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Guidance for the production of pure organic substance certified reference materials

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Guidance for the production of pure organic substance certified reference materials

Recommandations pour la production des matériaux de référence certifiés pour des substances organiques pures

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

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Introduction

Reference materials (RMs) play an important role in measurement processes and support sound, widely recognized measurement systems. ISO 17034 specifies general requirements to be met by reference material producers (RMPs), including for the production of certified reference materials (CRMs). CRMs play a key role in ensuring that measurements are comparable across time and space and are used by laboratories to establish metrological traceability of their measurement results to appropriate references.

This document outlines recommendations, which conform to general requirements of ISO 17034, for production of pure organic substance CRMs used to calibrate measuring instruments. These materials primarily comprise organic chemicals of specified, determinable structure. Guidance provided for characterization of pure organic chemical materials is also appropriate for those used to prepare pure organic substance solution CRMs. This document provides guidance on key aspects of the production of such CRMs, including the assessment of homogeneity and stability. Recommended approaches for characterization and assignment of certified purity values are described.

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Guidance for the production of pure organic substance certified reference materials

1 Scope

This document notes the requirements of ISO 17034 and provides specific guidance on technical considerations for the production of pure organic substance certified reference materials (CRMs) that are used by laboratories to calibrate measurement equipment and procedures and to establish metrological traceability of the respective results. The guidance is relevant only to CRMs comprising organic compounds whose structures are specifically defined, where polymeric materials are not included.

In this document, reference to a CRM is limited to pure organic substance certified reference materials, including candidate materials, unless otherwise noted.

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 9000, *Quality management systems — Fundamentals and vocabulary*

ISO/IEC 17000, *Conformity assessment — Vocabulary and general principles*

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

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 9000, ISO/IEC 17000, ISO Guide 30 and ISO/IEC Guide 99 and the following 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/

3.1
primary component
PC
principal chemical species of interest in the certified reference material

Note 1 to entry: A perfectly pure material is only an ideal concept because chemical species other than the PC will always exist in a material, even in very small amounts.

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3.2
purity
quantity ratio of the primary component in the certified reference material

Note 1 to entry: Purity is usually expressed as the mass fraction, amount-of-substance fraction or amount content of the PC.

Note 2 to entry: Purity is ideally close to 1, but it can be considerably lower than 1.

4 Technical and production requirements

4.1 General

The production of a CRM requires diligent planning. The requirements can be found in ISO 17034, and recommendations can be found in ISO 33405.[1][1)] Central to this effort is clear specification of the intended uses of the CRM and characterization appropriate for these purposes. The following subclauses provide an overview of considerations relevant to the production of CRMs.

4.2 Production planning

The production of a CRM includes the following steps:

a) specification of the CRM and its measurand;

b) candidate material sourcing and assessment of suitability, including verification of PC identity and adequate purity;

c) product packaging and specification of conditions for storage and safe handling;

d) determination of approaches to purity assessment of the CRM;

e) development and validation of procedures to achieve target measurement uncertainty;

f) assessment of homogeneity;

g) assessment and monitoring of stability;

h) characterization of the CRM;

i) consideration of metrological traceability of the certified property value;

j) preparation of certificates.

4.3 Specification of the CRM and its measurand

4.3.1 General

The intended use and relevant properties of the CRM should be clearly specified at the outset of the production process. This can include, but is not limited to, measurement procedures or type of measuring systems for which it is intended to be used, properties to be characterized, target purity, appropriate metrological reference of the certified value and target measurement uncertainty. Special attention is needed for these topics, as described in the following subclauses.

4.3.2 Specification of purpose

It is important to consider the intended use of the CRM because it can affect various aspects of the CRM production process, including the verification of the suitability of the sourced material. Pure substances constitute the source of primary measurement standards and higher-order metrological traceability in most

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traceability chains in chemistry. The demand for such a CRM is usually recognized through engagement with the intended user community. The measurement needs that are commonly served include improved accuracy of relevant measurement procedures, establishment of metrological traceability and regulatory compliance for chemical testing laboratories.

Such CRMs are typically used for the calibration of measuring instruments and measurement systems. An impurity in a CRM can create interferences in a measurement; while the presence of such interferences would not generally invalidate the certified purity value of the CRM, it can render the CRM suboptimal for some measurement methods. When a CRM is intended to be used for preparing a multiple-component calibration solution, it should be characterized to account for all relevant chemical entities because an impurity in the CRM can be the PC of another material intended to be mixed, leading to biases in certified values derived from the preparation process of the multi-component calibration solution. Quantities of all compounds of interest in each of these materials, present as either a PC or impurities, should be evaluated during the purity assessment. The decision on which quantities are significant depends on the targets for production of the CRM and the producer should define them as part of the specification for the material. An example of quantities which need to be considered is the amount of substance that can interfere with the PCs (of the CRMs used to prepare a multiple-component calibration solution CRM) in a measurement method that is expected to be used.

CRMs can also be used in chemical identification and validation of procedures for elemental analysis.

4.3.3 Specification of the measurand

A clear and unambiguous specification of the measurand is key to the production planning. The certified purity value of a CRM is usually expressed as the mass fraction, amount-of-substance fraction or amount content of a structurally specified chemical or set of chemicals within the material. The measurand requires specification of the organic chemical structure(s), including the assigned stereochemistry, when applicable, and the relevant units for expressing composition.

4.3.4 Definition of the metrological reference

ISO 17034 requires the metrological traceability of certified values to be established for CRMs in accordance with ISO/IEC 17025.[2]

The appropriate metrological reference system is principally dependent upon the purpose of the CRM and the measurement community it is intended to serve. The SI, a coherent system widely used in commerce and science, is the most appropriate system of units for most chemical measurements. The certified purity value of a CRM is ideally obtained by, but not limited to, the practical realization of SI measurement units.

For certified values of nominal properties, traceability to appropriate chemical references should be carefully considered for each case. Some CRMs have certified values for chemical identity. Valid evidence linking this characterization to the chemical structure of the PC should be provided.

4.3.5 Fitness for purpose

Fitness for purpose of a measurement is the extent to which the measurement result meets the stated requirement for which the measurements are being made. Formal definitions can be found in various sources, such as Reference [11]. For the CRM to be fit for purpose, the uncertainty in the delivered certified value should be small enough to be useful. For example, it is not appropriate to use a CRM of certified purity with 10 % relative standard uncertainty for calibrating procedures that aim to produce results with 1 % relative standard uncertainty.

NOTE 1 A measured property value without associated uncertainty does not conform to the definition for the certified value of a CRM specified in ISO 17034.

NOTE 2 Some pure organic substance RMs and their intended use are covered by other standards, for example pharmacopoeia assay standards, and uncertainties in property values are not typically specified. Rather, they are treated as negligible in relation to the defined limits of the method-specific assays for which they are used.

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4.3.6 Safety considerations

In regard to the workplace health and safety considerations, the reference material producer (RMP) should conduct a risk assessment, which can be replaced by the RMP's pre-established standard safety procedures, to establish that appropriate facilities and safeguards are in place to handle the candidate material.

4.3.7 Resources and approaches to purity analysis

Considerations for resource requirements are described in ISO 17034. CRM characterization should be fit for purpose and achievable with available laboratory resources, including labour, packaging materials and candidate materials. Allocation of these resources and anticipated cost recovery through CRM distribution are key considerations that govern the practicality of CRM production. Costs largely depend upon the rigour of analytical methods selected for characterization. For the CRMs, purity determination can be accomplished through either one or a combination of several basic approaches described in 4.6.

The target measurement uncertainty should be considered prior to attempting characterization.[12],[13] Use of two or more independent methods with different principles can evaluate possible systematic errors. Analyst expertise and preliminary experiments conducted for method development can generally inform realistic expectations of measurement uncertainty for specific measurement techniques and assist with experimental design for CRM characterization using either approach to purity analysis.

Statistical methods can also be employed to estimate optimal experiment design for a given set of constraints, including the target measurement uncertainty.[14] This experimental design should take into account sampling that is required to adequately assess homogeneity across the entire lot of candidate CRM.[1] As such, the number of units in the production lot should be known prior to development of methods for CRM characterization.

4.4 Candidate material sourcing and assessment of suitability, including verification of PC identity and adequate purity

4.4.1 Material sourcing

Candidate materials can be sourced commercially, through custom synthesis or from refinement of materials. Factors that should be considered in screening such materials include affordability, purity, homogeneity and stability.

Impurities can have a significant effect on the long-term stability of the material as well as on the accuracy of complex purity analyses. The RMP can conduct further purification of the sourced material when a sufficiently pure material cannot be sourced. The RMP should consider the advantages of purification against the recovery of PC during the process and any other potential changes to material composition of the sourced material during this process.

When the candidate material is sourced as a coarse powder or pellets, the RMP can grind and sieve the bulk material to produce a fine powder that is more suitable for its intended use, for example one that should be sufficiently homogenous for a small minimum sample size. Moreover, a more homogeneous particle size distribution is less prone to spatial stratification during packaging and transportation. When solid-state properties are relevant for a particular certification study, i.e. when the RMP intends to characterize the crystalline composition of the material or when these properties substantially affect the handling of the powder (e.g. hygroscopicity, electrostatic effects, dissolution rate or flow behaviour), the RMP can carry out preliminary tests with the candidate material to evaluate its suitability. When the RMP decides to purify the candidate material using processes such as recrystallization or drying, an interval of time before packaging the candidate batch can be useful to allow the stabilization of the moisture content of the bulk material and avoid future stability issues with water mass fraction.

4.4.2 Verification of PC identity

The identity of the PC is critical for any chemical CRM. ISO 17034 requires the RMP to address the verification of the identity of the PC. In addition to verifying chemical bond connectivity between atoms, knowledge of the geometric arrangement of the PC can be critical for the intended use of the CRM. Techniques executed

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to identify chemical components of the CRM should promote confident distinction of the PC from other inherent substances, especially those of similar structure.

The identity of the PC can be specified as a single precise organic chemical structure or as a closely related group of molecular entities. This structural specification should be governed by the intended use of the CRM to ensure that the measurand comprises only those chemical entities relevant for the intended use.

For example, when only the L arrangement of a chiral compound is biologically active, this quantity in a CRM should be specifically known, exclusive of the quantity of the compound having the D arrangement. Conversely, less specificity can define a measurand that includes related entities with slightly different structures, yet with similar or effectively the same properties, for example when the L and D arrangements serve the same purpose.

Specification of the measurand can consider the distinction of entities within the following classes of related chemical structures:

a) constitutional isomers – compounds with the same molecular formula, but different chemical bonding between atoms;

b) stereoisomers – compounds with the same molecular formula and bonding between atoms, but different three-dimensional spatial orientation of atoms within the molecule.

Tautomer and conformer structures of the PC should be considered if they are observed during candidate material characterization. When appropriate, they should be carefully attributed to the measurand.

NOTE Isotopologues, a molecular entity that differs only in isotopic composition (number of isotopic substitutions), for example CH_4, CH_3D, CH_2D_2, can be considered when required.

The RMP should utilize analytical techniques such as nuclear magnetic resonance (NMR), infrared (IR) spectroscopy and mass spectrometry (MS) to confirm the identity of the PC. NMR and MS can also support useful impurity identification. For crystalline compounds, a melting point determination can also be of value. As part of the planning process, it would be advantageous to source literature precedents for the structural identity of the analyte of interest.

For hydrate substances, identification should include determination of the ratio of water to the PC. For organic salts, identity of the counter ion should also be confirmed.

Examples of structure identification approaches can be found in Annex A.

4.4.3 Material suitability

A suitable candidate material is one that can be well characterized and has an acceptable level of impurities. A preliminary experimental effort should be made to verify that a candidate material meets acceptance criteria for purity. A suitability assessment of the candidate material should be conducted prior to material packaging using one or more analytical techniques available for purity determination and possibly other techniques to verify the absence of specific undesirable impurities. CRMs often contain significant impurities that have chemical structures similar to the PC. Suitable candidate materials typically contain a small proportion of these related impurities. The suitability assessment should be affordably conducted with the aim of verifying adequacy of a material and not necessarily conducted with the degree of rigour required for property value certification.

4.5 Product packaging and specification of conditions for storage and safe handling

4.5.1 General considerations

The nature of the product packaging, especially the primary packaging material, can widely affect the integrity of the material and the behaviour of the property values. Therefore, packaging should be selected carefully and studied under storage and transport conditions.

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Factors that can influence the choice of packaging material include, but are not limited to:

— hygroscopicity and/or light sensitivity of the material;

— the physical state of the material (e.g. liquid, solid, viscous);

— the amount per unit to be packed;

— temperature conditions for storage and transport;

— inertness;

— leaching;

— conformity with transport requirements and regulations;

— conformity with safety requirements and regulations;

— handling aspects at the laboratory of the user.

4.5.2 Selection and treatment of packaging materials

Preliminary studies to assess candidate packaging materials or different storage conditions are recommended. The CRMs can be packaged in primary containment glass vessels, such as sealed ampoules or vials. In order to protect the material from environmental conditions that can impact the integrity of the CRM (e.g. light, heat and humidity), the following packaging options should be considered:

— amber or clear glass vials;

— screw cap or rubber septum lid with crimped aluminium cap;

— inert gas or air to fill the glass storage vial headspace.

Ampoules are generally sealed under an inert atmosphere (e.g. argon), whereas with bottles this is not the case.

The RMP should also consider any necessary pre-treatment of the packaging materials, such as cleaning.

To ensure that the candidate material is properly transferred to a selected packaging material upon production, the process should be controlled and documented, see ISO 17034.

After the establishment of a suitable process for packaging or filling, the selection of appropriate packaging material and storage conditions, ISO 17034 requires the RMP to conduct a stability assessment for the behaviour of all relevant properties of the CRM under expected storage and transport conditions. Details can be found in ISO 17034 and ISO 33405.[1]

4.5.3 Storage and transportation issues

Containers for CRM storage should sufficiently isolate the material from the environment. Isolation from light, moisture and temperature can be suitable examples for the selection for the storage conditions for many CRMs.

Equally important is the definition of the transport conditions. Heat-sensitive material could be shipped on dry ice or similar, or the shipment duration could be limited. The conditions of shipment, including the provision to provide all necessary documents (e.g. permits, statement of origin) for customs clearance, is the responsibility of the RMP.

4.5.4 Label of containers

ISO 17034 requires appropriate labels to be applied during product packaging. The guidance can be found in ISO 33401.[3]

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4.6 Determination of approaches to purity assessment of the CRM

When purity assessment of candidate materials is conducted, ideally two or more independent methods should be used to determine purity. This allows an assessment of bias in one or both methods. It is generally recommended that one or more direct purity determination methods be used.

The RMP should plan a measurement strategy for measurement of purity of the candidate material that is fit for the intended use. Development of this strategy should consider measurement procedures that collectively ensure:

a) adequate specificity for PC measurement;

b) an adequate survey of impurities;

c) sufficient accuracy of measured purity value;

d) sound evidence for assigning a sufficiently small measurement uncertainty.

NOTE Numerous complementary instrumental techniques are available for purity assessment. Hence, it is possible for the strategy adopted to vary with the instrumentation and other resources available to the RMP.

The use of one or a combination of appropriate measurement procedures can meet the objectives for producing a CRM with metrologically traceable certified values.

Methods for organic chemical purity assessment are generally conducted through direct and indirect approaches to determining PC quantities.

Direct approach: determination of relative quantities, such as mass fraction, of the PC without necessarily quantifying all impurities. This approach commonly implements techniques such as quantitative nuclear magnetic resonance (qNMR), coulometry, titrimetry, freezing or melting point depression and stable isotope ratio mass spectrometry (ID-MS). qNMR, titrimetry and ID-MS methods require a pre-established CRM for comparison and assigning relative values For the pure organic substance CRMs, qNMR is a widely used technique for direct measurement of purity.

Indirect approach: determination of purity through a survey of impurity components, where the purity, w_{PC}, is calculated using Formula (1):

$$w_{\mathrm{PC}} = 1 - \sum w_{\mathrm{I}_i} \tag{1}$$

where

w_{PC} is the mass fraction of the PC;

w_{I_i} is the mass fraction of the ith impurity component.

A thorough indirect approach can require more resources and varied expertise than a direct approach and this should be realistically accounted. Possible impurities to be investigated generally belong to the following classes of chemical components:

a) structurally related organic compounds;

b) volatile organic compounds;

c) water;

d) inorganic substances;

e) unrelated non-volatile organic impurities, for example polymeric compounds or biological substances.

Purity assessments of candidate materials can leverage information gathered with techniques employed for both approaches[15–17]. Ideally, direct and indirect determinations yield consistent results, though valuable insight about the material composition can be gained even if they do not. A rigorous assessment can directly

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measure the PC quantity and collect important information about the entire material composition. This is especially useful if the material contains impurities that introduce systematic errors to the direct PC determination or that can give rise to potential interferences in the intended use of the CRM. Inconsistency between direct and indirect determination results indicate bias associated with either approach that should ideally be reconciled or accounted for in the measurement uncertainty.

The selection of methods for purity measurement should leverage information about material composition gathered during the suitability analysis. A preliminary investigation of impurities should indicate the most appropriate methods for purity measurement. Furthermore, the achievable uncertainty in the certified value is likely larger for materials with complex impurity profiles than for those with few impurities. Especially for an indirect determination, purity assessment of a material with many impurities requires confident measurement of several substances. Effort should be made to ensure that these impurities do not interfere with accurate measurement of the PC. When applying the mass balance approach to assess purity of a candidate material, the time and effort required to identify and quantify each impurity increases as the number of impurities increases. If such an analysis becomes too complicated or costly, the RMP should consider the purification of the candidate material to remove as many impurities as possible and reduce the effort required for purity assessment. Materials of higher purity are also generally more suitable for the purposes of the end user.

More detailed information for the purity assessment can be found in Annex B.

4.7 Development and validation of procedures for characterization, including achieving target measurement uncertainty

4.7.1 General

Specification of acceptable uncertainty in the certified purity value should be made with a clear understanding of the intended use of the CRM.

The certified purity value of a metrologically traceable CRM should have an associated uncertainty that contributes a reasonably small fraction of the total uncertainty budget in results achieved through this application. The certified purity value of a CRM that is used to establish metrological traceability for a measurement result should have an associated uncertainty that is fit for intended use compared to the total uncertainty of the measurement result.It is also crucial that the uncertainty of the certified purity value realistically reflects the homogeneity and stability of the production batch. General guidance for the evaluation of measurement uncertainty is provided in ISO/IEC Guide 98-3 (GUM)[4] and its supplements.[5],[6] Assessment of batch homogeneity and stability for CRM production is discussed in ISO 33405.[1] These sources of uncertainty should be approximated during material suitability tests and considered when planning experiments. Characterization of a candidate material should be conducted after it is packaged into individual units.

An optimal experiment design is one which uses a minimum amount of resources to provide a sufficient amount of information. For CRMs, this means efficiently conducting measurements to achieve results with suitably small uncertainty. Expert judgement should ultimately decide the combination of appropriate analytical procedures best suited to the nature and composition of the material. In addition to achieving the smallest practical measurement uncertainty of a certified value, the execution of a plan for adequate characterization is contingent upon resources available to the RMP. Batch size is an important factor in sampling schemes and experiment design. General guidance on approaches to experiment design and adequate material sampling to achieve target measurement uncertainty under these criteria is available.[1],[10],[14],[18]

Examples of purity analyses for characterization of CRMs are provided in Annex C.

4.7.2 Multiple methods for purity determination

When well-characterized CRMs are needed, the use of multiple methods is strongly recommended.

Multiple independent measurements of purity can provide a collective body of evidence that is complementary or self-validating. When multiple measurement results are consistent, confidence gained

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