PROTOCOL

Guidance for characterization of in-house reference materials for light element stable isotope analysis

Philip J. H. Dunn [ID] | Dmitry Malinovsky [ID] | Gill Holcombe | Simon Cowen | Heidi Goenaga-Infante [ID]

National Measurement Laboratory, LGC Limited, Middlesex, UK

Correspondence
P. J. H. Dunn, National Measurement Laboratory, LGC Limited, Queens Road, Teddington, Middlesex TW11 0LY, UK.
Email: philip.dunn@lgcgroup.com

Rationale: Preparation of in-house reference materials (RMs) is an important aspect of light element stable isotope analysis. While some relevant information is available, there is as yet no clear set of guidelines available covering all aspects of in-house production and characterization of RMs.

Methods: To address this need, the experience of production of certified reference materials under accreditation to ISO 17034:2016 and ISO/IEC 17025:2017 has been distilled into guidance for production of in-house RMs that are fit-for-purpose.

Results: The guidance provided covers five areas: (i) planning; (ii) material considerations including preparation, packaging, and storage; (iii) measurements and assessments; (iv) value and uncertainty assignment; and (v) monitoring and use.

Conclusions: In-house RMs prepared by following this guidance can be used to provide traceability to measurement results when used for normalization or for quality control and/or assurance purposes.

1 | INTRODUCTION

Reference materials (RMs) are a vital part of stable isotope delta measurements of all light elements (i.e. hydrogen, H; carbon, C; nitrogen, N; oxygen, O; and sulfur, S). RMs allow measurement results to be calibrated to the international reporting scales through a process often termed normalization and thereby ensure traceability.[1–7] RMs can also be used for method validation as well as for quality control (QC) and/or assurance (QA) purposes.[1] There are various sources of guidance available for the use of isotope ratio RMs.[1,2,6,8] These all emphasize the need to adhere to the so-called principle of identical treatment ("IT principle") whereby RMs and samples are analyzed concurrently and identically.[3]

A relatively wide variety of RMs for the light elements is commercially available including simple single chemicals such as carbonates, nitrates, sulfides, and amino acids,[4,9] as well as more complex matrices such as hair,[10,11] whole wood,[12] and defatted

beef.[13] More RMs are added to the existing suite by RM producers each year.[e.g.14] Nevertheless, the number of different matrices and/or isotopic compositions for stable isotope delta RMs required to support the ever-growing diversity of applications cannot be supported by the currently commercially available RMs and RM producers alone. Nor can isotope delta scales be easily maintained for decades into the future if RMs providing the (current) highest metrological realization of such scales, such as IAEA-603 and VSMOW2,[15,16] are used daily by laboratories. Therefore, the production and characterization of in-house RMs by stable isotope laboratories has been encouraged both anecdotally and also by some suppliers limiting purchase of commercial RMs to small numbers of units for each laboratory.[1,17–19]

Commercial RM producers have past experience and may have accreditation to international standards such as ISO 17034:2016 and/or ISO/IEC 17025:2017 or familiarity with other similar guidance such as ISO Guide 80:2014.[20–22] Other stable isotope laboratories,

however, may not be in the same fortunate position and would benefit from clear guidance of how to prepare, characterize, assign values and uncertainties to, store, and use their in-house RMs. There is some limited guidance available specifically aimed at isotope ratio RMs, for example in both editions of the Forensic Isotope Ratio Mass Spectrometry (FIRMS) Network's Good Practice Guide for Isotope Ratio Mass Spectrometry,[1,17] and a small number of other publications.[e.g.19,23] Other sources of information include publications that describe the preparation and characterization of RMs from commercial RM producers,[e.g.10,12,24–26] or RMs from other parties.[e.g.9,14] The certificates or other documents that may accompany commercial RMs may also provide some information applicable to characterization of in-house RMs. Clear guidance that is easily followed, which summarizes all aspects of in-house RM production for light element isotope ratio analysis, particularly for value assignment, is nonetheless missing.

In this work we use the National Measurement Laboratory's (NML) experiences of (i) being a certified RM (CRM) producer accredited to ISO 17034:2016; (ii) also applying the principles of ISO Guide 35:2017 to the production of RMs and CRMs; and (iii) maintaining a variety of Calibration and Measurement Capabilities (CMCs) within the International Committee of Weights and Measures (CIPM) Mutual Recognition Arrangement (MRA) which underpin the CRMs produced by the NML. These experiences have included production of RMs and CRMs in existing and emerging areas including trace elements, elemental species (i.e. characterizing the abundance of particular oxidation states of an element rather than the total elemental abundance), nanoparticles,[27] and isotope ratios.[7,25,28,29]

The comprehensive approach required to meet the requirements of accreditation goes beyond what is, in our opinion, required of an in-house RM for light element stable isotope analysis. There is, however, much to be learned from the process under accreditation (for full description, see supporting information). Using our experiences, we distil the requirements for RM production under accreditation into simple and clear guidance for production of in-house RMs for stable isotope ratio analyses that are fit-for-purpose. This guidance covers five areas for in-house RM production: (i) planning and prerequisites; (ii) material selection, preparation, packaging, and storage; (iii) measurements and assessments; (iv) value assignment and uncertainty estimation; and (v) monitoring and use. These stages are what we regard as the minimum effort needed to characterize and assign an isotope delta value with associated uncertainty to an in-house RM and are summarized in Figure 1. The terminology and definitions used in this guidance as well as additional details and examples can be found in the supporting information.

2 | METHODS

2.1 | Scope

Given the vast array of possible in-house RMs and requirements, we cannot provide specific advice for every situation without producing an unwieldy set of guidelines. Instead, we provide general guidance applicable in most situations and therefore have limited this guidance to situations where:
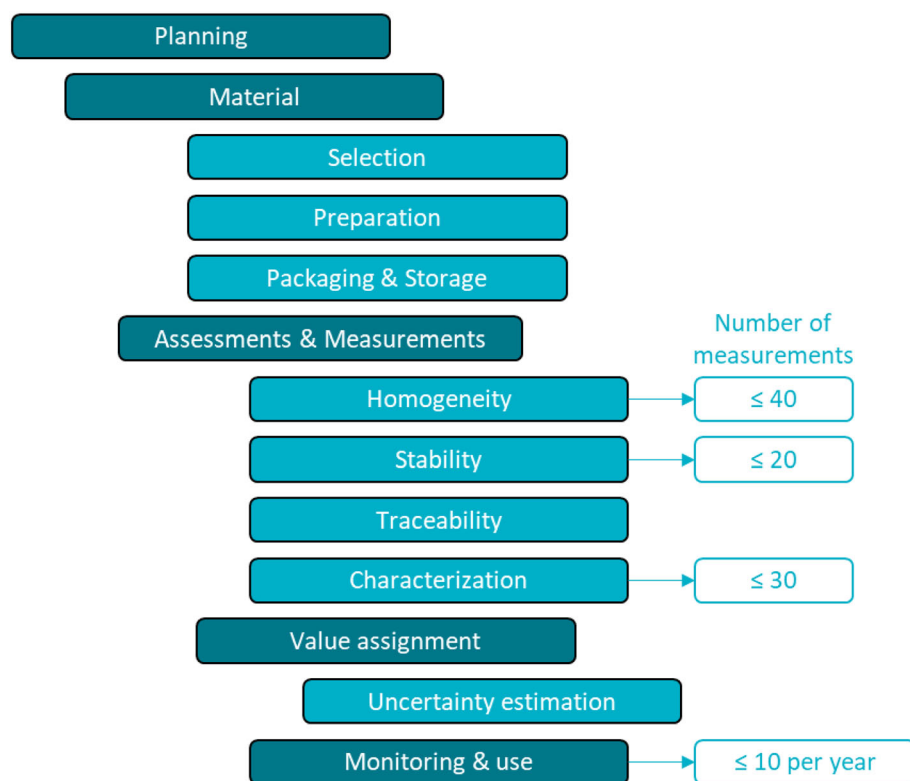

FIGURE 1 Suggested stages of production and characterization of an in-house RM for isotope delta measurements together with an indication of the number of replicate measurements of the candidate material required

1. Only a single laboratory will be involved in the process.
2. The in-house RMs are neither volatile liquids nor gases.
3. The in-house RM will be stored in a small number of units (i.e. less than or equal to 20 but greater than 1).
4. Each unit contains up to a few tens of grams of material and therefore sufficient material for hundreds to thousands of replicate analyses per unit.
5. The units are able to be sub-sampled more than once (i.e. they can be re-sealed and the in-house material maintains its desired properties).

We also assume that a laboratory has assessed the need for a particular in-house RM so that effort is not wasted by assessing a material which might never be used.

The general principles covered by this guidance can also be applied to in-house RMs for other elements beyond H, C, N, O, and S.

2.2 | Prerequisites

The prerequisites for characterizing an in-house RM include a developed and fully validated instrumental analysis method to determine the isotope delta value(s) for the new in-house RM, documented in a standard operating procedure (SOP). Guidance for validation of stable isotope ratio methods is provided elsewhere.[1,30] The desired properties of the new in-house RM should also be known, in particular the isotope delta value range and magnitude of associated uncertainty, such that assessments can be planned which are able to meet these needs. A candidate in-house RM should be checked for isotopic composition to meet the former requirement before proceeding.

2.3 | Planning

Before any practical work or measurements commence, careful planning of the whole process is very useful. The more detail is covered by the plan, the easier it is to follow through to fruition. The plan should cover each of the remaining sections of the guidance provided here.

2.4 | Material selection, preparation, packaging, and storage

2.4.1 | Selection

The IT principle has a crucial role to play in material selection as any in-house RM should be matrix-matched with the relevant samples. We recommend that only materials with no foreseen long-term stability issues be selected as this removes the requirement for a specific long-term stability assessment before value assignment.

The desired uncertainty in the assigned value should be considered during planning as it will influence the design of subsequent assessments during characterization. This need not be a hard limit where the material is rejected should the final uncertainty be somewhat larger than planned, provided it is still fit-for-purpose.

2.4.2 | Preparation

If the desired material is not already a liquid or a sufficiently homogeneous solid, homogenization of an in-house RM will be required. This can be both time-consuming and difficult to apply. Producing solutions of simple single chemicals is one approach to ensuring homogeneity.[23] Those solutions could also be freeze-dried in sufficiently small droplets if a solid form is required.[9]

For more complex matrices such as biological tissues or soil, material preparation can become laborious. There may be a need to combine several portions of starting material. Processes such as freeze-drying or defatting may also be prudent depending on the nature of the RM. Other processes such as grinding, mixing/tumbling, sieving, and sterilization using γ-irradiation may also be required. It is important that the effect of these sample preparation stages on the isotopic composition of the candidate in-house RM be assessed.

2.4.3 | Packaging and storage

Packaging (i.e. container type) and storage (i.e. how those containers themselves are stored) of the new in-house RM must be planned thoroughly and will build upon prior knowledge of the material in question. General considerations for in-house RM packaging and storage include the physical and chemical properties of the material, the total amount of material to store, sub-sampling regime, and the number of units being prepared. As noted in the scope, this guidance only considers situations where sub-bulks or smaller units are used for long-term storage and where the total number of units/containers is less than 20. We do not recommend having only one bulk container as this runs the risk of contamination or accident affecting the entire stock of material. Production of a number of small, individual units requires careful consideration of between-unit homogeneity and, consequently, more laborious material preparation but eliminates these risks. A few sub-bulk containers may provide a good compromise.

2.5 | Assessments and measurements

Assessment of in-house RM properties can involve expert judgement based upon prior knowledge and experience as well as experimental measurements. Characterization to determine the assigned isotope delta value must always be performed experimentally.

2.5.1 | Homogeneity assessment

Homogeneity assessment provides an estimate of both between-unit and within-unit variation. The former provides a contribution to the uncertainty of the assigned isotope delta value of the in-house RM, u_{Hom}.

A homogeneity assessment will need to consider the following:

1. Number of units produced. Testing all units maximizes the chance of uncovering unit-unit variation, or detecting "outlier" units that display much wider scatter of results than other units. This is more feasible when a small number of units is produced.
2. Probability of uncovering an issue with homogeneity when only a selection of units are used during the homogeneity assessment (the probability will be larger, the higher the number of units selected, and the higher the number of replicate measurement per unit).
3. The degree of heterogeneity that is expected for the material. This will generally be small as judicious selection of material will generally lead to in-house RMs with a high level of homogeneity.
4. Precision of the analytical method.
5. Practical constraints to experimental design (e.g. the number of analyses that are possible within a single sequence).

A comprehensive assessment of 20 units with duplicate analyses per unit is only a total of 40 measurements within a single sequence and therefore not too arduous when this number of units is produced. Testing a randomly selected subset of 6–10 units would also provide a reasonable estimate of u_{Hom} and a good chance of detecting problematic outlier units while halving the number of analyses required. If a lower number of units is prepared, then the number of measurements required during a homogeneity assessment may fall still lower. More replicates per unit might be valuable if there are only a few large units produced.

All homogeneity measurements should, ideally, be performed by a single analyst, using a single sequence on a single day (i.e. under repeatability conditions). Measurements and the selection of units if not all are assessed should both be randomized. In this way, the results obtained will reflect more closely the variation which is under investigation rather than other confounding factors. To extract the contribution to the uncertainty in the assigned isotope delta value of the in-house RM arising from homogeneity, u_{Hom}, various statistical approaches can be used. In general, these include an approach based upon analysis of variance (ANOVA) to obtain the between- and within-unit variances, but more complex methods may be appropriate depending on the design of the study.[31] Examples of different approaches to estimating u_{Hom} specifically for stable isotope ratio CRMs have been published elsewhere.[24–26]

When the magnitude of the between-unit variance is smaller than the within-unit variance, there is no detectable between-unit heterogeneity. Either u_{Hom} can be assumed to be zero, or a more conservative approach can be employed by assigning a value for u_{Hom} equal to the within-unit variance (which is assumed to be masking any

between-unit variance) divided by the square root of the number of replicate measurements per unit. This latter is also appropriate if a small number of units is produced in total.

2.5.2 | Stability assessment

For an in-house RM, material selection should exclude matrices that might require a long-term stability study before use. Given that an in-house RM is for internal use and is therefore not shipped anywhere, an accelerated stability study is also, generally, superfluous. These aspects of stability testing are therefore not covered by these guidelines, although some information can be found in the supporting information.

A limited accelerated study of stability for a new in-house RM does have some value as it can reveal how the material might be affected if not stored under the recommended conditions for some time (e.g. accidentally placed into, left out of, or power loss from a freezer over a weekend).

A stability assessment designed with this aim in mind consists of a study of a limited number of temperatures different to the usual storage conditions with two units or aliquots of material at each temperature with analysis of each unit/aliquot in duplicate. There would only need to be two time points – the start and a few days or a week later – as this would be sufficient to demonstrate if the material exhibited stability problems.

An isochronous experimental design should be employed such that all exposures to different conditions end at the same time. The measurements should be performed under repeatability conditions with all analyses on a single day using a random run order. The result of such an accelerated stability assessment is a simple yes or no fitness-for-purpose statement with no additional contribution to the uncertainty of the assigned isotope delta value.

2.5.3 | Traceability

Ensuring metrological traceability of the assigned value for the new in-house RM is vital. It is therefore important to identify and obtain RMs that will be used during characterization and other measurements of the new in-house RM and will provide that traceability through normalization. We recommend that only RMs that are listed in the IUPAC Technical Report on stable isotope ratio RMs,[4] or more recently produced RMs that have been calibrated against listed RMs, be used to provide traceability to the international reporting scales for isotope delta.[7] For each RM used for normalization, the assigned value and associated uncertainty should be noted.

One feature of characterizing in-house or indeed commercial RMs which does not apply to routine analyses is that there will, on occasion, be a need to apply the IT principle less strictly. As we noted recently,[7] this is because either the new in-house RM is of a new matrix or it lies outside the range of isotopic composition covered by

existing RMs and serves to extend the range available for routine analyses. In these instances, method validation or verification is a crucial prerequisite to these guidelines to demonstrate that the method employed is fit-for-purpose.

2.5.4 | Characterization

For characterization, i.e. the measurements that are used to derive the assigned isotope delta value for the in-house RM, a relatively small number of measurements can suffice provided a validated method is used. Three units analyzed in triplicate on each of three different days for a total of 27 measurements can suffice when even many units are produced. A similar number of measurements is appropriate for an in-house RM, although there may be fewer units with more replicates from each. In general, the design of the characterization study will depend on the desired target uncertainty to be assigned together with the precision of the method particularly the magnitude of the intermediate precision. Large day-to-day or sequence-to-sequence effects and/or poor repeatability will require a larger number of replicate analyses to achieve the same uncertainty.

Characterization measurement results provide both the assigned isotope delta value of the in-house RM as well as a contribution towards the associated uncertainty (u_{Char}) following statistical analysis. The choice of statistical approach will depend on the relative magnitude of the between- and within-day/sequence variances, the distribution of results (e.g. normal), the presence of outliers, and/or the presence of significant trends within sequences and/or days of analysis, etc. Simple estimators such as the arithmetic mean, robust estimators such as the median, or more complex methods may be required.

The estimation of u_{Char} must include contributions to measurement uncertainty associated with traceability, i.e. the uncertainties in both measured and assigned isotope delta values of the RMs used for normalization. These contributions may need to be added separately depending on how u_{Char} is obtained.

It can also be possible to assign an isotope delta value to an in-house RM from the homogeneity study data. This would substantially reduce the number of replicate analyses required to characterize an in-house RM.

2.5.5 | Commutability

Commutability of RMs is important when they are value-assigned using one method of analysis, but a different method is applied when using the RM routinely. A RM is commutable if the ratio of measurement results obtained for the RM and for test samples does not change with a change in method.[21] The outcome of a commutability study is generally a report stating which methods the RM is commutable for. Provided that the element in the in-house RM and in test samples is quantitatively converted into the analyte gas and measurement results are normalized to the internationally accepted isotope delta scales, then there should be no commutability issue requiring assessment by experimentation.

2.6 | Value assignment and uncertainty estimation

The isotope delta value assigned to the new in-house RM is derived from the characterization measurements. While this involves relatively few analyses of the material, a validated method is employed whose performance has been comprehensively studied in the past and therefore the small number of measurements is still sufficient to be sure of the assigned value.

The uncertainty associated with the assigned isotope delta value for the new in-house RM must be determined from the various measurements and assessments previously described (Figure 2). For an in-house RM within the scope of these guidelines the uncertainty in the assigned isotope delta value is generally a combination of u_{Char} and u_{Hom} only as the result of a limited accelerated stability assessment is fitness-for-purpose statement rather than a contribution to uncertainty (Figure 2). Note that there may be situations where u_{Hom} is a negligible contribution.

Combination of the individual uncertainty components for value assignment and homogeneity is achieved using the square root sum of squares approach (Equation 1) as each term is independent. As noted above, u_{Char} should include uncertainty associated with normalization/traceability.

$$u_{in-house\,RM} = \sqrt{\left(u_{Char}\right)^2 + \left(u_{Hom}\right)^2} \tag{1}$$

2.7 | Ongoing monitoring

Ongoing stability monitoring is always useful as it can reveal contamination and degradation of the material and can be as simple as collating measurement results of the in-house RM in a control chart each time it is analyzed. Alternatively, a schedule of test measurements investigating the ongoing stability of the in-house RM can be planned and implemented. When comparing values obtained during ongoing stability monitoring, the uncertainty of the measurement procedure must be taken into account as well as the uncertainty of the assigned value. Note that the former can improve with time.

Should on-going stability measurements highlight a problem with the isotope delta value or uncertainty of the in-house RM, then action must be taken. This might involve using a different unit or sub-bulk if contamination has occurred, widening the uncertainty in the assigned value or a revision to the assigned value itself. These actions should be clearly documented for future reference. Provided that the production process of the in-house RM has been well planned, these actions should be rare – although we note that such actions can be required even for commercial isotopic RMs.[e.g.32,33]
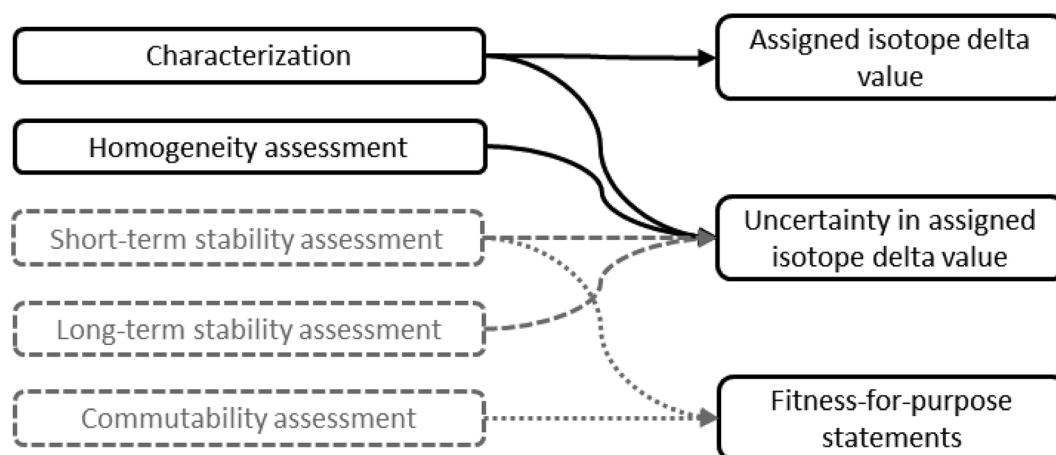
FIGURE 2 Flowchart illustrating which of the characterization measurements contribute to the assigned isotope delta value for an in-house RM and which contribute to the uncertainty associated with the assigned value. Fainter dashed lines are used to indicate characterization measurements that may not be needed

3 | RESULTS AND DISCUSSION

Following the guidance provided above will result in in-house RMs that can be used to provide traceability to international reporting scales when used for normalization and also underpin QC and QA procedures. For the former, it may be desirable to have the uncertainty associated with the assigned value as small as possible and therefore the use of a more precise method and a more thorough characterization study may be warranted such that u_{Char} is as small as possible. For materials destined for instrumental monitoring the uncertainty associated with the assigned value of such RMs should be small enough that changes in obtained isotope delta values for the material resulting from poor instrument performance can be distinguished.

The total number of analyses required to follow this guidance will generally be 50 to 100 including some of the ongoing stability monitoring (Figure 1). With careful planning, these can be performed over a small number of sequences.

3.1 | Using existing accumulated data

As mentioned above, it is possible to use existing accumulated data as the basis for assigning an isotope delta value and uncertainty to an in-house RM. For example, if a material has been analyzed many times within a laboratory, then numerous measurement results exist even if there has been no thorough/planned investigation into the material.

The assigned value and u_{Char} should certainly be extractable if such a dataset contains sufficient independent measurements of the material. This might be as simple as the mean and standard deviation of the mean of replicate analyses combined with contributions to measurement uncertainty from the calibrations used, but more complex statistical analysis may be required. If the dataset includes a

sufficient number of analyses of the candidate RM that cover either a number of different small units, or different locations within a larger sub-bulk container, then it might also be possible to extract a representative value for u_{Hom}. Some additional planned measurements might still be necessary when using an existing dataset, for example an accelerated stability study. As each accumulated dataset will be different, we cannot provide more specific recommendations.

4 | CONCLUSIONS

This guidance should prove useful to laboratories seeking to calibrate their own in-house RMs for use either during normalization or for QC and/or QA purposes.

For situations outside the scope of these guidelines we recommend consulting ISO 17034:2016 and/or ISO/IEC 17025:2017 and/or ISO Guide 80:2014.[21,22,34] For DI-IRMS applications where carbonates and waters will often be the most valuable in-house RMs to prepare, the recent manuscript from Hélie and Hillaire-Marcel is also a valuable source of information.[19]

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1002/rcm.9177.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Philip J. H. Dunn https://orcid.org/0000-0002-3848-6187

Dmitry Malinovsky https://orcid.org/0000-0002-7055-2359

Heidi Goenaga-Infante https://orcid.org/0000-0002-2416-9666

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.