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Approaches for the production of reference materials with qualitative properties

Approches pour la production de matériaux de référence avec des propriétés qualitatives

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Foreword

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This document was prepared by Technical Committee ISO/TC 334, *Reference materials*.

Any feedback or questions on this document should be directed to the user’s national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

In 2015, ISO/TC 334 (formerly ISO/REMCO) published ISO/TR 79, which summarized the state of the art of the production of reference materials (RMs) with qualitative properties. The lack of an international vocabulary for terms and definitions for qualitative properties added an extra challenge in 2015 and ISO/TR 79 did not define or limit the use of the term "qualitative property". "Qualitative property" was therefore used as superordinate for nominal and ordinal properties. "Categorical properties" is a synonym for "qualitative properties". ISO/TR 79 lists examples of RMs that either have a certified value for a qualitative property or can be considered as in-house RMs characterized for a qualitative property. The examples listed are based on the principles elaborated in ISO 33405 and ISO Guide 80, but ISO/TR 79 did not undergo a consensus-building process.

For RMs, nominal properties are a particular kind of qualitative property (the other kind are ordinal properties). The identity of a polychlorinated biphenyl (PCB) and the species of a maple tree (genus *Acer*) are nominal properties where the values of the properties are the particular chemical species name or biological species name (e.g. PCB 105 and *Acer saccharinum*, respectively). The former has more than 200 possible values, the latter more than 160. The only meaningful comparison between values of a nominal property is whether they are identical or different.

Ordinal properties have values that can be ordered (i.e. ranked) from smallest to largest or from lowest to highest, but for which neither differences nor ratios are meaningful, even when their values are represented numerically.

EXAMPLE 1 Stage, as defined by the American Joint Committee on Cancer, is a property of solid tumour cancers (e.g. breast, colon or lung), whose possible values are the Roman numerals I, II, III and IV. However, one is not entitled to say either that stage IV is two times “worse” than stage II or that the difference in severity between stages III and I is the same as the difference in severity between stages IV and II.

EXAMPLE 2 The Mohs hardness of a mineral is expressed relative to a scale ranging from 1 (for talc) to 10 (for diamond) and can include half-integer values (e.g. 5 ½ for enstatite). However, fluorite (4) is not two times harder than gypsum (2), nor is the difference in hardness between topaz (8) and apatite (5) the same as the difference in hardness between quartz (7) and fluorite (4).

There are no unambiguous rules for expressing qualitative properties in various fields such as chemistry and biology. The following examples illustrate the confusion that exists. Qualitative properties can be described in different ways depending on the individual property or even on the way in which a specific property is expressed. For example, "colour" can be seen as a qualitative property of which "red" is a value. Alternatively, it has been proposed that "colour" is a general property of which "red" is an individual case. Moreover, a pure colour can be described by the corresponding wavelengths of light, with a band from 625 nm to 740 nm for red light. Hence, the qualitative property "colour" can be assigned a quantitative (or semi-quantitative) value such as 700 nm.

Qualitative value assignments can also differ according to the intended use. For example, "ethanol" may be treated as the identity of a specific compound or as an instance of a family of compounds with the general property "alcohols", which in turn can be seen as an instance of the general property "chemical species".

Seeing the progress and the increasing number of RMs characterized or certified for qualitative properties, ISO/REMCO decided in 2018 to start drafting internationally harmonized guidance for the production of such RMs.

This presents several issues with respect to terminology. The ISO Guide 30 definition of a certified reference material (CRM) requires it to have an RM certificate that provides the values of the specified properties, associated uncertainties and statements of metrological traceability. The relevance of metrological traceability to RMs with qualitative property values can, however, be unclear. Notes of the RM and CRM definitions in ISO Guide 30 clarify that the concept of value includes a qualitative property, such as identity or sequence, and that uncertainties for qualitative values can be expressed as probabilities or levels of confidence[18]. However, a qualitative property has no numerical value and at present ISO/IEC Guide 98-3 (GUM) provides no methodology for assigning an uncertainty to such property values. Metrological traceability is defined in ISO/IEC Guide 99 (VIM) as a property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations. Hence, it too is inapplicable to qualitative property values. Nevertheless, RMs with qualitative properties are needed now and are being produced in increasing numbers. In order to provide meaningful guidance on these aspects of RM production, this document:

— describes how confidence in qualitative assigned values can be expressed;

— describes the relevance of a documented unbroken chain of qualitative comparisons in assigning qualitative values by comparison with qualitative references or reference information;

— notes that determination of many qualitative properties depends on data obtained with quantitative measurements and that measurement uncertainty and metrological traceability are relevant to these measurements.

These issues are discussed in detail in 5.2.2 and 5.3.2.

General requirements, structural requirements, resource requirements and management requirements for the production of RMs are described in ISO 17034. These requirements apply to the production of RMs with qualitative properties. This document supplements ISO 17034 and related guidance on the production of RMs by providing additional guidance on the value assignment and the assessment of homogeneity, stability and commutability for RMs with qualitative properties.

Approaches for the production of reference materials with qualitative properties

1 Scope

1.1 This document notes the requirements of ISO 17034 and provides guidance on the implementation of ISO 17034 in the production of RMs having one or more assigned qualitative property values, for expressing uncertainties for qualitative property values, and for establishing traceability.

NOTE The concepts of traceability and uncertainty address characteristics similar to those addressed by the concepts of traceability and measurement uncertainty as used in the metrology of quantitative properties.

1.2 This document therefore does not describe aspects related to the production of RMs with quantitative property values.

NOTE Annex A provides examples of types of RMs within the scope of this document.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 17034, *General requirements for the competence of reference material producers*

ISO 33401, *Reference materials — Contents of certificates, labels and accompanying documentation*

ISO Guide 30, *Reference materials — Selected terms and definitions*

ISO/IEC Guide 99, *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 17034, ISO 33401, ISO Guide 30, and ISO/IEC Guide 99 apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

4 Qualitative properties

Qualitative properties, also called categorical properties, can be nominal or ordinal. A nominal property has values that divide the set of materials that have it into classes such that all the materials in the same class have the same value of the property, and the only comparison that can be made between values of the property is of whether they are identical or different. An ordinal property is similar, except that the comparisons that can be made between two values of the property are of relative rank order, i.e. whether one is lower, equal to or higher than the other. Qualitative properties can have two or more possible values. This document focuses on nominal properties.

5 Meeting technical and production requirements

5.1 Characterization

5.1.1 General considerations

5.1.1.1 As outlined in ISO 33405 and ISO/TR 79, materials can be characterized for qualitative properties such as colour, odour or shape. In some cases, the result of a qualitative characterization can be expressed as a qualitative or quantitative property value. Examples are particle shapes or colour according to the Hunter system[19]. This transforms the problem to the characterization of a quantity, which could be an operationally defined measurand. For colour especially, characterization of the absorbance or reflectance spectrum may also be considered.

5.1.1.2 Many qualitative properties are not meaningfully quantifiable, for example identity of a substance, species of an organism or gender of an animal.

5.1.1.3 Approaches to characterization for qualitative properties include:

— characterization using one or more qualitative determinations;

— characterization based on provenance (5.1.2);

— characterization using measurements of quantitative properties (5.1.3);

— characterization by a combination of methods (5.1.4).

5.1.2 Materials characterized based on provenance

5.1.2.1 An RM may be characterized based on knowledge of the origin of the material, i.e. the provenance of the material. To support characterization based on provenance, the reference material producer (RMP) should obtain documentary or other evidence of the origin of the material that shows an unbroken chain of evidence from origin to final packaging. All evidence should be retained for the lifetime of the material.

NOTE The term 'provenance' is used here in the sense of origin or place of origin. The term can also apply to the evidence of the origin or place of origin.

5.1.2.2 RMPs should have procedures in place to ensure that the provenance is maintained. These procedures should include handling of the material (e.g. sampling, homogenization, packaging, storage) and prevention of contamination by other materials.

NOTE For biological materials, provenance can include evidence of parentage or continuous culture from an authentic specimen (including an RM).

5.1.2.3 Characterization based on provenance should be supported by additional evidence to confirm identity of the material (see, for example 5.1.3, 5.1.4).

5.1.3 Materials characterized for identity based on measurements

5.1.3.1 General consideration for materials characterized for identity based on measurements

As outlined in ISO 33405, when characterizing the identity of a substance based on measurements, several aspects should be considered, including the following:

— Characterization can be based on measurement results from one or several methods. For example, chemical shifts and areas of peaks in a nuclear magnetic resonance (NMR) spectrum or a combination of colour, melting point, relative molecular mass, etc.

— Slight heterogeneity and instability of the material does not necessarily change the conclusion of identity. The guiding principle for the assessment of homogeneity and stability is applicability of the material, i.e. whether it still allows unequivocal identification.

— Different substances can share the same properties for the identification methods chosen. Information on the source of the raw material and on the processing steps of the material to be characterized is therefore vital for the certification of identity.

— As with any material, the project planning should establish a clear definition of the need for identity information based on the intended use of the material.

EXAMPLE For DNA, the intended use could require only a statement of species identity, a complete sequence or additional information on the degree of methylation.

NOTE Identity is sometimes determined by expert judgement (e.g. for asbestos fibres, histopathological examination). However, this judgement is usually based on observations and comparison with characterization criteria and, for example, RMs or reference data recognized by the relevant community of users. Expert judgement based on observations falls within the scope of 5.1.3.1; it can be used, for example, in identification of the species of a plant based on comparisons with voucher specimens.

5.1.3.2 Criteria for characterization of identity by measurement

5.1.3.2.1 As outlined in ISO 33405, testing for identity of a material involves comparison of a set of measurement results on that material with predefined acceptance criteria (e.g. melting point range, degree of similarity with a reference DNA sequence) for these measurement results.

NOTE Sequence similarity can be reported as "percent identity", i.e. the percentage of characters that match between two sequences.

EXAMPLE An organic polymer material could be identified based on comparison with a reference infrared (IR) spectrum using the following criteria:

— all peak frequencies in the reference spectrum are matched within 3 cm^{-1};

— relative peak intensities match the reference spectrum within 5 % relative absorbance;

— all peaks present in the reference spectrum are present in the candidate RM spectrum;

— all peaks present in the candidate RM spectrum are present in the reference spectrum.

5.1.3.2.2 Sources of criteria can include internationally recognized compendia (e.g. pharmacopoeia sources[20] and other collections of reference data[21]). Such information can change outside the control of the RMP. RMPs should therefore clearly state the criteria used for the assignment of identity, either as a set of values or as a dated reference on the RM document to applied criteria.

5.1.3.2.3 When defining criteria, RMPs should compare various literature data, establish the range of reported values and establish and document criteria for each measurand reflecting the ranges and reliability of the information used. Preference should be given to reference data which have undergone peer review.

5.1.3.2.4 An assignment of identity (of a substance, biological species, etc.) should be certified only when such assignment is made beyond sufficiently high confidence for the intended use (see 2.11 in Reference [22]).

5.1.3.2.5 Comparison of results with predefined acceptance criteria also applies to other qualitative properties characterized using measurement.

5.1.4 Characterization by a combination of methods

5.1.4.1 As outlined in ISO 33405, this approach is especially suitable for defined chemical substances of a small to medium molecular mass. A number of methods should be chosen that probe different properties of the candidate RM. Frequently used methods include, for example, determination of melting point, relative molecular mass, ultraviolet (UV), IR, NMR and mass spectra. Sensory methods may also be applied. Together with information on the raw material and its processing steps and the sampling and transport to the RMP, the collection of methods should be sufficient to establish the identity of the material. If detailed published criteria (e.g. pharmacopoeial criteria for identification) exist, the choice of methods can be restricted to those listed.

NOTE The nature and number of methods required to establish identity varies with the number of potentially similar products (e.g. there are more organic than inorganic substances) and the information on the origin and processing steps.

EXAMPLE 1 When using a standard strain of a bacteria from a recognized culture preservation centre, macroscopic features (characteristics on typical media), microscopic features (e.g. characteristics of gram stain, identification of coccus or bacillus), phenotypic features (characteristics in biochemical reactions) and other features where applicable (e.g. plasma coagulase assay, antioxidant enzyme test, serology test) can be necessary in the documentation.

EXAMPLE 2 A seed of a plant obtained from an institute with only morphological features will possibly not support the taxon of this plant; it can require further evidence or documentation.

5.1.4.2 All test and measurement procedures used must be properly validated and the results must fulfil the requirements for traceability. Where available, appropriate control materials should be examined alongside the RM during characterization.

5.1.4.3 The results of each of the tests and measurements made should be compared with the criteria for the proposed substance. Published procedures for comparisons should be followed, where available. Where no such prescribed procedures exist, measurement results should not differ from any of the specified values when taking the combined uncertainty of measurement and specified value into account. If the results agree with the published criteria, identity is established with a negligible uncertainty.

NOTE A judgement on whether the accumulated measurement and provenance information is sufficient to establish identity is somewhat subjective. Peer review can help to increase confidence in the assignment.

5.1.4.4 Where applicable, a suitable assessment or statement of purity of the RM should be made.

NOTE When a combination of qualitative and quantitative determinations is used for characterization, it can be useful to use similarity measures to support characterization. ISO/TR 79 gives an example for similarity measures.

5.2 Application of metrological traceability to qualitative determinations

5.2.1 General

Metrological traceability is defined in ISO/IEC Guide 99 as a "property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty." This approach for achieving comparable results is applicable to quantitative measurements, including where quantitative measurement results are used to determine qualitative characteristics of materials. It cannot be applied directly to qualitative property values in accordance with the terminology in ISO/IEC Guide 99 since these are not measured values based on calibration. Nevertheless, the need for consistent measurement data remains and the guidance in 5.2.2 to 5.2.4 describes several ways in which this can be achieved. First, many assignments of qualitative property values depend on measurement of one or more quantitative values for which metrological traceability can be stated in the usual way. Second, traceability of qualitative property values may be established by comparison with a reference. For qualitative properties, the reference to which traceability is claimed will not be a unit of the International System of Units (SI) but some reference recognized by the relevant scientific community, including users of the RM. This can be an artefact such as a CRM or can take the form of authoritative data such as, for example, published photographs and associated descriptions. Finally, qualitative properties can be assigned through the provenance of the material. For example, if an RM is claimed to be characteristic of a specific plant, its provenance should be sufficient to confirm its origin. Documentation of the provenance in this way is sometimes referred to as trackability but it fulfils the same aims for qualitative values as metrological traceability for quantitative values. These three approaches are described in more detail in 5.2.2.

5.2.2 Metrological traceability

5.2.2.1 Metrological traceability applies to the determination of quantitative properties, including conditions for tests yielding a qualitative result. Many qualitative value assignments include the measurement of one or more quantitative characteristics, such as melting point or pH. Others can include the application of test procedures which include quantitative conditions, such as times, temperatures and concentrations. The need for statements of metrological traceability for these parameters is discussed in 5.2.2.2 and 5.2.2.3.

5.2.2.2 Where a qualitative value assignment depends upon measurements or tests that include quantitative conditions, the measurements and/or tests should meet the metrological traceability requirements of ISO/IEC 17025.

EXAMPLE 1 In a structure assignment using spectroscopic methods, the wavelength or frequency scale describing the location of signals is checked or calibrated.

EXAMPLE 2 In a qualitative analytical test which requires application of a reagent at a stated concentration, the reagent is prepared using appropriately calibrated equipment to provide a reliable concentration.

5.2.2.3 Where a qualitative value assignment depends upon measurements or tests that include quantitative conditions, a statement of metrological traceability relating to the relevant measurements and/or tests should be included on the RM certificate.

NOTE ISO/TR 16476 and Reference [23] provide further information on the expression of metrological traceability.

5.2.3 Reference data and reference materials for qualitative determinations

5.2.3.1 Value assignment for qualitative properties can depend on comparison with reference data or with another RM already value-assigned for the qualitative property concerned. An appropriate RM for value assignment can be, for example, a sample whose identity has been reliably established or an independently characterised example of the class of interest.

EXAMPLE A herbal material is identified based on microscopic comparison with a reference sample held by a national repository or archive.

5.2.3.2 Where value assignment of a qualitative property depends critically upon comparison with particular reference data or a particular RM, the reference should be stated in the RM documentation accompanying the RM being produced.

NOTE Value assignment depends critically on a particular comparison when the particular comparison is essential to the assignment of the qualitative value.

5.2.4 Qualitative value assigned based on provenance

5.2.4.1 Value assignment based on provenance – knowledge of the origin of the RM – is described in 5.1.2. In the case of value assignment based on provenance:

— the RMP should maintain full documentation of the provenance of the material, including the source of the material, changes in ownership and procedures to avoid contamination or replacement of the material with any other;

— the basis of the assignment, including the source of the material, should be made available in the RM document.

5.2.4.2 Where assignment is based upon provenance supported by confirmatory measurements or tests, the provisions of 5.2.2 and 5.2.3 apply for the confirmatory measurements or tests.

5.3 Measurement uncertainty and confidence in qualitative values

5.3.1 General considerations

5.3.1.1 Every assignment of value to a property is surrounded by uncertainty. The techniques for uncertainty evaluation described in ISO/IEC Guide 98-3 are not applicable to evaluate uncertainties associated with value assignments to qualitative properties. Nevertheless, it is important to provide users of these RMs with guidance on the reliability of the assigned value. Many assignments of qualitative (nominal) properties depend on measurement of one or more quantitative values for which usual measurement uncertainty estimates are available. There is also a wide range of other information that can allow the user to assess confidence in the assigned value. It is important to document all such information.

5.3.1.2 While measurement uncertainty is well defined (see ISO/IEC Guide 98-3) and applies unambiguously to the values of quantities, the meaning of "uncertainty" as it applies to values on ordinal scales or to nominal values is not well established. There is also little or no harmonised guidance on conveying the degree of uncertainty, or the degree of confidence, that the user can have in the assigned value of a qualitative property. Pending a harmonised framework, the principles adopted in this document are as follows:

— The term "confidence" refers to the degree of belief one has in the value assigned to a qualitative property. Such confidence may be expressed qualitatively, using an ordinal scale (e.g. "most confident", "very confident", "moderately confident") or quantitatively (e.g. as a likelihood ratio or as a probability distribution on the set of possible values of the qualitative property).

— Users of RMs with qualitative values should have sufficient confidence in the values provided for the intended use of the material. In particular, where assigned qualitative values are certified the RMP should clearly state the justification for their confidence in the value.

— All assignments of value to qualitative properties should be qualified with a statement of confidence, even if this statement is itself qualitative and expresses a subjective expert opinion. Quantitative statements of confidence in assigned qualitative values are not required but are permitted where they do not give a misleading impression of reliability of the value.

NOTE Annex B gives further information on expression of confidence for qualitative values.

5.3.2 Measurement uncertainty

5.3.2.1 Measurement uncertainty as described in ISO/IEC Guide 98-3 impacts qualitative measurements in two ways:

— Control of uncertainties in test conditions, such as times, temperatures or lengths, is important for reliable qualitative value assignment when it involves measurements of quantities or control of (quantitative) test conditions.

— Measurement uncertainty related to intermediate measurements can contribute to the estimation of false response rates; for example, where classification depends on measurement results exceeding a threshold.

5.3.2.2 Where a qualitative value assignment depends upon measurements or upon tests that include quantitative conditions, the RMP should ensure that the measurement uncertainties are sufficiently small that they have no significant impact on the confidence in the assigned qualitative value. This should include one or more of the following:

— Control of conditions affecting the test result to within well-established and documented tolerances.

— Demonstration that the uncertainty is sufficiently small to have no significant influence on the outcome of the test.