Water Technologies & Solutions
application note

understanding uncertainty of certified reference materials

purpose

Many companies require a risk evaluation so proactive measures may be taken to mitigate known risks and prevent adverse events. In pharmaceutical and semiconductor industries, where accurate measurements are critical, understanding and evaluating risk factors of a process or product line is an important part of the business plan and quality management system.

SUEZ, with its Sievers* product line of analytical instruments and consumables, recognizes the contribution that instrumentation and reference materials can have on a process risk assessment. The measurement uncertainty of Sievers products has been well-characterized to provide end-users with a comprehensive assessment of how these products fit into a larger risk evaluation. This document provides details on the determination of Sievers certified reference materials' uncertainty and how it complies with the International Organization for Standardization's (ISO) document 17034, General Requirements for the Competence of Reference Material Producers.

overview

Uncertainty represents a possible range of values in which a measurement result will lie; it can be thought of as a quantified indication of doubt of a measured value. Understanding uncertainty and how it fits into an overall quality management system is integral to ensuring appropriate risk management and decision making.

When reporting a measured value of a sample, such as Total Organic Carbon (TOC), it is critical to have a high degree of confidence in the quality and reliability of the reported measurement. It is important to understand the uncertainty of a measurement system and the parameters that contribute to it. Two major factors that can contribute to the overall uncertainty of a measurement include:

- the uncertainty of the measuring instrument
- the uncertainty of the certified reference material used to calibrate or verify that instrument.

The uncertainty of the instrument can be based on several factors such as the resolution of the instrument, maintenance of the instrument, and other environmental conditions[1]. For reference materials, it is important to understand the material's associated uncertainty, what uncertainty means with respect to the certified value, and how to interpret its effect on the application for which the material is being used. Understanding a reference material's uncertainty is important when evaluating the potential range of results and how that range can affect the process or product being measured.

When evaluating different vendors for certified reference materials, understanding how to interpret the information on the vendors' certificates is important to ensure internal and regulatory requirements are met. The uncertainty stated on the certificate of analysis of a certified reference material should not be used as the acceptance criteria for the material. When establishing acceptance criteria, it is important to consider both the uncertainty of the reference material as well as any bias or uncertainty that comes from the instrument performing the measurement. The stated uncertainty of a reference material is specific to the factors that contribute to

possible error in the certified value of the material itself.

The following sections walk through the five terms required by the ISO 17034 standard that make up the overall uncertainty shown on certificates of analysis for accredited certified reference materials. The stated uncertainties of several reference material vendors are compared with respect to ISO 17034 requirements. This discussion focuses on TOC, but the same principles apply for any certified attribute, including conductivity.

uncertainty factors

ISO 17034 is the international standard that defines the requirements for certified reference materials, including the overall uncertainty (U_{CRM}). This ISO document dictates five terms that must be included in each certified reference material's uncertainty calculation[2]:

$$U_{CRM} = k * \sqrt{u_{lts}{}^2 + u_{sts}{}^2 + u_{hom}{}^2 + u_{char}{}^2}$$

- u_{lts} is the variability from long term stability.
- u_{sts} is the variability from short term stability.
- u_{hom} is the variability from the homogeneity of the batch of material.
- u_{char} is the variability from the preparation of the material.
- k is the coverage factor.

long-term stability

Uncertainty due to long term stability, u_{lts}, describes the change in TOC throughout the shelf life of the standard. TOC standards can change over time, so it is important to quantify this instability as the same lot of standard can report different results at different times throughout the shelf life. Generally, this has been found to be the most significant contributor to the overall uncertainty. Factors that contribute to the stability of the TOC standard include the stability of the chemical, the preservatives used (if any), and the storage condition of the standard.

short-term stability

Uncertainty due to short term stability, u_{sts}, describes the change in TOC during transport. TOC standards can change when exposed to different storage conditions such as varying temperature or light exposure, so uncertainty associated with these short-term changes must be considered. Often, this term can be neglected if the vendor provides a proper transport condition.[3]

homogeneity

The uncertainty term u_{hom} describes the homogeneity of the lot, which is the variation within a single batch.[4] To calculate u_{hom}, there are two factors that must be considered: the "within-bottle" variability (u_{wb}) and the "bottle-to-bottle" variability (u_{bb}).[4] For TOC standards, there is always some variability between individual vials within a batch (u_{bb}) and within a single sample (u_{wb}), thus it must be accounted for and quantified. Factors that contribute to the homogeneity of a TOC standard include cleanliness of the containers used to store the TOC standard, the cleanliness of the production area, and the overall robustness of the production process to ensure homogeneity of the solution. Homogeneity can be a significant factor to the overall uncertainty depending on the quality of the product.

characterization

Characterization uncertainty, u_{char}, describes the uncertainty associated with the process of assigning the certified value of the reference material. For TOC standards, this equates to the uncertainty of the preparation process. Factors that contribute to u_{char} include the uncertainty of the equipment and raw material used, skills of the technician, and the quality and consistency of the overall manufacturing process. Generally, u_{char} is a smaller factor of the overall uncertainty as certified reference material providers put in significant effort to train highly skilled operators, maintain high-quality equipment, and have well-defined processes. Common manufacturing processes for producing TOC standards use calibrated balances and glassware. The uncertainty of high-quality glassware per ISO 4787 or ASTM E438 tends to be between 0.1% and 1%.[5] For a typical TOC standard manufacturing process, u_{char} can be estimated to be in the range of 0.5% of the expected value, assuming that a calibrated balance is used and the technicians are well trained.

coverage factor

The coverage factor, k, provides a level of confidence to the reported overall uncertainty. This coverage factor defines the range within which a percentage of

the standards are likely to fall. The coverage factor used for certified reference materials is determined by the vendor based on the desired level of confidence the vendor wants to provide. A smaller coverage factor will result in a smaller stated uncertainty but also reduces the level of confidence that the actual uncertainty of the standard will fall within the range stated on the certificate of analysis. A k factor of 2 is commonly used to provide a level of confidence of approximately 95%.[4]

vendor comparison

A comparative study was performed to evaluate stated uncertainties with actual test results for multiple reference standard vendors. As shown in **Table 1**, SUEZ and Vendor A have comparable uncertainties reported on their certificates of analysis. Vendor B's reported uncertainty is significantly lower, suggesting the factors they use in their uncertainty calculation differ from those used by the other vendors and may not fully comply with ISO 17034 requirements.

Table 1. Reported uncertainties for two certified products from various vendors. Uncertainties shown are from sample Certificates of Analysis from each vendor.

Reported Uncertainty	SUEZ	Vendor A	Vendor B
500 ppb USP Sucrose	3.4%	4.54%	0.69%
500 ppb USP Benzoquinone	1.8%	2.64%	0.69%

Data collected in the comparative study suggest the actual uncertainties for the two certified products from Vendor B are roughly 3 times higher than the stated uncertainty, when using a coverage factor of 2 as stated on the products' certificates of analysis. The measured uncertainty for long-term stability (u_{lts}) alone was higher than the overall uncertainty reported on Vendor B's certificate.

Critical processes must have well-defined and well-understood bounds to ensure control of product within those bounds. Processes using materials with poorly defined uncertainties could increase process risk, leading to costly excursions.

summary

The uncertainties associated with certified reference materials are an important factor to include in an overall assessment of a process's potential uncertainty and must be considered in a company's risk management evaluation. Sievers certified reference materials are rigorously tested and characterized, allowing them to be accredited to ISO 17034.

SUEZ is dedicated to providing the highest quality products that meet global regulations and the needs of customers across industries. Our technical staff can help analyze and explain how Sievers products' uncertainties fit into your business requirements, so you can operate efficiently and with high confidence. In the event of an out-of-specification occurrence, a Sievers Failure Analysis Report is available to help close out an investigation quickly and with less liability. From instrumentation and certified reference materials to quality and technical support, SUEZ offers a total solution to ensure success and minimize risks.

References

1. Joint Committee for Guides in Metrology. (2008, September). Evaluation of Measurement Data-Guide to the Expression of Uncertainty in Measurement.
2. International Organization for Standardization. (2016). ISO 17034: 2016-General Requirements for the Competence of Reference Material Producers.
3. Lensinger, T. P., Van der Veen, A. M., & Lamberty, A. (2001). Uncertainty Calculation in the Certification of Reference Materials 3. Stability Study. Accreditation and Quality Assurance, 257-263.
4. International Organization for Standardization. (2017). Guide 35-Reference Materials-Guidance for characterization and assessment of homogeneity and stability. Geneva, Switzerland.
5. American Society for Testing and Material. (2018). ASTM E438-Standard Specification for Glasses in Laboratory Apparatus. Conshohocken, PA, USA.