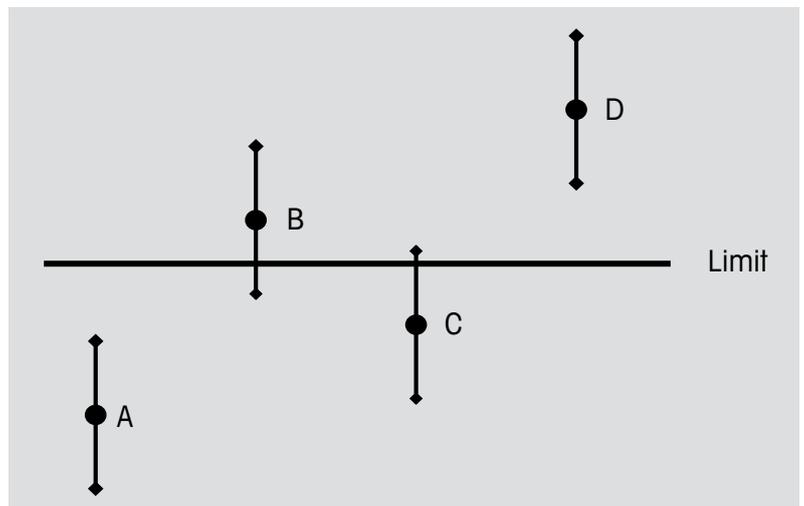
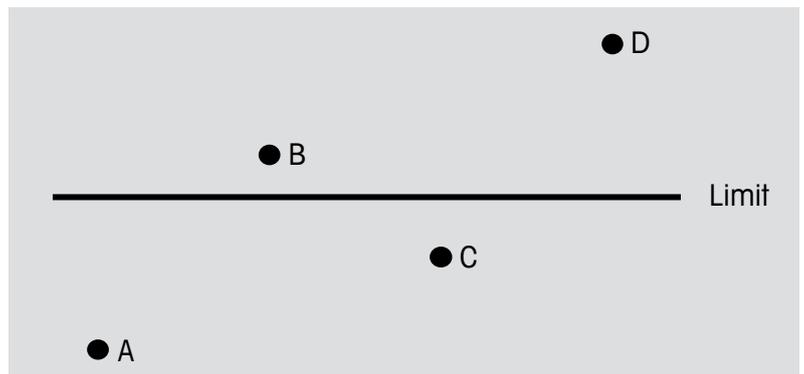


Figure 9: The measurement uncertainty enables one to evaluate the titration results. Result A is clearly below and Result D clearly above the limit. Results B and C are unclear and require individual evaluation.

## 4. Further Information

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## 5. References and Notes

- [1] Evaluation of measurement data – Guide to the Expression of Uncertainty in Measurement (GUM); JCGM 100:2008 (GUM 1993 & 95 with minor corrections) <http://www.bipm.org/en/publications/guides/gum.html>
- [2] Eurachem/CITAC Guide CG 4: "Quantifying Uncertainty in Analytical Measurement (QUAM)" 2nd Edition, 2002; [www.measurementuncertainty.org](http://www.measurementuncertainty.org)
- [3] The purity of the potassium hydrogen phthalate refers to its functional composition as a primary standard and not to the purity of the substance as for example in HPLC. Here we mean the number of free acidic protons in relation to the overall number of molecules of KHP. Purities can therefore be >100%.
- [4] S.L.R. Ellison, V.J. Barwick – Accred. Qual. Assur. 3, 101–105 1998
- [5] A detailed discussion of the calculation of the combined standard uncertainty for the molar mass of a primary standard can be found in the second example of the QUAM publication.
- [6] 95.45% of all measured values of a normal distribution (Gaussian) are found within the interval of  $\pm 2s$  from the mean value. ( $s$  = standard deviation)

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