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Smernica za validacijo fizikalno-kemijskih analiznih metod

Guideline for the validation of physico-chemical analytical methods

Anleitung zur Validierung physikalisch-chemischer Analysenverfahren

Lignes directrices pour la validation des méthodes d'analyse physico-chimiques

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Anleitung zur Validierung physikalisch-chemischer Analysenverfahren

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
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European foreword

This document (CEN/TS 16800:2015) has been prepared by Technical Committee CEN/TC 230 “Water analysis”, the secretariat of which is held by DIN.

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Introduction

Environmental monitoring of chemical substances is increasingly carried out within a European framework, and there is concern about the comparability of data at the European level. In particular methods used for the monitoring of substances with recent interest have often not been properly validated either in-house (i.e. within a single laboratory) or at the international level.

These issues may be addressed by adopting a harmonized approach towards method development and validation. The main objective of this document is to provide a common European approach to the validation of chemical methods for the respective monitoring of chemical substances in a broad range of matrices. Although the development of this approach was triggered by the needs for monitoring of emerging pollutants, it is of general nature and can be applied to the measurement of a wide range of substances in a variety of matrices.

This guidance takes into account the different requirements for the level of method maturity and validation at different stages of the investigation or regulation of chemical substances.

In the case of a specific monitoring task, this protocol will guide the user through the following steps:

— classification of existing methods with respect to their status of validation, and the selection of the appropriate validation approach;

— development of a method so as to extend its application; for example, if a method for determining a required target compound in a particular matrix is available, but is not suitable for the same compound in a different matrix of interest;

— the validation procedures to be carried out in order to effectively demonstrate the validation status of a selected method according to the two approaches adopted.

Many (national and international) standards currently contain in their scope a statement like “this method is applicable from a concentration level of xx µg/l or yy mg/kg dry matter”, without any statement how this concentration level was established. When the limit of quantification (LOQ) is evaluated using the procedure of this Technical Specification, there is a possibility that it does not meet the lower limit of the claimed range.

1 Scope

This Technical Specification describes an approach for the validation of physico-chemical analytical methods for environmental matrices.

The guidance in this document addresses two different validation approaches, in increasing order of complexity. These are:

a) method development and validation at the level of single laboratories (intra-laboratory validation);

b) method validation at the level of several laboratories (between-laboratory or inter-laboratory validation), with a focus on methods that are sufficiently mature and robust to be applied not only by a few expert laboratories but by laboratories operating at the routine level.

The concept of these two approaches is strictly hierarchical, i.e. a method shall fulfil all criteria of the first level before it can enter the validation protocol of the second level.

This Technical Specification is applicable to the validation of a broad range of quantitative physico-chemical analytical methods for the analysis of water (including surface water, groundwater, waste water, and sediment). Analytical methods for other environmental matrices, like soil, sludge, waste, and biota can be validated in the same way. It is intended either for analytical methods aiming at substances that have recently become of interest or for test methods applying recently developed technologies.

The minimal requirements that are indispensable for the characterization of the fitness for purpose of an analytical method are: selectivity, precision, bias and measurement uncertainty. The aim of validation is to prove that these requirements are met.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 78-2, *Chemistry — Layouts for standards — Part 2: Methods of chemical analysis*

ISO 5725, *Chemistry — Layouts for standards — Part 2: Methods of chemical analysis*

ISO 11352:2012, *Water quality — Estimation of measurement uncertainty based on validation and quality control data*

ISO 21748:2010, *Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation*

ISO/IEC Guide 99:2007, *International vocabulary of metrology — Basic and general concepts and associated terms (VIM)*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO/IEC Guide 99:2007 (VIM) and the following apply.

3.1
accepted reference value
value that serves as an agreed-upon reference for comparison, and which is derived as:

a) a theoretical or established value, based on scientific principles;

b) an assigned or certified value, based on experimental work of some national or international organization;

c) a consensus or certified value, based on collaborative experimental work under the auspices of a scientific or engineering group;

d) when a), b) and c) are not available, the expectation of the (measurable) quantity, i.e. the mean of a specified population of measurements

[SOURCE: ISO 3534-2:2006, definition 3.2.7]

3.2
accuracy
closeness of agreement between a test result and the accepted reference value

[SOURCE: ISO 3534-2:2006, definition 3.3.1]

Note 1 to entry: The term accuracy, when applied to a set of test results, involves a combination of random components (usually expressed by a precision measure) and a common systematic error or bias component (usually expressed by a measure for trueness).

Note 2 to entry: The technical term "accuracy" should not be confused with the term ‘trueness’ (see definition of "trueness").

3.3
analyte
substance to be analysed (chemical species or physical parameter)

Note 1 to entry: The quantity of an analyte is the measurand (3.15).

3.4
bias
difference between the expectation of a test result or measurement result and a true value

Note 1 to entry: Bias is the total systematic error as contrasted to random error. There may be one or more systematic error components contributing to the bias. A larger systematic difference from the accepted reference value is reflected by a larger bias value.

Note 2 to entry: The bias of a measuring instrument is normally estimated by averaging the error of indication over an appropriate number of repeated measurements. The error of indication is the: "indication of a measuring instrument minus a true value of the corresponding input quantity".

Note 3 to entry: In practice, accepted reference value is substituted for the true value.

[SOURCE: ISO 3534-2:2006, definition 3.3.2]

3.5
blank
sample or test scheme without the analyte known to produce the measured signal

Note 1 to entry: Use of various types of blanks enable assessment of which proportion of the measured signal is attributable to the measurand and which proportion to other causes. Various types of blank are available (see definition of reagent blank and blank sample).

3.6
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication

Note 1 to entry: A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty.

Note 2 to entry: Calibration should not be confused with adjustment of a measuring system, often mistakenly called "self-calibration", nor with verification of calibration.

[SOURCE: ISO/IEC Guide 99:2007, definition 2.39]

3.7
certified reference material
CRM
reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures

[SOURCE: ISO/IEC Guide 99:2007, definition 5.14]

3.8
fitness for purpose
degree to which data produced by a measurement process enables a user to make technically and administratively correct decisions for a stated purpose

3.9
intermediate precision
precision under intermediate precision conditions

[SOURCE: ISO 3534-2:2006, definition 3.3.15]

3.10
intermediate precision conditions
conditions where test results or measurement results are obtained with the same method, on identical test/measurement items in the same test or measurement facility, under some different operating conditions

Note 1 to entry: There are four elements to the operating condition: time, calibration, operator and equipment.

[SOURCE: ISO 3534-2:2006, definition 3.3.16 and ISO 11352:2012, definition 3.10]

3.11
limit of detection
measured quantity value, obtained by a given measurement procedure, for which the probability of falsely claiming the absence of a component in a material is β, given a probability α of falsely claiming its presence

Note 1 to entry: IUPAC recommends default values for α and β equal to 0,05.

Note 2 to entry: The abbreviation LOD is sometimes used.

Note 3 to entry: The term “sensitivity” is discouraged for ‘detection limit’.

[SOURCE: ISO/IEC Guide 99:2007, definition 4.18]

Note 4 to entry: The LOD is the lowest concentration of measurand in a sample that can be detected, but not necessarily quantitated under the stated conditions of the test.

3.12
limit of quantitation
lowest concentration of a measurand that can be determined with acceptable precision under the stated conditions of the test

3.13
reporting limit
specific concentration at or above the limit of quantification that is reported to the client with a certain degree of confidence

Note 1 to entry: The reporting limit is often defined on a project-specific basis. If the reporting limit is set below the limit of quantification by the client, method modification is required.

[SOURCE: ISO/TS 13530:2009, 4.4.7]

3.14
linearity
ability of the method to obtain test results proportional to the concentration of measurand

Note 1 to entry: The linear range is by inference the range of measurand concentrations over which the method gives test results proportional to the concentration of the measurand.

[SOURCE: EURACHEM Guide]

3.15
measurand
quantity intended to be measured

Note 1 to entry: The specification of a measurand requires knowledge of the kind of quantity, description of the state of the phenomenon, body, or substance carrying the quantity, including any relevant component, and the chemical entities involved.

Note 2 to entry: In chemistry, “analyte”, or the name of a substance or compound, are terms sometimes used for “measurand”. This usage is erroneous because these terms do not refer to quantities.

[SOURCE: ISO/IEC Guide 99:2007, definition 2.3]

3.16
measurement
process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity

[SOURCE: ISO/IEC Guide 99:2007, definition 2.1]

3.17
measurement uncertainty
non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used

[SOURCE: ISO/IEC Guide 99:2007, definition 2.26].

3.18
outlier
member of a set of values which is inconsistent with the other members of that set

Note 1 to entry: ISO 5725-2 specifies the statistical tests and the significance level to be used to identify outliers in trueness and precision experiments.

[SOURCE: ISO 5725-1:1994, definition 3.21]

3.19
precision
closeness of agreement between independent test results obtained under stipulated conditions

Note 1 to entry: Precision depends only on the distribution of random errors and does not relate to the true value or the specified value.

Note 2 to entry: The measure of precision is usually expressed in terms of imprecision and computed as a standard deviation of the test results. Less precision is reflected by a larger standard deviation.

[SOURCE: ISO 3534-2:2006, definition 3.3.4]

Note 3 to entry: „Independent test results“ means results obtained in a manner not influenced by any previous result on the same or similar test object. Quantitative measures of precision depend critically on the stipulated conditions. Repeatability and reproducibility conditions are particular sets of extreme conditions.

3.20
proficiency testing
evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons

[SOURCE: EN ISO/IEC 17043:2010, definition 3.7]

3.21
quality assurance
part of quality management focused on providing confidence that quality requirements will be fulfilled

[SOURCE: EN ISO 9000:2015, definition 3.3.6]

Note 1 to entry: A major part of quality assurance is quality control.

3.22
quality control
part of quality management focused on fulfilling quality requirements

[SOURCE: EN ISO 9000:2015, definition 3.3.7]

3.23
quantity
property of a phenomenon, body, or substance, where the property has a magnitude that can be expressed as a number and a reference

[SOURCE: ISO/IEC Guide 99:2007, definition 1.1]

3.24
working range
interval, being experimentally established and statistically proved by the calibration of the method, between the lowest and highest quantity possibly measured by the method

Note 1 to entry: The lowest possible limit of a working range is the limit of quantification of an analytical method.

3.25
reagent blank
all reagents used during the analytical process (including solvents used for extraction or dissolution) are analysed in isolation in order to check whether they contribute to the measurement signal

Note 1 to entry: The measurement signal arising from the measurand can then be corrected accordingly.

3.26
recovery
extent to which a known, added quantity of determinant in a sample can be measured by an analytical system

Note 1 to entry: It is calculated from the difference between results obtained from spiked and unspiked aliquots of sample, and is usually expressed as a percentage.

[SOURCE: ISO 6107-8:1993/Amd 1:2001-12]

3.27
reference material
RM
material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process

[SOURCE: ISO Guide 30:2015, definition 2.1.1, modified – Notes to entry have not been included.]

3.28
repeatability
precision under repeatability conditions, i.e. conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time

[SOURCE: ISO 3534-2:2006, definition 3.3.5 and 3.3.6 , modified – These definitions were combined.]

3.29
reproducibility
precision under reproducibility conditions, i.e. conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment

[SOURCE: ISO 3534-2:2006, definition 3.3.10 and 3.3.11, modified – These definitions were combined.]

3.30
residual
difference between the observed response and that predicted by a calibration function