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An isotope dilution mass spectrometry overview: tips and applications for the measurement of radionuclides†‡

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This article proposes a practical guide including good laboratory practices followed by a critical review about the application of isotope dilution mass spectrometry (ID-MS) measurement to radionuclide analyses. Several national and international scientific institutions (French Alternative Energies and Atomic Energy Commission, French Radioprotection and Nuclear Safety Institute, European Commission, International Atomic Energy Agency, and Belgian Nuclear Research Centre) participated in this review by sharing their good laboratory practices. ID-MS is one of the primary ratio methods of measurement in the International System of Units. It can produce highly accurate results, as potential sources of bias can be controlled. Many hints are given to obtain the best performance. In addition, a script written with the open source software Octave is provided to calculate the optimal parameters of the {sample–spike} mixture easily. Radionuclide analysis by ID-MS applies to many different fields (environmental, biological, reference materials, irradiated samples, process control, nuclear safeguards and nuclear forensics).

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1. Introduction

Radionuclides are unstable radioactive nuclides which emit radiation during their decay to gain more stability. They can be naturally occurring such as ^{14}C or ^{129}I that come from cosmogenic processes or ^{210}Pb or ^{230}Th that are decay products of uranium isotopes. However, the majority of radionuclides are artificial, being end-products or by-products. For example, ^{99m}Tc or ^{131}I isotopes are used in medicine. ^{99m}Tc, ^{90}Sr and ^{137}Cs are fission products generated by nuclear fission in reactors or during nuclear weapons tests, while Pu and Am isotopes are produced in nuclear reactors.

The accurate assay of radionuclides is essential for various reasons. For example, U and Pu are the main elements of interest in the nuclear fuel cycle as some of their isotopes are used as fissile materials. As such, U and Pu accountancy is of prime importance in the nuclear fuel cycle and for safeguards purposes.[1,2] Pu is present in common spent fuel at 1% by weight, in Mixed OXide fuel (MOX) at 5–10% by weight for use in pressurized water reactors and at 20–30% by weight for use in fast-neutron reactors.[3] Its measurement with high accuracy (*i.e.* measurement trueness and precision[4–6]) is essential to manage criticality issues, to verify fuel pellet conformity and for nuclear material accountancy. Am is also an important element in the nuclear fuel cycle as it is the major contributor to the long-term radiotoxicity coming from the waste, once Pu has been removed. Its reliable analysis is required for waste management and is also important for safeguards and nuclear forensics as it acts as a clock since the last separation of Pu.[7]

Age dating of nuclear materials is also an area of growing interest for safeguards and nuclear forensics purposes. The main radio-chronometers that are subject to analytical developments are ^{230}Th–^{234}U and ^{231}Pa–^{235}U for uranium and ^{241}Am–^{241}Pu, ^{236}U-^{240}Pu and ^{235}U–^{239}Pu for plutonium.[8–11] The

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† In memoriam: René Brennetot

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accurate measurement of radionuclides is necessary to decrease the uncertainty of the calculated material age. Radionuclides are typically measured by radiometric counting methods (alpha, beta and gamma spectrometry) and mass spectrometry techniques (Inductively Coupled Plasma Mass Spectrometry (ICP-MS), accelerator mass spectrometry, Thermal Ionization Mass Spectrometry (TIMS), Resonance Ionization Mass Spectrometry, Secondary Ion Mass Spectrometry or Glow Discharge Mass Spectrometry).[12–14]

The isotope dilution (ID) method is used for quantification purposes and is based on the internal calibration principle. The origin of ID is not well known. ID is similar to the mark–recapture method used in ecology to estimate animal population size.[15] The mark–recapture method is based on reintroducing a small number of marked animals to an original population considered as a closed system. Later a group of animals is captured and the proportion of marked animals helps to estimate the total number of animals. This method was first used in 1896 by Petersen to estimate plaice[15] and may have been used to estimate rare bird species living on islands.[16] An assumption of this method, fundamental also to ID, is the perfect mixing of the animals.

The principle of ID is also very simple. A sample of an element with a known isotope composition but unknown number of atoms is mixed with a spike solution containing a known number of atoms of the same element enriched in an isotope and with a known isotope composition. After isotope equilibrium, the isotope ratio of the {sample–spike} mixture reflects the sample analyte amount. The application of ID was invented by Hevesy and Paneth in 1913 to determine the solubility of lead sulfide in water.[17] In the 1950s, ID was extended to actinides.[18,19] As it is based on isotope ratio determination, an accurate technique for isotope ratio measurements must be preferred to reach the best performance for ID. Measurements by TIMS have been mostly used since 1950 for this purpose due to its highly accurate measurement of isotope ratios.[20] Since the 1990s, the use of ID applied to mass spectrometric measurement (ID-MS) has grown considerably due to the widespread application of ICP-MS and the availability of certified reference materials (CRMs) from different institutes.

ID-MS has been listed as a primary method, together with coulometry or gravimetry.[21] The definition of the Consultative Committee for Amount of Substance (CCQM) of a primary method of measurement in the International System of Units (SI) is a method having the highest metrological qualities, for which a mathematical model and realization are completely described and understood in terms of SI units.[22] Two concepts are defined: a primary direct method and a primary ratio method. A primary direct method measures the value of an unknown quantity without reference to a standard of the same quantity, such as coulometry or gravimetry. A primary ratio method measures the value of an unknown to a standard of the same quantity; its operation must be completely described by a measurement equation, such as ID-MS.[21] In both cases, the results must be accompanied by a complete uncertainty statement.[22] From the list of primary methods, ID-MS is the most widely used one in U and Pu amount determination interlaboratory comparisons (ILCs).[23] Furthermore, the International Atomic Energy Agency (IAEA) considers ID-MS as one of the most accurate methods in terms of the International Target Values (ITVs) for measurement uncertainties applied on safeguarding nuclear materials.[24,25] TIMS and ICP-MS are the techniques of choice to measure the isotope ratio of most elements,[26] for example radionuclides such as Sr,[27] Cs,[28–30] Nd,[31–34] Th,[35,36] U,[33,37–41] Pu,[3,33,38,40,42–45] Am[7,31,38] and Cm.[31,46] ID-MS is a versatile tool for radionuclide quantity measurement and the "gold standard" for nuclear safeguards.

Several reviews have described ID-MS for CRM characterization,[20] element speciation,[47,48] proteomics[49] and geochemical analysis.[50] Some articles have discussed the general concept of ID-MS.[26,51–54] To our knowledge no general reviews on radionuclide measurement by ID-MS have been published.

The Commission for the Establishment of Analytical Methods (CETAMA) is a unit of the French Alternative Energies and Atomic Energy Commission (CEA), which has a goal of measurement quality improvement within the nuclear field.[23,55–58] The main activities of CETAMA are to develop and provide CRMs for nuclear analysis laboratories worldwide, to organize ILCs and to participate in the standardization of analytical methods. One of the CETAMA's working groups is dedicated to ID-MS which gathers several national and international scientific bodies (CEA, French Institute for Radiation Protection and Nuclear Safety (IRSN), Joint Research Centres (Europe), IAEA, Belgian Nuclear Research Centre (SCK)) that share their know-how in radionuclide analysis by ID-MS.

This review describes the good laboratory practices of the ID-MS working group members and proposes a critical review about the applications of ID-MS to radionuclide measurement. After a brief theoretical description of ID, the uncertainty budget expression is explained in more detail, including how to minimize it. The implementation and good laboratory practices of ID-MS are further described. The review covers the application of ID in different fields: environment, biology, reference material production, irradiated sample analysis, process control, nuclear safeguards and nuclear forensics. The final chapter is dedicated to the description of different ILCs available for testing the performance of radionuclide measurement by ID-MS.

2. Theory

2.1. General formula

The principle of ID is illustrated in Fig. 1. Isotope "A" is the major isotope of the element "E" in the sample. Isotope "B" is the major isotope of the element "E" in the spike. For clarity and conciseness, the following nomenclature is used throughout the manuscript:

- Subscripts:
  - ○ Mix refers to the {sample–spike} mixture;
  - ○ T refers to the spike (or tracer);
  - ○ S refers to the sample.
- R is the B/A ratio in mol mol^{-1}.

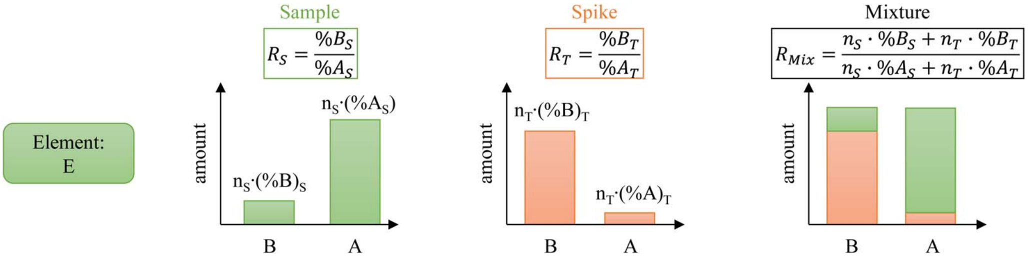

Fig. 1 Illustration of the isotope dilution principle.

- R' is the A/B ratio in mol mol^{-1}.
- %A refers to the isotope abundance in percent of mol mol^{-1} of A.
- %B refers to the isotope abundance in percent of mol mol^{-1} of B.
- n refers to the amount of substance (mol).
- w refers to the mass fraction in g g^{-1}.
- M refers to the molar mass in g mol^{-1}.
- m refers to the mass in g.
- u is the standard uncertainty with a coverage factor of $k = 1$.
- u_r is the relative standard uncertainty with a coverage factor of $k = 1$.
- α refers to the sample amount; spike amount ratio ($\alpha = n_\text{S}/n_\text{T}$) in mol mol^{-1}.
- LOD is the limit of detection.

The mixture isotope ratio (R_Mix) can be calculated from the atom number or number of moles of an element and the isotope abundance of isotopes A and B.

$$R_\text{Mix} = \frac{n_\text{S} \cdot \%\text{B}_\text{S} + n_\text{T} \cdot \%\text{B}_\text{T}}{n_\text{S} \cdot \%\text{A}_\text{S} + n_\text{T} \cdot \%\text{A}_\text{T}} \tag{1}$$

Introducing $\%\text{B}_\text{S} = \%\text{A}_\text{S} \cdot R_\text{S}$ and $\%\text{B}_\text{T} = R_\text{T} \cdot \%\text{A}_\text{T}$ in eqn (1) leads to the general form of the isotope dilution equation (eqn (2)).

$$n_\text{S} = n_\text{T} \cdot \frac{\%\text{A}_\text{T}}{\%\text{A}_\text{S}} \cdot \frac{R_\text{T} - R_\text{Mix}}{R_\text{Mix} - R_\text{S}} \tag{2}$$

Eqn (2) can be converted into mass fractions by taking into account the masses of the sample and spike, and the atomic masses of the element in the sample and spike (eqn (3)).

$$w_\text{S} = w_\text{T} \cdot \frac{m_\text{T}}{m_\text{S}} \cdot \frac{M_\text{S}}{M_\text{T}} \cdot \frac{\%\text{A}_\text{T}}{\%\text{A}_\text{S}} \cdot \frac{R_\text{T} - R_\text{Mix}}{R_\text{Mix} - R_\text{S}} \tag{3}$$

Another form is also commonly used to show the major isotopes in the spike and in the sample ($\%\text{B}_\text{T}$ and $\%\text{A}_\text{S}$) in the ID formula (eqn (4)). Eqn (2) and (4) correspond to each other and will give the same results.

$$n_\text{S} = n_\text{T} \cdot \frac{\%\text{B}_\text{T}}{\%\text{A}_\text{S}} \cdot \frac{R'_\text{Mix} - R'_\text{T}}{1 - R'_\text{Mix} \cdot R_\text{S}} \tag{4}$$

2.2. Formula used for environmental samples

A single (eqn (5)) and a double isotope dilution equation (eqn (6)) are commonly used in environmental samples for the mass fraction determination of ^{238}U using a spike enriched in the ^{236}U isotope and the ^{230}Th/^{238}U ratio using a spike enriched in the ^{229}Th and ^{236}U isotopes. Obviously, these equations can be applied for other target radionuclides by using the appropriate spike and the respective atomic masses.

$$w_\text{S}\left({}^{238}\text{U}\right) = \left(\frac{{}^{238}\text{U}}{{}^{236}\text{U}}\right)_\text{Mix} \cdot \frac{M\left({}^{238}\text{U}\right)}{M\left({}^{236}\text{U}\right)} \cdot w_\text{T}\left({}^{236}\text{U}\right) \cdot \frac{m_\text{T}}{m_\text{S}} \tag{5}$$

$$\frac{w_\text{S}\left({}^{230}\text{Th}\right)}{w_\text{S}\left({}^{238}\text{U}\right)} = \left(\frac{{}^{230}\text{Th}}{{}^{229}\text{Th}}\right)_\text{Mix} \cdot \left(\frac{{}^{236}\text{U}}{{}^{238}\text{U}}\right)_\text{Mix} \cdot \frac{w_\text{T}\left({}^{229}\text{Th}\right)}{w_\text{T}\left({}^{236}\text{U}\right)} \cdot \frac{M\left({}^{236}\text{U}\right) \cdot M\left({}^{230}\text{Th}\right)}{M\left({}^{238}\text{U}\right) \cdot M\left({}^{229}\text{Th}\right)} \tag{6}$$

The mass fraction and mass fraction ratio are then converted into activity ratios by considering the radionuclide atomic masses and their respective half-lives ($t_{1/2}$). It should be noted that the double isotope dilution in combination with a double spike (*i.e.* ^{229}Th–^{236}U) is a powerful tool that helps to minimize weighing errors and eliminate errors due to differential evaporation of spike solutions. Indeed, the spike weight does not play a role in eqn (6).[59]

It should be noticed that spikes usually contain isotopic impurities (for instance, a ^{236}U spike usually contains traces of ^{234}U, ^{235}U and ^{238}U isotopes). In many cases, especially for the less abundant isotopes at ultra-trace levels, eqn (5) and (6) must be modified to include and correct for the contribution of these isotopic impurities.

2.3. Estimation of the limit of detection

The LOD is the minimum concentration or quantity of an analyte that can be detected with a reasonable certainty for a given analytical procedure.[60] Eqn (7) can be used to obtain a conservative estimate of the LOD of the element E using ID ($\text{LOD}_\text{ID}(E)$) for a specific spike.[61]

$$\text{LOD}_\text{ID}(E) = \frac{\sqrt{\text{LOD(B)}^2 + R_\text{T} \times \text{LOD(A)}^2}}{\left|\frac{\%\text{B}_\text{S}}{100} - R_\text{T} \times \frac{\%\text{A}_\text{S}}{100}\right|} \tag{7}$$

where LOD(B) and LOD(A) are the LOD for B and A isotopes, respectively. $\mathrm{LOD_{ID}}(E)$, LOD(B) and LOD(A) units must be identical.

3. Implementing isotope dilution

A careful implementation is needed to obtain the best performance for ID-MS. The highest level of quality can be reached when a weighed aliquot of the sample is mixed with a weighed aliquot of the spike. Volumetric mixing can only achieve a lower level of uncertainty. The uncertainty will also be minimum when an optimal ratio between the sample and the spike is reached.

Successful ID requires achieving complete isotope equilibration between the sample and spike. This is practically only possible when the mixture is in solution. Due to isobaric interferences in many instances a separation step to obtain the pure element is needed. Theoretically this separation does not introduce a source of error since after isotope equilibration, losses of the substance have no influence on the final result, an important advantage compared to other methods. In all cases, the appropriate ID-MS spike should be added to the sample aliquots before starting the sample preparation and should be added before the separation protocol. It is therefore also clear that any loss of substance before reaching full equilibrium is a source of error and to be avoided. Another advantage is the compensation of matrix effects as any factor influencing the sensitivity of the analyte is the same for the sample and spike nuclide.

The main disadvantages of the method are its destructive nature and that the preparation steps consume time and resources. The disadvantages are generally balanced out by the advantages. The spike availability is for most elements no issue as the laboratories produce their own spikes or procure them from CRM producers.

The weighing procedure, the preparation of the {sample–spike} mixture, the choice of the spike, spike management, and isotopic homogenization are the main criteria to be taken into consideration when implementing ID-MS. These various influencing parameters are discussed in the ensuing paragraphs. Isotope ratio measurements by MS are also an important parameter to take into account and are largely described in the literature.[12,62–68]

3.1. Weighing procedure

3.1.1. General recommendations. An accurate weighing and mass determination of the sample and the spike are essential for a correct ID-MS assay with low uncertainties. There are many weighing techniques, but in this section those most commonly used for radionuclide analyses are presented.

In the case of solid samples, the material is normally dissolved taking a sample quantity sufficiently large to obtain a representative sample of the material. The mass of the dissolved sample generally exceeds 0.1 g to optimize the uncertainty contribution from mass measurements (see Section 4.2). The solution is diluted, if needed, to match the target sample/spike ratio (see Section 3.2). For mass spectrometric measurements, typically picogram to microgram amounts of spike are used. Therefore, a similar quantity of the sample is required for assay determination by ID-MS. The mass of the sample and of the spike used to prepare the mixture solution should also exceed 0.1 g for the same reasons.

For ID-MS, the amounts of spike and sample are typically small. Thus, the uncertainties in the mass determination contribute significantly to the overall uncertainty budget. Therefore, it is important to consider the different effects that can lead to a significant bias, some of which are related to the weighing itself (buoyancy, electrostatic effects), some to the sample preparation (evaporation, moisture content and stability, type and mass of vials) and others to effects that might happen during aliquoting such as cross-contamination.

The availability of a high-precision analytical balance is a prerequisite, typically with a resolution of at least 0.1 mg. The balance must be assessed before use with appropriate standard weights to ensure proper balance function.

Electrostatic effects can be avoided when needed by using specific tools to prevent or eliminate electrostatic charges. Moreover, properly trained analysts and good analytical practices can improve the mass determination, for instance performing daily check weighings prior to using the balance for critical measurements, and ensuring the correct placement of vials on the balance.[69]

3.1.2. Weighing by difference. The most common weighing technique for radionuclide measurement is weighing by difference: *i.e.* placing a container on the balance, noting the mass, and then adding the sample or spike to it and noting the mass again. The difference between the two masses is the mass of the sample or spike added to the container.

The weighing procedure can be summarized as follows: the balance is tared with the vial and the cap, then the sample is added and the cap placed on the vial to avoid evaporation, and the mass displayed is the sample aliquot, m_S.[70] After another tare of the balance, the spike is added and weighed with the cap on the vial. The mass displayed is the spike aliquot, m_T.

A different procedure, employing the technique of weighing by difference, was established in the nuclear safeguards laboratories of the Joint Research Centre (JRC) Karlsruhe, the double-weighing method.[71] In this procedure, the aliquot mass of the sample, or spike, is determined twice:

1. The mass dispensed from a Pasteur pipette determined by the mass difference between a filled and an emptied pipette (eqn (8)):

$$m_\mathrm{ip} = m_\mathrm{pf} - m_\mathrm{pe} \tag{8}$$

where m_ip is the mass of the sample or the spike (i = S or T), m_pf is the mass of the filled pipette and m_pe is the mass of the emptied pipette.

2. The mass received into a vessel, the mass difference between the spike vial with and without the aliquot (eqn (9)):

$$m_\mathrm{iv} = m_\mathrm{vf} - m_\mathrm{ve} \tag{9}$$

where m_iv is the mass of the sample or the spike (i = S or T), m_vf is the mass of the filled vial with the sample or spike and m_ve is the mass of the empty vial.

Once the consistency between the two mass determinations has been demonstrated, they should not differ from one another by a laboratory determined limit, and the mass dispensed from the pipette (eqn (8)) is taken as the true aliquot mass. This procedure can minimize the impact of some of the undesirable effects encountered during weighing, and offers a built-in consistency check so that a bad weighing can be detected before mass spectrometric measurements.

3.1.3. The substitution method. For very accurate determinations, *e.g.* preparation or characterization of certified reference materials, the substitution method (also known as ABBA or SUUS) is used. In this method, the mass is determined through comparison with mass standards of similar nominal value.[72] The substitution method consists of weighing the mass reference standard A and the mass to be determined B, one after another on the same load carrier according to the weighing cycle A–B–B–A or also in the sequence B–A–A–B. The balance is used as a comparator eliminating possible linear drifts of the balance. The mass of the sample or spike is determined using the mass of the standard (S) and the difference between the readings, ΔX (eqn (10)):

$$\begin{aligned} m_{\mathrm{i}} &= S + \Delta X \\ \Delta X &= \frac{X_{\mathrm{B1}} + X_{\mathrm{B2}} - X_{\mathrm{A1}} - X_{\mathrm{A2}}}{2} \end{aligned} \tag{10}$$

Uncertainties on the order of tens of μg can be achieved with the substitution method.[73,74] However, this method requires many standards and is time consuming, and hence is usually restricted to metrological labs and is not routinely used in analytical labs.

3.1.4. Air buoyancy and electrostatic effects. The air buoyancy effect is well known and corrections can be applied,[75] see eqn (11), although for many nuclear applications the effect can be negligible:

$$m_{\mathrm{true}} = (\Delta X - \delta) + a\left(\frac{1}{r} - \frac{1}{r_0}\right)\Delta X \tag{11}$$

where m_{true} is the true mass, $\Delta X = X - X_0$ the read mass between the in-load and the no-load indications of the balance, δ is the correction for the bias, a is the air density, and r and r_0 are the densities of the sample and of the standard used for calibration, respectively.

The need to correct for air buoyancy depends on how accurate the results must be and on the density of the samples. It is particularly critical when the target total uncertainty is less than 1% (metrological purposes for example) and for aqueous solutions with a density close to 1000 kg m^{-3}, because such a density is far removed from that (8000–8100 kg m^{-3}) of the stainless steel calibration standards.

The expression for the correction factor, K, for air buoyancy is given in eqn (12)

$$K = \frac{\left(1 - \dfrac{\rho_{\mathrm{air}}}{\rho_{\mathrm{std}}}\right)}{\left(1 - \dfrac{\rho_{\mathrm{air}}}{\rho_{\mathrm{sol}}}\right)} \text{ with } m_{\mathrm{corrected}} = K \times m_{\mathrm{as\ read}} \tag{12}$$

If the requirement in terms of weighing uncertainty is 0.1%, it is not necessary to measure the air density experimentally in order to calculate the K factor for an aqueous sample with a density of 1000 kg m^{-3}. Knowing the density of the sample, the conventional value, 1.2 kg m^{-3}, for the density of air is sufficient to express K and correct the read mass. For solid samples and the same requirement in terms of the uncertainty level, corrections are not necessary.

In the case of ID-TIMS, the weights are expressed in the equation in the form of a ratio, $\frac{m_{\mathrm{T}}}{m_{\mathrm{S}}}$. If the solutions are alike (*e.g.* same nitric acid concentrations), their densities and K factors will be identical and the ratio of the masses as read will correspond to the ratio of true masses (corrected masses). No corrections will be needed. The same conclusions can be drawn if serial dilutions are made using solutions with similar characteristics.

If higher accuracy is required, corrections for air buoyancy should be considered throughout the entire preparation of sample. For example, when a solid is dissolved, the K factor for the solid is 1; whereas for a solution is greater than 1. By considering a density solution of 1100 kg m^{-3} ($\approx$3 mol L^{-1} nitric acid solution), the K factor for this solution can be written as in eqn (13)

$$K = \frac{\left(1 - \dfrac{1.2}{8000}\right)}{\left(1 - \dfrac{1.2}{1100}\right)} = 1.0009 \tag{13}$$

The relative mass correction of the solution is approximately +0.1%. The mass fraction for the dissolved solid should then be corrected inversely by −0.1%. In other words, not taking the air buoyancy into account would lead to an overestimation of the mass fraction of the sample.

3.2. Optimization of the {sample–spike} mixture

ID-MS requires an optimum spiking ratio to obtain the best accuracy (*i.e.* the minimum relative uncertainty of n_{S}, eqn (2)). Several studies have been reported in the literature.[37,52,76–80] Here, three different methods are detailed. The first derives the error multiplication factor (F) as a function of the mixture isotope ratio, leading to a very simple formula to derive the optimal isotope ratio for the mixture. The second derives the F factor as a function of the ratio between the amount of sample and the amount of spike which makes it straightforward to prepare the mixture experimentally. The third method is broader, in that it considers all isotope ratio uncertainties. Lastly, the choice of the spike isotope and examples are discussed.

The three methods have been implemented in a script written with the open source software Octave,[81,82] version 8.3.0. The method calculating the LOD as a function of the spike's isotope ratio (eqn (7)) was also implemented. To start the script, download the "startup_ID.m" file available in the ESI.‡ Start the Octave software and set the browser directory to the appropriate folder where the file "startup_ID.m" is located. Starting the script is performed by typing "startup_ID" in the Octave command window. The script then prompts the user to select an optimization method. All parameters must be selected. Once the calculation has been completed, the optimum parameters are displayed in the Octave command windows. The plot is also displayed. The plot can be saved as an 8 cm × 8 cm ".png" file. The results and the raw data can be saved as a ".txt" file.

3.2.1. Error multiplication factor as a function of the mixture isotope ratio. This method helps calculate the F factor as a function of the mixture isotope ratio.[76–79,83] Using the law of error propagation, the n_S uncertainty can be calculated by considering the R_{Mix} contribution only (eqn (14)). The contributions of R_S and R_T are considered as negligible.

$$\left|\frac{\mathrm{d}n_S}{n_s}\right| = F\left|\frac{\mathrm{d}R_{\mathrm{Mix}}}{R_{\mathrm{Mix}}}\right| \tag{14}$$

The F factor is obtained from eqn (15).

$$F = \frac{(R_S - R_T)\cdot R_{\mathrm{Mix}}}{(R_{\mathrm{Mix}} - R_S)\cdot(R_T - R_{\mathrm{Mix}})} \tag{15}$$

Finding the optimal value of R_{Mix} is simply a matter of locating the minimum F factor in the function $F = f(R_{\mathrm{Mix}})$. The minimum of a function is obtained when the derivative is equal to zero (eqn (16)).

$$\frac{\mathrm{d}F}{\mathrm{d}R_{\mathrm{Mix}}} = \frac{R_S - R_T\cdot\left({R_{\mathrm{Mix}}}^2 - R_S\cdot R_T\right)}{\left((R_{\mathrm{Mix}} - R_S)\cdot(R_T - R_{\mathrm{Mix}})\right)^2} = 0 \tag{16}$$

Eqn (16) is equal to zero if the numerator is equal to zero. After rearrangement, eqn (17) is obtained. The optimum mixture ratio ($R_{\mathrm{Mix,opt}}$) can be calculated using the square root of the product of R_S and R_T.

$$R_{\mathrm{Mix,\,opt}} = \sqrt{R_S\cdot R_T} \tag{17}$$

Eqn (17) is a very simple equation for deriving the optimum mixture isotope ratio. However, one prerequisite is the lower R_S and R_T uncertainties compared to R_{Mix} uncertainties. This condition is generally true: R_T uncertainty is usually very low as coming from the CRM certificate or can be accurately measured in the case of an in-house spike; R_S can be measured several times to decrease its uncertainty.

The blue curve in Fig. 2 shows the F factor as a function of R_{Mix} (eqn (15)) for a sample with 3.0% of ^{235}U and 97% of ^{238}U (%A_S = 97%, %B_S = 3.0%, $R_S = 0.0309$) using a spike enriched with the ^{235}U isotope such as IRMM-054 CRM (93.2% of ^{235}U and 5.4% of ^{238}U: $R_T = 17.3$). Using this raw data, the optimum isotope ratio of the mixture is $R_{\mathrm{Mix,opt}} = 0.73$. In this example, the parameters are robust since the F factor varies little in the region around the optimum value.

When the major spike isotope is absent from the sample ($R_S = 0$), eqn (17) can be simplified (eqn (18)).

$$F = \frac{R_T}{R_{\mathrm{Mix}} - R_T} \tag{18}$$

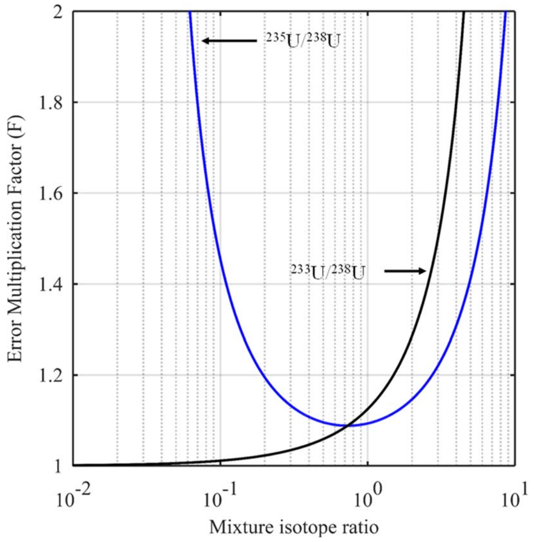

Fig. 2 Error multiplication factor as a function of the ^{235}U/^{238}U mixture isotope ratio (blue curve) for a sample with ^{235}U/^{238}U = 0.0309 and for a spike enriched with the ^{235}U isotope (^{235}U/^{238}U = 17.3), and as a function of the ^{233}U/^{238}U mixture isotope ratio (black curve) for a sample with ^{233}U/^{238}U = 0 and for a spike enriched with a ^{233}U isotope (^{233}U/^{238}U = 9).

Evaluation of the optimum isotope ratio of the mixture can be done graphically. An example is shown in Fig. 2 (black curve), for a uranium sample with ^{233}U/^{238}U = R_S = 0 and a spike enriched at 90% in the ^{233}U isotope (^{233}U/^{238}U = R_T = 9). The F factor tends to 1 as R_{Mix} gets closer to R_S and becomes larger as R_{mix} approaches R_T. The best choice would appear to be $R_{\mathrm{Mix}} = R_S$ (*i.e.* when no spike is used), but this makes no sense for an ID measurement. A compromise needs to be reached between the minimum F factor and spike addition. In the example in Fig. 2 (black curve), mixture isotope ratios in the range 0.1 to 1 seem to provide an interesting compromise between a low F factor and needing to add a spike.

3.2.2. Error multiplication factor as a function of the ratio between the amount of sample and amount of spike. This method calculates the F factor as a function of the ratio between the amount of sample and the amount of spike.[52] It is essentially eqn (15), rewritten, by introducing α (n_S/n_T atomic ratio) into eqn (1), which leads to eqn (19)

$$R_{\mathrm{Mix}} = \frac{\alpha\cdot\%\mathrm{B_S} + \%\mathrm{B_T}}{\alpha\cdot\%\mathrm{A_S} + \%\mathrm{A_T}} \tag{19}$$

By combining eqn (15) and (19), the F factor as a function of α can be calculated (eqn (20)).

$$F = f(\alpha) = \frac{(R_S - R_T)\cdot\dfrac{\alpha\cdot\%\mathrm{B_S} + \%\mathrm{B_T}}{\alpha\cdot\%\mathrm{A_S} + \%\mathrm{A_T}}}{\left(\dfrac{\alpha\cdot\%\mathrm{B_S} + \%\mathrm{B_T}}{\alpha\cdot\%\mathrm{A_S} + \%\mathrm{A_T}} - R_S\right)\cdot\left(R_T - \dfrac{\alpha\cdot\%\mathrm{B_S} + \%\mathrm{B_T}}{\alpha\cdot\%\mathrm{A_S} + \%\mathrm{A_T}}\right)} \tag{20}$$

Determining the α optimum value is simply a matter of locating the minimum F value. To understand how the F factor varies around the optimum α value, the F factor can be plotted as a function of α (eqn (20)). This plot is useful for illustrating how robust the optimal value is. In practice, the sample amount is generally not accurately known. It is therefore difficult to mix the sample and spike in the exact optimal proportions.

Combining eqn (4) and (17) helps to quickly obtain the optimal sample amount over spike amount ratio (α_{opt}, eqn (21)).

$$\alpha_{\text{opt}} = \frac{\%\,\text{A}_\text{T}\cdot\sqrt{R_\text{S}\cdot R_\text{T}} - \text{B}_\text{T}}{\%\,\text{B}_\text{S} - \%\,\text{A}_\text{S}\cdot\sqrt{R_\text{S}\cdot R_\text{T}}} \tag{21}$$

This way of expressing the F factor provides the analyst with a simple way to derive the {sample–spike} mixture. As for the previous method, one prerequisite is that the uncertainties of R_S and R_T are lower than that of R_Mix. In cases where the major isotope of the spike is absent from the sample ($R_\text{S} = 0$), eqn (20) cannot be applied. In this case, the optimum ratio of sample amount to spike amount can be determined graphically.

The curves in Fig. 3 show the F factor as a function of α (eqn (20)) for a sample with 3.0% of ^{235}U and 97.0% of ^{238}U using a spike enriched with the ^{235}U isotope such as IRMM-054 CRM (blue curve, 93.2% of ^{235}U and 5.4% of ^{238}U, same example as for Fig. 2) and for a sample with 70.0% of ^{239}Pu and 1.0% of ^{242}Pu using a spike enriched with a ^{242}Pu isotope like the IRMM-049d CRM (black curve, 0.2% of ^{239}Pu and 94.7% of ^{242}Pu). Using these raw data, the optimal α values are 1.3 and 0.5 for uranium and plutonium samples respectively. In these examples, the F factor varies little in the region around the optimum value of α.

3.2.3. Optimal mixture isotope ratio by taking into account all isotope ratio uncertainties. This method derives the optimum mixture isotope ratio by taking into account all isotope ratio uncertainties.[37] In this method, the uncertainties of R_S and R_T are taken into account. Considering eqn (2), n_T, %A$_\text{T}$ and %B$_\text{T}$ terms have no effect on the optimum ratio. From the uncertainty point of view, eqn (4) can be simplified and become eqn (22): using this equation and the law of propagation of uncertainty, eqn (23) is obtained.

$$n_\text{S} \Leftrightarrow \frac{R_\text{T} - R_\text{Mix}}{R_\text{Mix} - R_\text{S}} \tag{22}$$

$$u^2(n_\text{S}) = \left(-\frac{R_\text{T} - R_\text{Mix}}{(R_\text{Mix} - R_\text{S})^2}\right)^2\cdot u^2(R_\text{S}) + \left(\frac{1}{R_\text{Mix} - R_\text{S}}\right)^2\cdot u^2(R_\text{T}) + \left(\frac{R_\text{S} - R_\text{T}}{(R_\text{Mix} - R_\text{S})^2}\right)^2\cdot u^2(R_\text{Mix}) \tag{23}$$

The optimum spiking should minimize the relative uncertainty of n_S, which can be expressed as a function of R_Mix (eqn (24)).

$$u_\text{r}(n_\text{s}) = \frac{u(n_\text{S})}{n_\text{S}} = f(R_\text{Mix}) \tag{24}$$

Determining the optimal value of R_Mix is simply a matter of locating the minimum relative uncertainty of n_S ($u_{\text{r,min}}(n_\text{S})$). To understand how the F factor varies around the R_Mix optimal value, the error of the relative uncertainty as a function of R_Mix can be plotted (eqn (25)).

$$\frac{u_\text{r}(n_\text{s})}{u_{\text{r,min}}(n_\text{s})} - 1 = f(R_\text{Mix}) \tag{25}$$

If the uncertainties of R_S and R_T are equal to zero, then this solution is identical to that obtained by using method 1 (eqn (15)).

To illustrate this method, a sample with 3% of ^{235}U and 97% of ^{238}U was considered: %A$_\text{S}$ = 97%, %B$_\text{S}$ = 3%, $R_\text{S} = 0.0309$ and $u_\text{R}(R_\text{S}) = 0.5\%$. A spike, enriched in the ^{235}U isotope (such as the IRMM-054 CRM), was used: $R_\text{T} = 17.3$ and $u_\text{R}(R_\text{T}) = 0.03\%$. The R_Mix relative uncertainty was fixed at 0.07%, corresponding to the ITV value.[24] In this example, the optimum isotope ratio of the mixture is $R_{\text{Mix,opt}} = 1.03$. It should be noted that the optimum isotope ratio of the mixture (1.03) determined by taking into account all uncertainties is slightly different from, but not dissimilar to, the value (0.73) when not taking into account uncertainties of the isotope ratio R_S and R_T (eqn (15)).

Just as for the previous two methods, in cases where the major isotope of the spike is absent from the sample ($R_\text{S} = 0$), the optimum isotope ratio of the mixture can be determined graphically.

3.2.4. Choice of the spike isotope. Isotope selection of the spike is a key step. A good choice will simplify the preparation of the {sample–spike} mixture and improve the quality of the measurement as well as minimize the uncertainty. It is recommended to follow a few rules for the selection of the spike isotope:[52,66]

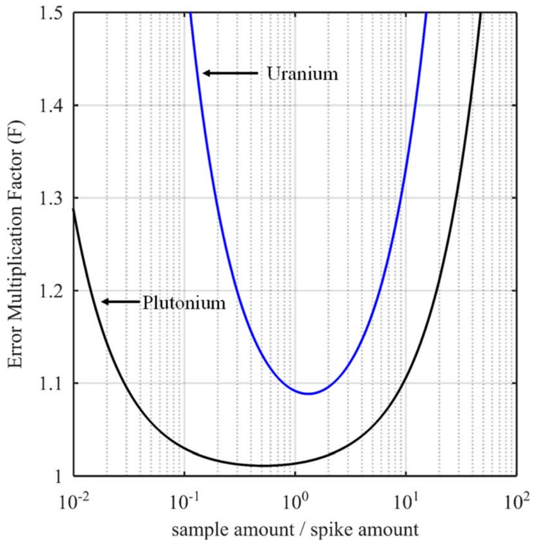

Fig. 3 Error multiplication factor as a function of the sample over spike amount for uranium (blue curve, sample with 3% of ^{235}U and 97% of ^{238}U using a spike enriched with 93.2% of ^{235}U) and plutonium (black curve, sample with 70% of ^{239}Pu and 1% of ^{242}Pu using a spike enriched with 94.7% ^{242}Pu).

- It is better if the spike isotope is absent from the sample or has the lowest isotopic abundance in the sample.

- A spike enrichment higher than 90% is recommended, allowing the accuracy of the ID to be practically independent of the mixture preparation.

- It is better if the spike isotope has no isobaric interference.

For uranium, the most common spikes are ^{233}U, ^{235}U or ^{236}U, since the main uranium isotope in most samples is generally ^{238}U (excluding highly enriched uranium material). For plutonium, ^{240}Pu, ^{242}Pu or ^{244}Pu spike isotopes are commonly used, since ^{239}Pu is usually the main major isotope in most samples. For americium, since the samples have ^{241}Am as the major isotope, a spike enriched in the ^{243}Am isotope is a good option.[56] In the case of U, Pu and Am, the choice is easy as the sample has one major isotope and spikes highly enriched in minor isotopes are commercially available. It is worth noting, for the radioactive spike, the isotope abundance and mass fraction must be updated for the day of analysis to correct for the radioactive decay.

For certain other elements, the choice of the spike isotope is not as straightforward. For example, in the case of neodymium measurement with natural isotopic composition, several choices are possible. In theory, the best choice of reference isotope in the sample is the ^{142}Nd isotope since it is the most abundant isotope in such a sample. However, since ^{142}Ce can be an isobaric interference on the ^{142}Nd isotope, the ^{144}Nd isotope is generally preferred as a sample isotope.[31] Fig. 4 shows the F factor as a function of the sample/spike amount ratio for different Nd isotopes as the major isotope in the spike. The curves for ^{148}Nd and ^{150}Nd lie close together and overlap each other, as shown in Fig. 4. Since ^{148}Nd and ^{150}Nd are the two least abundant isotopes, in a sample with natural neodymium isotopic composition, a spike enriched in either ^{148}Nd or ^{150}Nd is the best choice to obtain the lowest uncertainty (*i.e.* minimum F factor) and the easiest to implement (because the plot of the F factor is almost flat in the region around the optimum value). Since all other Nd isotopes in such a sample have higher abundances, choosing an isotope other than ^{148}Nd or ^{150}Nd as the spike isotope will generate a higher minimum F factor and a narrower range around the optimal F factor. Fig. 5 shows the F factor as a function of the sample/spike amount ratio for different spike enrichments when using a spike enriched in the ^{150}Nd isotope. The higher the spike enrichment is, the smaller the optimal F factor is. Moreover, the region around the optimal F factor value is relatively flat for spikes with $R_T > 9$ (*i.e.* spike enrichment higher than 90%), which makes it easier to implement ID. The LOD, in arbitrary units, as a function of the spike isotope ratio is presented in Fig. 6 for different major isotopes of the spike, assuming the LOD of A and B isotopes is equal to 1 in arbitrary units (eqn (7)). The curves for ^{148}Nd and ^{150}Nd isotopes overlap in Fig. 6. The LOD decreases from $R_T = R_S$, tending towards lower LOD values at higher spike enrichments. It should be noted that the choice of spike isotope has no significant influence on the LOD when R_T is high enough. In this example, all LODs are similar irrespective of the spike isotope chosen when $R_T > 6$. In this way, for the measurement of natural Nd by ID-MS, a judicious choice is a spike enriched in ^{148}Nd or ^{150}Nd isotopes with an enrichment greater than 90%. The optimal sample/spike amount ratio in the mixture is then calculated as a function of the spike enrichment (Fig. 5).

Some laboratories do not calculate the optimal parameters for every new sample when measuring U or Pu. Instead, the mixture is prepared in such a way as to obtain a 1/1 ratio between the amounts of spike and sample. This method works well if the conditions for the selection of the spike are fulfilled: the spike isotope is absent from the sample or has the lowest

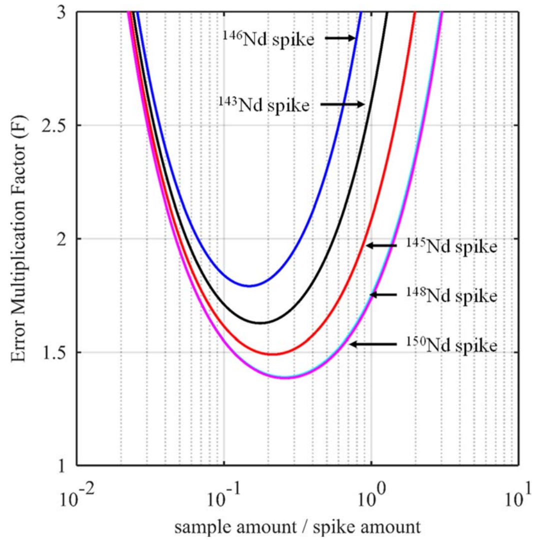

Fig. 4 Error multiplication factor as a function of the sample/spike amount ratio for ^{143}Nd (black line), ^{145}Nd (red line), ^{146}Nd (blue line), ^{148}Nd (cyan line) and ^{150}Nd (purple line) spikes ($R_T = 9$ for all spikes) with a neodymium sample of natural isotopic composition. The ^{144}Nd isotope is used as a reference sample isotope.

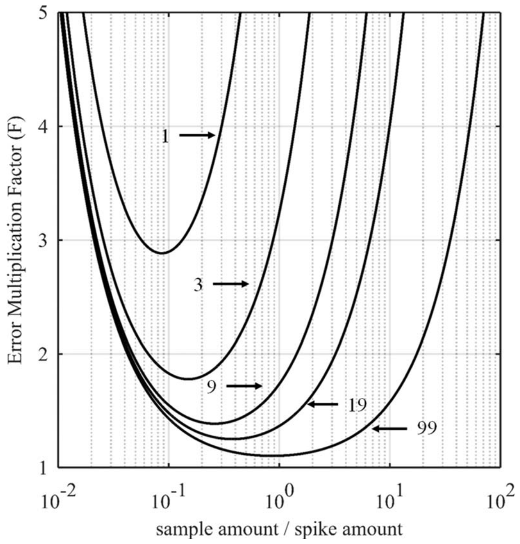

Fig. 5 Error multiplication factor as a function of the sample/spike amount ratio for different ^{150}Nd/^{144}Nd spike isotope ratios ($R_T = 1$, 3, 9, 19 or 99) for measuring natural neodymium.

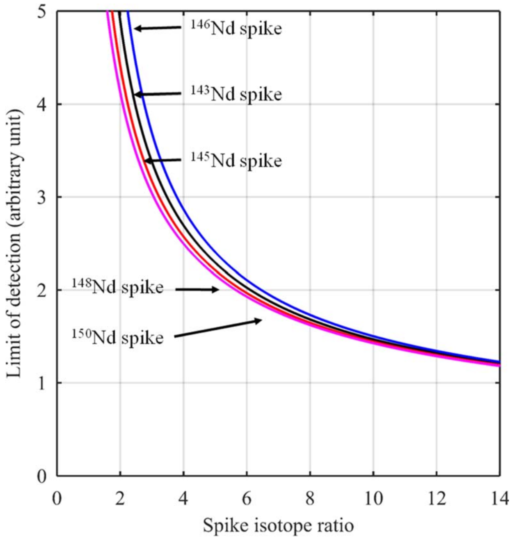

Fig. 6 Limit of detection (arbitrary unit) for a natural sample of neodymium as a function of the spike isotope ratio for spikes enriched in ^{143}Nd (black line), ^{145}Nd (red line), ^{146}Nd (blue line), ^{148}Nd (cyan line) and ^{150}Nd (purple line) isotopes.

isotopic abundance in the sample and the spike enrichment is high enough (Fig. 3). In these examples, the optimal n_S/n_T ratio is found to be 1.3 (F factor = 1.088) for the uranium sample and 0.5 (F factor = 1.011) for the plutonium sample. However, at values around $n_S/n_T = 1$, the F factor (1.093 for uranium and 1.014 for plutonium) is very similar to that at the optimum ratio. In these cases, employing a 1/1 ratio between the amount of the spike and the sample instead of the optimal amount ratio will have no impact on the ID-MS accuracy.

3.3. Spike monitoring

Assessment of the spike stability and homogeneity of liquid spike materials is crucial to ensure the quality of the ID analysis results and their reliability. The behavior of spike materials is difficult to predict reliably solely from stability studies over short periods. Due to evaporation, the observed differences in element mass fraction can be higher than 0.1% after several weeks, which is generally larger than the element mass fraction uncertainty of the spike. To overcome this issue, several solutions are presented in this section.

When using liquid spikes in the form of ampoules, it is recommended to consume the spike solution immediately after opening, or alternatively to dry the prepared aliquots as small-size dried spikes for later use, eliminating the need to correct evaporation effects and additional uncertainty due to dilution. However, due to the scarcity and costs of commercially available spikes, this option is not often applied.

IRMM-1027 Large-Sized Dried (LSD) and LSD spikes produced by the IAEA, prepared from U and Pu metal CRMs, are applied to measure the uranium and plutonium content of dissolved fuels in reprocessing plants.[73,84–86] LSD spike vials have certified masses of uranium (^{235}U and ^{238}U) and ^{239}Pu and isotopic composition with associated uncertainty. The main advantage is that they are to be used on an undiluted sample solution containing mg amounts of U and Pu. A further advantage is that cross-contamination is limited precisely because of the large amounts of the analyte in both the spike and the sample. However, they are prepared for a specific and single use, and until the spikes were in a dried nitrate form, it was not easy to maintain their integrity over longer periods. Nowadays, organic stabilizing substances are used to prolong shelf-life and guarantee stability during shipment.[73]

Liquid spikes are often used after dilution to prolong the operational lifetime of the spike and to adjust the spike solution mass fraction. In this case, not only spike solution evaporation but also the associated uncertainty of performing gravimetrical dilution needs to be considered. Spike solutions in glass ampoules with a screw-cap were introduced by JRC-Geel to replace the flame sealing of ampoules, and are a good choice to reduce the evaporation effects during use. The storage in glass ampoules for U, Pu or Am spikes shows glass–solution interactions have no effect on the spike concentration. Due to safety reasons ampoule sealing by a flame or laser is not commonly applied in analytical laboratories, but with the use of screw-capped ampoules it is possible to verify the evaporation of the spike solution by weighing.

The Atalante Analysis Laboratory of the CEA (CEA/LAAT) and the JRC-Karlsruhe adapted a similar system,[87] where the CRM spike is first gravimetrically diluted to a known mass fraction suitable for mass spectrometry, at the μg g^{-1} level. Approximately 10 mL aliquots of this diluted spike solution are then stored in sealed borosilicate glass ampoules. Upon opening a sealed ampoule of a diluted spike, the diluted spike solution is divided into several vials with caps, each containing a known amount (*i.e.* mass) of spike. The vials can be stored in racks for up to several weeks before use. Any evaporation of this solution will affect the mass fraction of the spike in the vials but not the amount (*i.e.* mass) of spike in the vials. The sample is added to the vials to produce the {sample–spike} mixture. This entire mixture is then evaporated to dryness, thereby eliminating any influence of potential changes in the spike mass fraction due to evaporation during storage. This step ensures the trueness of the isotope ratio in the mixture. The dried {sample–spike} mixture is then dissolved in nitric acid medium for ID-MS measurement (*e.g.* mass spectrometric measurement or separation step). The dilution of the CRM spike is verified annually by means of inter-laboratory comparison exercises.

3.4. Isotopic homogenization of the sample–spike mixture

Essential for correct ID analysis is the isotopic equilibrium in the mixture which may be defined as the homogeneous distribution between the isotopes coming from the sample and the spikes in the mixtures.[88]

In the nuclear field, most of the samples and spikes are in the same strong acidic media. The isotope homogenization is therefore quite easy and fast for most of the radionuclides (U, Th, Am, Cm, lanthanides…). Manual or mechanical shaking of the mixture is carried out for several seconds or minutes to ensure the homogenization.[54] Some laboratories may also heat overnight under reflux to homogenize the mixture or dry the mixture and re-dissolve it in nitric acid.

The analyte in the sample and the spike should be in the same form or species to reach an isotopic equilibrium. For example, in case of Pu ID-MS measurements, the Pu contained in the spike and the Pu coming from the sample may not have the same oxidation state due to the multiple possible redox states of Pu in aqueous solution (+III, +IV, +V, +VI). The Pu in the mixture may be discriminated if a redox cycle is not performed before a separation step to adjust the Pu to a unique valency. Different redox reagents can be used: hydrogen peroxide, an iron II solution, sodium nitrite, potassium metabisulfite or titanium(III) chloride.[89–93] The optimum time to reach the Pu valency adjustment is variable: the Fe(II)/$NaNO_2$ method requires a waiting time of 20 min whereas the hydrogen peroxide requires a minimum waiting time of 2 h.[58]

4. Uncertainty evaluation

4.1. Weighing uncertainty

4.1.1. Expression of the true mass uncertainty. For the true mass (m_{true}), the measurand expression that takes into account the bias in trueness and the correction for air buoyancy is described in eqn (11). The uncertainty associated with m_{true} is derived by propagating the uncertainties of the terms in eqn (11) according to the Guide to the Expression of Uncertainty in Measurement (GUM, eqn (26)).

$$u^2(m_{\text{true}}) = u^2(\Delta X) + u^2(\delta) + \left(\frac{\Delta X}{r} - \frac{\Delta X}{r_0}\right)^2 u^2(a) + \left(\Delta X \frac{a}{r^2}\right)^2 u^2(r) \tag{26}$$

The term $u^2(\Delta X)$, described as the weighing result component, depends on parameters such as the resolution of the balance and the repeatability of the measurement. The term $u^2(\delta)$ is the trueness component, which is also dependent on the resolution and repeatability of the balance, but also on the uncertainty of the standard used for calibration and the uncertainty of its durability. It also takes into account (i) the effect of the air density variation, (ii) the effect of temperature variation and (iii) the effect of eccentricity on the trueness of measurement during calibration.[72] The final terms of the equation, $\left(\frac{\Delta X}{r} - \frac{\Delta X}{r_0}\right)^2 u^2(a) + \left(\Delta X \frac{a}{r^2}\right)^2 u^2(r)$, concern the uncertainty on the corrections for air buoyancy and the effects of variation in air density and that of the sample density under the measurement conditions. It is evident that, even for one measurement, evaluating the uncertainty of a weighing is quite tedious and time consuming.

4.1.2. Expression of the weighing uncertainty from the maximum permissible deviation. In practice, the calibration of the balance consists of determining the δ and the $u(\delta)$ terms for a series of standard masses that are representative of the range of the balance. A specification of performance in accuracy is defined for the balance in the form of a maximum permissible deviation (MPE) according to its class, its range and its resolution.

A metrological confirmation of the balance is then carried out (calibration + verification) to ensure the following inequality after calibration of the balance (eqn (27)).

$$|\delta| + 2u(\delta) \leq \text{MPE}(\Delta X) \tag{27}$$

If this condition is respected over the entire considered mass range, the balance is metrologically confirmed and the MPE can be used for the expression of the weighing uncertainty in a simpler manner.

Assuming that the statistical distribution of weighing measurements follows a continuous uniform law with a span of 2 MPE, the standard uncertainty equals half the span of the distribution (MPE) divided by the square root of 3 (eqn (28)).

$$u(m_{\text{true}}) = \frac{\text{MPE}}{\sqrt{3}} \tag{28}$$

For example, a class 1 balance having a range of 200 g and a resolution of 0.1 mg would traditionally be assigned an MPE of 1 mg, resulting in a standard uncertainty of 0.6 mg according to eqn (28). The mass weight of 0.5 g would then be associated with an expanded uncertainty of 1.2 mg at a confidence level of 95%, corresponding to a relative uncertainty of 0.24%. For such a balance, in order to guarantee a weighing uncertainty on the order of 0.1%,[69] it is recommended to weigh only masses greater than 1 g.

4.1.3. Uncertainty with the substitution method. This method of weighing consists of comparing the sample mass to that of a standard having an almost identical mass, according to a specific scheme, usually an ABBA or SUUS scheme (see Section 3.1 and eqn (10)). The true mass expression becomes eqn (29), with m_{std} the mass of the standard.

$$m_{\text{true}} = m_{\text{std}} + (\Delta X - \delta) + a\left(\frac{1}{r} - \frac{1}{r_0}\right)m_{\text{std}} \approx m_{\text{std}} + \Delta X + a\left(\frac{1}{r} - \frac{1}{r_0}\right)m_{\text{std}} \tag{29}$$

The uncertainty of m_{true} (eqn (30)) is derived from eqn (29).

$$u^2(m_{\text{true}}) = u^2(\mathrm{m}_{\text{std}}) + u^2(\Delta X) + u^2(\delta) + \left(\frac{m_{\text{std}}}{r} - \frac{m_{\text{std}}}{r_0}\right)^2 u^2(a) + \left(m_{\text{std}} \frac{a}{r^2}\right)^2 u^2(r) \approx u^2(m_{\text{std}}) + u^2(\Delta X) \tag{30}$$

This method is not sensitive to balance drift if weighing measurements are spaced regularly over time and if the drift is linear. The trueness error δ is then reduced drastically, because ΔX – the difference between the sample and the standard mass – is very small. The trueness error can then be neglected, as well as its uncertainty contribution when calculating the weighing uncertainty. In practice, only the contributions from standard mass uncertainty and from repeatability are retained, and hence very low uncertainties on the order of tens of μg can be achieved.[73,74]

4.2. Isotope dilution uncertainty

The various ways of estimating measurement uncertainty can be divided into two main categories: inter-laboratory and intra-laboratory approaches.[5] The result of an ID-MS measurement (*i.e.* w_S) can be expressed as a function of various parameters which makes it well suited to be used as an intra-laboratory approach with measurement modelling. Uncertainty estimation of the measurement model must be taken into account, at all the stages of the measurement process and for all input parameters coming from certified values or measured values. Here, we apply this approach to an example: the measurement result for the U mass fraction from CEA/LAAT during the 2022 "Nuclear Material Round Robin" (NMRoRo) ILCs organized by the IAEA. For this measurement LAAT used the IRMM-054 spike, which was first diluted in nitric acid to obtain a known mass fraction of approximately 10 μg g^{-1}. The NMRoRo ILC sample (a uranium oxide powder) was dissolved, after which the solution was diluted three times consecutively to produce a diluted sample. Three {diluted sample–spike} mixtures were gravimetrically prepared. The measurement model is reported in eqn (31). The different steps of spike dilution, sample dissolution and dilutions have been taken into account and only measured or certified data are used as inputs.

$$w_S = \frac{1}{M_T}\cdot\left(\frac{R_{48_S}}{R_{48_S}+R_{58_S}+R_{68_S}+1}\cdot M_4+\frac{R_{58_S}}{R_{48_S}+R_{58_S}+R_{68_S}+1}\cdot M_5+\frac{R_{68_S}}{R_{48_S}+R_{58_S}+R_{68_S}+1}\cdot M_6+\frac{1}{R_{48_S}+R_{58_S}+R_{68_S}+1}\cdot M_8\right)\cdot w_T\cdot\frac{m_T}{m_S}\cdot\frac{A_{8_T}}{\dfrac{1}{R_{48_S}+R_{58_S}+R_{68_S}+1}}\cdot\frac{1/R_{85_T}-R_{58_{Mix}}}{R_{58_{Mix}}-R_{58_S}}\;\frac{m_{4fS}}{m_{4iS}}\;\frac{m_{3fS}}{m_{3iS}}\;\frac{m_{2fS}}{m_{2iS}}\;\frac{m_{1fS}}{m_{1iS}}\;\frac{m_{1iT}}{m_{1fT}} \tag{31}$$

where the measured quantities are: R_{48_S}, R_{58_S}, and R_{68_S}, the ^{234}U/^{238}U, ^{235}U/^{238}U, and ^{236}U/^{238}U ratios in the sample, respectively (mol mol^{-1}); $R_{58_{Mix}}$, the ^{235}U/^{238}U ratio in the mixture (mol mol^{-1}); m_T, mass of the diluted spike used (g); m_S, mass of the sample used (after dissolution and dilutions) (g); m_{1iS}, m_{2iS}, m_{3iS}, and m_{4iS}, mass of the sample before dissolution and sample solution before each of the three dilution steps (g), respectively; m_{1fS}, m_{2fS}, m_{3fS}, and m_{4fS}, mass of the sample dissolution solution and of the solution after each of the dilution steps of the sample dissolution solution (g); m_{1iT}, mass of the spike before dilution (g); m_{1fT}, mass of the spike solution after dilution (g); and where the certified quantities are: M_4, M_5, M_6, and M_8, the molar mass of ^{234}U, ^{235}U, ^{236}U and ^{238}U (g mol^{-1}) respectively;[94] M_T, molar mass of U in the spike (g mol^{-1}) from the IRMM-054 certificate;[95] w_T, the U mass fraction certified value in the spike (g kg^{-1}) from the IRMM-054 certificate;[95] A_{8_T}, isotope abundance of ^{238}U in the spike (mol mol^{-1}) from the IRMM-054 certificate;[95] R_{58T}, the ^{235}U/^{238}U ratio in the spike (mol mol^{-1}) from the IRMM-054 certificate.[95]

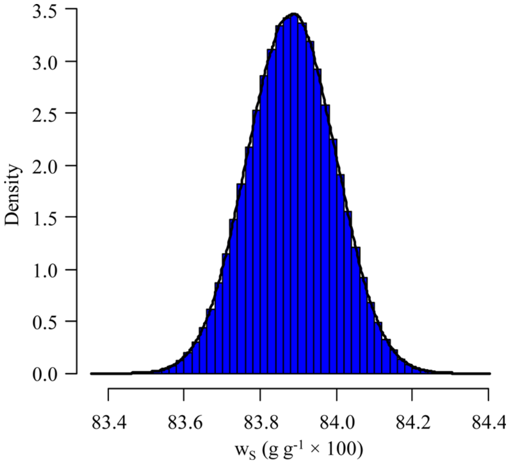

Fig. 7 Distribution law of w_s by MCM – LAAT measurement on the NMRoRo 2022 sample.

From the measurement process model, the uncertainty is estimated by propagating the uncertainty of the input data. This can be done using the Monte Carlo method (MCM), as recommended in supplement 1 of the GUM.[96] This approach requires no assumptions to be made about the distribution of the result, nor about any correlation between the input parameters. However, for each of the input parameters in the NMRoRo example, a particular distribution needs to be chosen, a most probable value and a standard deviation are required before performing the Monte Carlo simulation on the model (eqn (31)).

Using the information provided by the LAAT about the parameter values and their standard uncertainties, and assuming a uniform distribution for each of the masses and a normal distribution for the other parameters, a standard measurement uncertainty of 0.15%§ (probability density function (pdf) of w_s in Fig. 7) is obtained.

The simulated pdf of w_S is not significantly different from a normal law. The uncertainty budget can be established using the sensitivity indices (first-order and total Sobol indices):[97] the budget obtained for this example is illustrated in Fig. 8.

The contributions to the uncertainty of parameters R_{48_S}, R_{58_S}, R_{68_S}, M_4, M_5, M_6, M_8, and M_T are not significant and therefore the uncertainty calculation can be simplified here by treating these inputs as constants. Although some contributions from

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§ All the calculations presented in this paragraph were made using R software (free to use).[99]

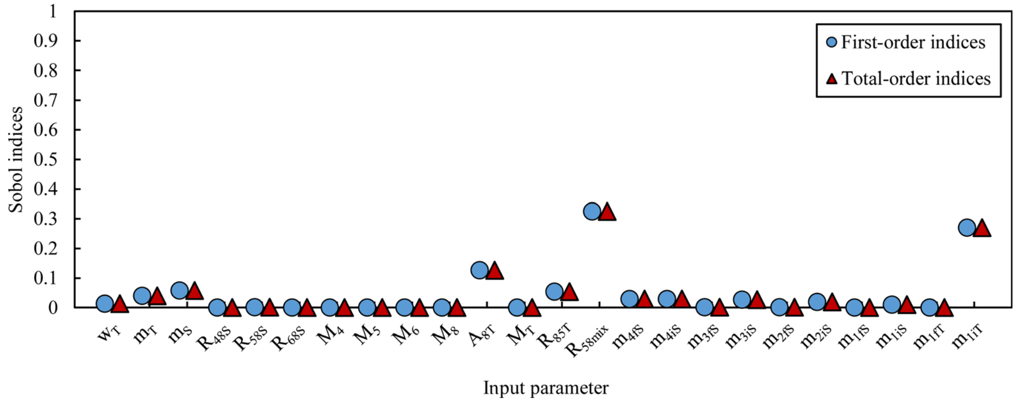

Fig. 8 Sobol indices – LAAT measurement on the NMRoRo 2022 sample.

masses weighed during dissolution or dilution are small, they have been retained in order to maintain the overall dissolution/dilution process, the total contribution of which is not negligible. The measurement model (eqn (31)) then becomes a simplified model (eqn (32)).

$$w_S = w_T \cdot \frac{m_T}{m_S} \cdot \frac{M_S}{M_T} \cdot \frac{A_{8_T}}{A_{8_S}} \cdot \frac{1/R_{85_T} - R_{58_{Mix}}}{R_{58_{Mix}} - R_{58_S}} \cdot \frac{m_{4fS}}{m_{4iS}} \cdot \frac{m_{3fS}}{m_{3iS}} \cdot \frac{m_{2fS}}{m_{2iS}} \cdot \frac{m_{1fS}}{m_{1iS}} \cdot \frac{m_{1iT}}{m_{1fT}} \tag{32}$$

where M_S is the molar mass of U in the sample (g mol^{-1}, eqn (33)) and A_{8S} is the isotope abundance of ^{238}U in the sample (mol mol^{-1}).

$$M_S = \frac{R_{48_S}}{R_{48_S} + R_{58_S} + R_{68_S} + 1} \cdot M_4 + \frac{R_{58_S}}{R_{48_S} + R_{58_S} + R_{68_S} + 1} \cdot M_5 + \frac{R_{68_S}}{R_{48_S} + R_{58_S} + R_{68_S} + 1} \cdot M_6 + \frac{1}{R_{48_S} + R_{58_S} + R_{68_S} + 1} \cdot M_8 \tag{33}$$

From this equation, we can conclude that (1) the result distribution is not significantly different from a normal distribution; (2) several influencing parameters contribute to the uncertainty, and (3) the first-order and total Sobol indices are very similar, meaning there is no correlation between the influencing parameters (Fig. 8). These findings mean that, if desired, the GUM approach[98] (quadratic cumulation method) without covariance can also be applied to the simplified model (eqn (32)). This approach leads to the same standard uncertainty on w_S as the MCM approach, *i.e.* 0.15%. The similarity between uncertainty budgets estimated with the MCM (recommended in GUM-S1) and by the quadratic cumulation method (recommended in GUM) for the NMRoRo sample at LAAT is illustrated in Fig. 9. For this measurement, the main contributors to the uncertainty are $R_{58_{Mix}}$ (33%), m_{1iT} (28%), A_{8_T} (13%), m_S (6%), R_{85_T} (5%), and m_T (4%).

In conclusion, the measurement uncertainty of ID-MS is estimated in several stages:

(1) The measurement process is modelled on the basis of eqn (31) or taking into account all the stages in the process (dissolution, dilution, *etc.*) and using input parameters with certified values or measured values (avoiding input parameters that are mathematical expressions).

(2) The propagation of the uncertainty by using the MCM, preferably, and assess the uncertainty budget (sensitivity indices).

(3) If needed or desired, simplify the measurement model by reducing the number of variables and considering other parameters as constants.

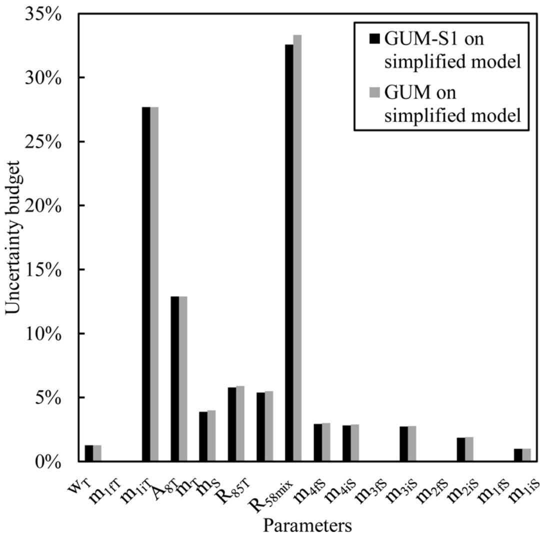

Fig. 9 Sensitivity indices obtained by the MCM or quadratic cumulation method – LAAT measurement on the NMRoRo 2022 sample.

(4) If needed or desired, in the case where (i) the result distribution does not differ significantly from a normal distribution, (ii) more than one parameter contributes to the uncertainty, and (iii) the first-order and total Sobol indices are very similar, we can apply the quadratic cumulation method (GUM) without covariance terms to the model.

Note: As calculations are easy and quick with R,[99] we recommend using the MCM approach (GUM-S1).

5. Application for radionuclide measurement

5.1. Environmental applications

5.1.1. Application in Earth sciences

5.1.1.1. U-series disequilibrium. The ID-MS technique plays a key role in the U-series disequilibrium studies in environmental and Earth sciences. U-series geochemistry provides a profound understanding of fundamental processes in widespread disciplines as diverse as geomorphology,[100] weathering and erosion of geological formations,[101] oceanography,[102] and environmental pollution science.[103,104] A wide range of U-series geochemistry applications to the Earth sciences was thoroughly summarized in "*Uranium-series Disequilibrium, Applications to Earth, Marine and Environmental Sciences*".[105] The uranium and thorium decay-series contain radioactive isotopes of many elements (in particular, $^{234,\ 235,\ 238}$U, $^{230,\ 232}$Th, ^{231}Pa, ^{226}Ra and ^{227}Ac) with varied physicochemical properties leading to a fractionation (mainly elemental fractionation) within the chain in different geological environments during geochemical processes. The accurate measurement of these radionuclides and more specifically their elemental ratios (*i.e.*, ^{230}Th/^{238}U, ^{238}U/^{232}Th, ^{231}Pa/^{235}U, ^{226}Ra/^{230}Th) allows the investigation of processes occurring on time scales from a hundred years to ~600 000 years. To this end, radionuclide concentrations are accurately determined in environmental samples by ID-MS. It is worth mentioning that isotopic compositions (*i.e.*, ^{234}U/^{238}U and ^{230}Th/^{232}Th) are also mandatory for disequilibrium studies, however this topic will not be addressed in this section, as it does not fall under the scope of ID-MS.

Sample preparation is a crucial step that strongly influences the quality of analytical results. Generally, natural solid samples undergo total dissolution in Teflon bombs or beakers. The digestion protocol is adapted according to the sample matrix. Usually for rocks, sediments and soils, concentrated HNO_3, HF, or $HClO_4$ (ref. 106 and 107) or alkaline fusion[108] is used. After sample digestion, separation protocols for U/Th,[106,109–114] Ra,[111,112,115–121] Pa[111,113,122,123] and Ac[124,125] extraction are used. An exhaustive review for Ra separation protocols can be found in Boudias *et al.*[126] Radionuclide separation helps concentrating the radionuclides of interest, minimizing matrix effects and reducing or removing polyatomic interferences.

For the determination of U concentrations in natural samples two kinds of spikes are commonly used: a single spike (^{233}U or ^{236}U) or a double spike (^{233}U–^{236}U) certified in both concentration and isotope ratio. The ^{233}U–^{236}U double spike method was first introduced by Dietz *et al.*[127] and thanks to this technique it is possible to proceed to ID by internally correcting the instrumental mass fractionation using the certified ratio ^{233}U/^{236}U (*i.e.* to correct the ^{238}U/^{236}U ratio).[106,128,129] If a single isotope is used for spiking, the standard-bracketing method should be employed to externally correct for the instrumental mass fractionation or the total evaporation method may be employed in the case of TIMS measurement to overcome the isotope fractionation.[37,130] With a new generation multi-collector-ICP-MS (MC-ICP-MS) equipped with high-efficiency desolvation systems, it is possible to achieve LODs of $\sim 10^{-7}$ and $\sim 10^{-8}$ ng g^{-1} for ^{233}U and ^{236}U, respectively.[131]

The ^{230}Th dating (based on the radioactive decay: $^{238}\text{U} \Rightarrow {}^{234}\text{U} \Rightarrow {}^{230}\text{Th}$) method has become one of the most important dating methods for quaternary research,[132] radiocarbon calibration[133] and also for weathering and erosion studies.[134] A major source of uncertainty for the ^{230}Th/^{238}U ratio is the accurate measurement of the amount of ^{230}Th. More commonly, ^{230}Th is measured by using an isotopically enriched ^{229}Th material as a spike.[135–138] This ^{229}Th spike can be an "in-house" standard or certified ^{229}Th standards such as the standard reference material (SRM) 4328C[139,140] and reference materials provided by the National Physical Laboratory (NPL)[141] or the Eckert and Ziegler company. However, to use an "in-house" spike, the analyst must expend considerable effort in producing, calibrating, and, if possible, establishing traceability. Recently, a new high purity ^{229}Th ($^{230}\text{Th}/^{229}\text{Th} = 5.18 \times 10^{-5}$ and $^{232}\text{Th}/^{229}\text{Th} = 3.815 \times 10^{-4}$) reference solution was commercialized by the National Institute of Standards and Technology (NIST).[36] This spike is ideal for measuring samples with very low $^{230,\ 232}$Th content (*i.e.* young carbonates, *etc.*). For the correction of the instrumental mass fractionation on the ^{230}Th/^{229}Th or ^{232}Th/^{229}Th (for ^{232}Th determination) ratios, the IRMM-035 CRM[142] and the standard-bracketing method are used. Thanks to the double isotope dilution method (eqn (6)), the ^{230}Th/^{238}U concentration ratio can also be accurately determined by using a double (^{229}Th–^{236}U or ^{233}U) or a triple spike (^{229}Th–^{223}U–^{236}U). A triple spike was used in U migration studies in marine sediments[143] and for environment pollution purposes.[103] The LODs of ^{230}Th for seawater samples are close to 0.15 fg kg^{-1}.[144] For analytical purposes, it is preferable in certain cases to measure the ^{230}Th/^{235}U ratio (as ^{230}Th is closer in terms of abundance to ^{235}U compared to ^{238}U), and subsequently calculate the ^{230}Th/^{238}U ratio by taking into account the natural ^{238}U/^{235}U ratio (137.818 ± 0.045).[145]

For ^{226}Ra determination in natural samples, a spike such as ^{228}Ra is used. It is worth mentioning that the natural ^{228}Ra contribution is considered negligible due to its very low natural abundance and its very short half-life ($t_{1/2} = 5.75$ years[146]) compared to that of ^{226}Ra ($t_{1/2} = 1600$ years[146]). However, in some specific cases for solid samples containing a high concentration of ^{232}Th, a pre-analysis before spiking for the determination of the ^{228}Ra/^{226}Ra ratio is mandatory to correct for the contribution of natural ^{228}Ra. The ^{228}Ra spike is commercially provided (*i.e.* NIST-SRM 4339B, NPL, *etc.*), but generally in geosciences, an enriched ^{228}Ra spike is prepared by milking the Ra fraction from an old pure thorium nitrate material (*i.e.* $Th(NO_3)_4$). The ^{228}Ra fraction can be used directly after its separation from ^{232}Th[120,121,147] or the ^{232}Th solution is purified from Ra (^{226,228}Ra) and then the purified thorium solution is set aside, and ^{228}Ra grows in through ^{232}Th decay.[148] As ^{226}Ra (impurities of ^{230}Th $\Rightarrow$ ^{226}Ra) grows much more slowly than ^{228}Ra, at the beginning of ^{232}Th decay (some months or years) a high ^{228}Ra/^{226}Ra ratio suitable for ID-MS can be obtained. The ^{228}Ra spike concentrations were calibrated against certified ^{226}Ra solutions (*i.e.* provided by NIST and NPL) or by using the Harwell Uraninite (HU-1)[119] that is known to be close to secular equilibrium.[128] Typical values of LOD of ^{226}Ra are close to $\sim$0.1 fg g^{-1} (3 mBq kg^{-1}).[149,150]

The ^{231}Pa/^{235}U radiochronometer is complementary to that of ^{230}Th/^{238}U and can be used to obtain more reliable age estimates, especially for samples with complex histories. Moreover, the ^{231}Pa/^{230}Th ratio is a very useful paleoproductivity and scavenging ocean tracer.[151,152] The measurement of ^{231}Pa concentration is performed by ID-MS with ^{233}Pa as the spike isotope.[153,154] Due to the short half-life of ^{233}Pa ($t_{1/2}$ = 26.98 days[155]), no certified ^{233}Pa spike exists. Rather, the ^{233}Pa spike is prepared by milking the Pa fraction from a ^{237}Np solution immediately prior to use and calibrated for ^{233}Pa concentration for its working-lifetime of approximately 3–4 months. The ^{233}Pa spike is calibrated using commercially available[156] or "in-house" ^{231}Pa standard solutions calibrated against the HU-1. Recent developments allow the measurement of quantities as low as 0.1 fg of ^{231}Pa by MC-ICP-MS.[102,157] TIMS protocols for ^{231}Pa analysis allow the determination of as little as a few tens of fg to a few ag.[153,158] Moreover, high resolution ICP-MS (HR-ICP-MS) reported LOD values were close to 0.02 fg kg^{-1}.[144]

Recently, the analysis of ^{227}Ac by ID-MS was developed for nuclear forensic purposes.[125] However, this technique has found important applications in environmental studies mainly in oceanography.[124] As there is no commercial spike for Ac, the method for isotope dilution measurement of ^{227}Ac uses a ^{229}Th standard to provide ^{225}Ac, which is used as the spike. ^{227}Ac determination by MC-ICP-MS in seawater makes reliable measurements with 10 L samples with ^{227}Ac concentrations of $\sim$2 ag kg^{-1} with a LOD of around 0.7 ag kg^{-1}.[124]

5.1.1.2. Other radiogenic elements: ^{87}Rb–^{87}Sr method. The ^{87}Rb–^{87}Sr method stands out as one of the earliest dating techniques in geology. It has been widely used, particularly since the introduction of the Sr evolution diagram which enabled the determination of both the age and initial ^{87}Sr/^{86}Sr ratio for sets of co-genetic samples.[159,160] Contrary to U-series applications where non-naturally occurring tracers could be used, in this case isotopically enriched tracers of natural isotopes (*e.g.*, ^{84}Sr or ^{86}Sr, ^{87}Rb at purities higher than 96%) are commonly used.[161] It should be noted that before analysis, Rb and Sr are chemically separated to avoid isobaric interference at *m*/*z* 87.

5.1.2. Application to environmental monitoring of nuclear facilities. Monitoring of the environment is a major concern for the nuclear industry. The main sources of anthropogenic radionuclides in the environment are fallout from nuclear weapons tests, releases during nuclear accidents, waste reprocessing and authorized discharges. In this context, ID is used both to quantify the activity of the radionuclides and to determine the isotopic ratios characteristic of the source of the deposit. When available, a known quantity of a certified spike is added in the beginning of the analysis, as specified in the norms for the analysis of radioactivity in the environment for isotopes of uranium[162] and plutonium[163,164] for example.

A good candidate spike for ID-MS has a half-life large enough to limit the activity handled, be readily available and contain few isotopic impurities. If the isotopic composition of the radioelement that is suspected to be present as a contaminant in the environmental sample is not known, it is important to ensure that the radioactive tracer added for ID is not already present in the sample. In such a case, the measured elemental concentration of the radioelement will be wrong. If suspected, an analysis without the addition of the spike is mandatory to correct for the presence of the isotope used as an ID spike in the environmental sample. If ID-MS is done with an isotope naturally present in the environmental sample, an analysis of the sample without and with the spike needs to be done. In any case, the purity of the spike has to be verified before use, to check that it does not contain the isotopes of interest in the sample, and if present to carry out the appropriate corrections. In many cases, the isotope composition of the spike, including impurities, is mentioned in the certificate. Otherwise, abundances of isotope impurities must be quantified with an appropriate technique, for instance by direct measurement of a significant amount of spike with the most accurate mass spectrometer available.

In the following, we describe the implementation of ID to the most common radioelements that can be measured by mass spectrometry and that may be the subject of environmental monitoring of nuclear facilities.

5.1.2.1. Uranium. The isotopes of interest for the survey of uranium in the environment are ^{234}U, ^{235}U, ^{236}U and ^{238}U. The measurement of the abundances of these isotopes (or isotope ratios with respect to ^{238}U) helps to distinguish an anthropogenic contribution from naturally occurring uranium. In particular, the abundance of ^{235}U is characteristic of the industrial origin of uranium and shows a significant difference with respect to that of natural uranium. Indeed, the abundance of ^{235}U in man-modified uranium ranges from $\sim$0.2% in depleted U to more than 20% for highly enriched U, reaching abundances higher than 90% in nuclear weapons.[165] By contrast, ^{235}U abundance in naturally occurring uranium shows very small variations around an average value of 0.725% (isotopic abundance). The ^{236}U isotope is also an excellent fingerprint of anthropogenic nuclear activities. Indeed, this isotope does not exist in measurable abundance in the environment (^{236}U/^{238}U < 10^{-12}), but it is produced in a nuclear reactor through neutron capture by ^{235}U nuclei. For instance, ^{236}U/^{238}U isotope ratios can reach 10^{-3} in spent fuel. So the detection of a significant abundance of ^{236}U by mass spectrometry is also characteristic of environmental marking through nuclear activities.[166] As a consequence, use of ^{236}U as an ID spike is not recommended when the presence of irradiated uranium is suspected. By contrast, ^{233}U is generally not present in nuclear materials (except in a few cases, for instance when ^{232}Th is irradiated) and so is absent in environmental samples.

Thus, the spike recommended for ID-MS is ^{233}U.[162] It can be provided with a good purity by NPL or JRC (IRMM-057) for example. Mass bias factor correction, and gain calibration of the detectors in the case of measurements with a multiple-collector mass spectrometer, can be performed with certified reference materials whose isotope ratios are certified (for example NBL CRM U030-A or IRMM-186).

5.1.2.2. *Plutonium.* Plutonium isotopes are produced in nuclear reactors through successive neutron captures: ^{239}Pu by capture of a neutron by a ^{238}U nuclei, ^{240}Pu by capture of a neutron by a ^{239}Pu nuclei, *etc.* The most common plutonium isotopes measured in environmental samples by ID-MS are ^{239}Pu, ^{240}Pu, ^{241}Pu and ^{242}Pu. It should be mentioned that extremely low concentrations of plutonium are present in soil samples, although they are measurable by combining thorough radiochemical separations with the most sensitive mass spectrometry techniques.[167] This is a worldwide marking which originates from the global fallouts of thermonuclear atmospheric nuclear weapons tests. So quantification of plutonium is not sufficient to identify a recent, man-made origin: measurement of isotope ratios is mandatory for that. Indeed, isotope ratio compositions of plutonium from global fallout and from various nuclear activities (separation of military or civilian plutonium, reprocessing, *etc.*) show significant differences. For example, the ^{240}Pu/^{239}Pu and ^{241}Pu/^{239}Pu atomic ratios of the global fallout of atmospheric nuclear weapons tests are respectively 0.182 and 9.7×10^{-4},[168] whereas the ratio of ^{240}Pu/^{239}Pu in environmental samples from nuclear weapons test sites at the atolls of Mururoa is 0.018 ± 0.005 (at./at. $\pm 2\sigma$).[169] In the fuel cycle facilities, isotope ratios of Pu are slightly different. In the pressured water reactor using oxide enriched uranium fuel, the isotope ratios of ^{240}Pu/^{239}Pu and ^{241}Pu/^{239}Pu are around 0.4 and 0.2 (w_t/w_t) respectively, and in MOX fuel the ratios are around 0.9 and 0.4 (w_t/w_t) respectively.[170] The ^{240}Pu/^{239}Pu ratio is the easiest ratio to measure in the environment as ^{239}Pu and ^{240}Pu are generally the most abundant isotopes. ^{241}Pu is a short-lived isotope ($t_{1/2} = 14.325$ years[171]) whose abundance can be correlated with that of its decay product ^{241}Am.[172] However, ^{238}Pu is generally measured by alpha spectrometry because of the non-negligible interference of ^{238}U at the same mass and its relatively short radioactive period ($t_{1/2} = 87.74$ years[173]). The spike commonly used for ID-MS is ^{242}Pu in water[163] and solid matrices,[172] but ^{244}Pu can also be chosen if ^{242}Pu is expected in the sample.[163,174] A ^{242}Pu spike can be provided with a very high purity by NIST (SRM 4334) or JRC (IRMM-049) and a ^{244}Pu spike by IRMM (IRMM-042a). ^{242}Pu can also be used as a spike for alpha spectrometry measurements.[164] Mass bias can be corrected with a ^{235}U/^{238}U certified ratio.

5.1.2.3. *Americium.* Traditionally, ^{241}Am ($t_{1/2} = 432.6$ years[146]) was measured by alpha spectrometry. In the past few decades, ICP-MS has been more and more widely used as a fast and highly sensitive technique for the measurement of ^{241}Am.[175] Indeed, new generations of ICP-MS/MS are more sensitive and help to better remove the interferences. For example, for 1 g of ash sediment sample, the measurement of ^{241}Am with an ICP-MS/MS coupled with the APEX Ω sample introduction system and the addition of O_2/He gas to remove the ^{241}Pu interference, allows a LOD of ^{241}Am of 20 mBq kg^{-1} to be reached.[175] The most suitable long-lived americium isotope suitable for the determination of the ^{241}Am mass fraction in environmental samples by ID-MS is ^{243}Am ($t_{1/2} = 7370$ years[146]).[176] The ^{243}Am spike can be provided by NPL (A14063), CETAMA (STAM CRM) or JRC (IRMM-0243) with good purity.[56]

5.1.2.4. *Technetium-99.* ^{99}Tc is a long-life fission product ($t_{1/2} = 2.115 \times 10^5$ years[146]). For ^{99}Tc, the best candidates for ID-MS are ^{97}Tc ($t_{1/2} = 2.6 \times 10^6$ years[177]) and ^{98}Tc ($t_{1/2} = 4.2 \times 10^6$ years[178]) due to their long half-life. Unfortunately, they are not commercially available.[179] However, natural ^{185,187}Re is commonly used, as an analog of Tc, to estimate the radiochemical recovery, or the short-lived ^{99m}Tc ($t_{1/2} = 6.00660$ h[180]) measured by gamma spectrometry. Another point to consider is that interferences such as ^{98,99,100}Ru and ^{97,98,100}Mo may still be present even after a high decontamination factor of the sample. Thus, even with the use of ^{97}Tc for ID-MS, interferences have to be corrected by calculation or eliminated by the introduction of an appropriate gas into the collision–reaction cell of an ICP-MS. For instance, Yang *et al.* implemented an ICP-MS/MS with O_2, as a reaction gas, to remove Mo.[179]

5.1.2.5. *Radio-cesium.* The ^{135}Cs/^{137}Cs ratio is a new relevant anthropogenic signature in environmental samples that emerged after the Fukushima accident, thanks to the new possibilities offered by ICP-MS/MS. Both are fission products with half-lives of $t_{1/2}(^{135}\text{Cs}) = 2.3 \times 10^6$ years and $t_{1/2}(^{137}\text{Cs}) = 30.018$ years.[146] The ^{135}Cs/^{137}Cs ratio is useful for identifying the origin of radio-cesium. It can be determined after a high purification of the sample and the use of gas in the collision–reaction cell for ICP-MS measurement.[28,29] However, no radioactive spike is available for ID-MS and no certified solutions of the ^{135}Cs/^{137}Cs ratio are available commercially to correct the mass bias effect. Then, the chemical yield can be estimated by gamma measurement of the intrinsic ^{137}Cs of the sample before and after purification of the sample as an internal isotope dilution standard. Moreover, a solution qualified by a more accurate method (TIMS for example) can be used to correct for the mass bias effect. In addition, reference materials such as IAEA-330, IAEA-375 and IAEA-385 can be analyzed to validate the analysis.[28,29]

5.1.2.6. *Iodine-129.* Recent publications present the possibility of measuring ^{129}I, a very long-life decay product ($t_{1/2} = 1.614 \times 10^7$ years[181]), by mass spectrometry in environmental samples with a lower LOD than γ-spectrometry.[182] However, even if its long half-life is favorable for MS measurement, its volatility and the numerous interferences can be challenging. Also, an important memory effect of I in ICP-MS has been reported.[183] The quantification of ^{129}I is usually based on the isotopic dilution technique using stable ^{127}I as an internal standard and the mass shift mode of the ICP-MS/MS. The initial amount of ^{127}I is then quantified with an external calibration.[182] The use of ^{125}I present in certified NIST SRMs 4407H and 4407L is also mentioned to quantify ^{129}I by ID because the abundance of ^{129}I in the CRMs is negligible.[183]

5.1.2.7. *Neptunium-237.* The measurement of Np by ID-MS is difficult. In radioactive samples originating from the nuclear fuel cycle, the ^{237}Np isotope is the only isotope of Np with a long half-life. The only other isotope of Np with a long half-life is the ^{236}Np isotope ($t_{1/2} = 1.55 \times 10^5$ years[146]) which might permit the determination of ^{237}Np by ID-MS. However, ^{236}Np is not commercially available and its production is difficult.[184,185] If a laboratory happens to have a ^{236}Np solution, it is possible to create an in-house spike by measuring the ^{236}Np amount fraction by ID-MS using a commercially available ^{237}Np material. The in-house ^{236}Np spike can then be used to measure the ^{237}Np in a sample by ID-MS.[186] In the absence of a ^{236}Np spike, a ^{242}Pu spike can be used to measure the ^{237}Np by ID-MS.[184,187] In that case, measurements must be made by ICP-MS, and not by TIMS, due to the different behaviors to sublimation between Pu and Np during the measurements.

5.2. Nuclear forensics

In the framework of nuclear forensic investigations, seized materials are characterized as completely as possible by complementary techniques, to carry out physical characterization (size and weight) and determine the chemical, elemental, and isotopic compositions, as well as concentrations of non-radioactive and radioactive impurities. It is the combination of all these parameters that provides clues to determine the origin or the processing history of the nuclear material intercepted outside regulatory control.[188–190] Of all these analyses, age dating measurement gives an indication of the time elapsed since a nuclear material last underwent chemical purification. The date of the purification (also called "model age") is obtained by measuring the ratio between a nuclide and its daughter product. The "model age" is calculated by using the equation derived from Bateman's equations (eqn (34)). This equation is valid provided that all the daughter products have been removed during the last chemical operation on the material (at the production stage), and the system has been kept closed ever since (no contamination, no elemental segregation).

$$t = \frac{1}{\lambda_\mathrm{p} - \lambda_\mathrm{d}} \ln\left(1 - \frac{n_\mathrm{d}}{n_\mathrm{p}} \times \frac{\lambda_\mathrm{d} - \lambda_\mathrm{p}}{\lambda_\mathrm{p}}\right) \quad (34)$$

with λ_p and λ_d being the decay constants of the parent and daughter products, and $n_\mathrm{d}/n_\mathrm{p}$ being the atomic ratio of the daughter nuclide to its parent nuclide.

This $n_\mathrm{d}/n_\mathrm{p}$ ratio is derived from the concentration measurement of each nuclide in the nuclear material. The accuracy of the age calculation depends directly on the accuracy of these concentrations and the accuracy of the half-lives involved in the calculation. To this end, ID-MS is the method that can achieve the best results, provided there is rigor in the choice of the isotopic spikes, in the chemical purification of the material and in the mass spectrometric measurements. The uncertainties of the half-lives of the parent nuclides and of the daughter products (mainly ^{234}U–^{230}Th, ^{235}U–^{231}Pa, ^{234}U–^{238}Pu, ^{235}U–^{239}Pu, ^{236}U–^{240}Pu, ^{238}U–^{242}Pu and ^{241}Pu–^{241}Am) are very low (between less than 0.01% and 0.4% (for ^{231}Pa)) and their contribution to the global uncertainty is generally negligible.

In the preceding decade, there has been a large international effort made to improve the methods for uranium age dating measurements, through the development of reference materials or round robin exercises.[8,10,191,192] Uranium has two commonly used chronometers: ^{230}Th/^{234}U and ^{231}Pa/^{235}U. To quantify the different uranium isotopes, most laboratories use a ^{233}U spike. For ^{230}Th quantification, a spike enriched in the ^{229}Th isotope can be used.[36] The method used to calibrate an ID spike can influence the uncertainty. For example, ^{229}Th spikes are often calibrated by means of alpha spectrometry, which leads to a large relative uncertainty (>1%) in the determination of the ^{230}Th concentration and the necessity to convert the certified ^{229}Th specific activity to molality using the ^{229}Th half-life. Bias in this half-life value will affect the accuracy of the results. Production of a new ^{229}Th reference material certified by mass spectrometric measurements[36] in combination with the publication of coherent values for ^{229}Th half-life[193–196] have enabled the development of uranium age dating with the ^{230}Th–^{234}U chronometer.

The ^{231}Pa–^{235}U chronometer is not as widely used. One of the main reasons for this is the difficulty in obtaining a calibrated isotopic dilution spike. ^{233}Pa is obtained by milking a ^{237}Np solution. The short half-life of ^{233}Pa ($t_{1/2} = 26.98$ days[155]) makes it difficult to have a commercially available certified spike. Laboratories must prepare it, when required, for immediate use. The ^{233}Pa solution can be calibrated by various methods: gamma measurement, ID-MS with a rock at secular equilibrium,[197] ID-MS with a ^{231}Pa solution or after decay of the ^{233}Pa, by measuring the concentration of the decay product (^{233}U).[198] ^{233}Pa and its decay product (^{233}U) are isobars. The chemical purification has to be optimized to eliminate U from the Pa fraction, and the Pa measurements have to be performed immediately after purification. If the measurement is delayed, a correction for ingrowth of ^{233}U has to be included in the calculation, which increases the measurement uncertainty.

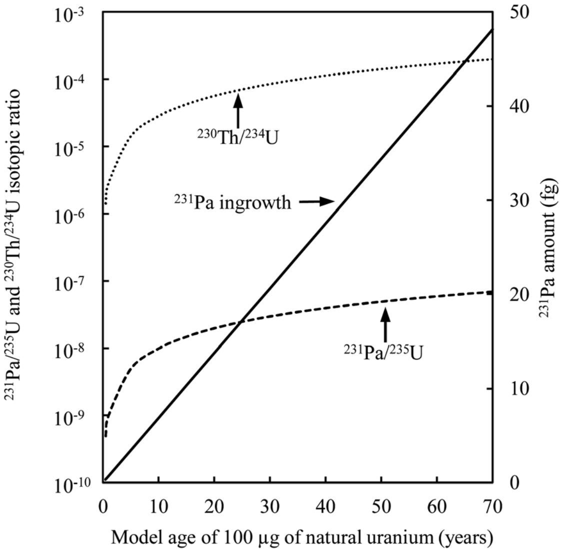

Fig. 10 Temporal evolution of the daughter/parent isotopic ratio for 100 µg of natural uranium. The dotted line is for the ^{230}Th–^{234}U chronometer, dashed line is for the ^{231}Pa–^{235}U chronometer and solid line is for the ingrowth of ^{231}Pa in fg.

As illustrated with Pa, the decay of the spike is important for age dating measurement. This is also the case for thorium, where ^{229}Th is the daughter product of ^{233}U. If ^{233}U is used as a spike for U ID-MS, the aliquot for Th ID-MS must be prepared separately.

Another difficulty with U age dating is the variability in the atomic abundance of the parent nuclide compared to its daughter product (Fig. 10). The amount of sample to be analyzed has to be carefully defined before spiking the different aliquots and starting the analyses. The laboratory environment must be considered. The use of a large amount of spike or sample will affect the laboratory and instrumental background, thereby leading to biases in the measurement. When the chemical purification is optimized and if the instrument is very sensitive, it is possible to date small masses of nuclear materials,[9] thereby economizing on reagents and the amount of precious spike.

It should be noted that, in the case of plutonium, although five radio-chronometers are potentially measurable, ^{234}U–^{238}Pu, ^{235}U–^{239}Pu, ^{236}U–^{240}Pu, ^{241}Am–^{241}Pu and ^{238}U–^{242}Pu, only three different spikes are required, ^{233}U for U ID-MS, ^{244}Pu for Pu ID-MS and ^{243}Am for Am ID-MS. The use of the ^{244}Pu isotope enables one to determine the concentration of all the Pu isotopes from ^{239}Pu to ^{242}Pu. Due to the isobaric interference at mass 238 from ^{238}U, it is preferable to measure the ^{238}Pu by alpha spectrometry. Also simultaneous measurements of ^{238}U and ^{238}Pu are reportedly possible by TIMS.[199,200] The impact of the minor isotopes in the ^{244}Pu spike depends on the composition of such spike. A new ^{244}Pu reference material has been released recently,[43] which is really pure (the main impurity is ^{242}Pu with ^{242}Pu/^{244}Pu < 10^{-4}). With such spike the ID-MS has no impact on the spike's minor Pu isotopes on the final uncertainties. If the level of minor isotopes is around the percent level, it is then recommended to do an independent isotopic measurement of the material, and to use ID-MS to quantify only the major Pu isotope.

For completeness, it should also be mentioned that grand-daughter–parent chronometers (such as ^{226}Ra–^{234}U and ^{227}Ac–^{235}U) can be used for age dating determination. However, this is not very common.[125]

5.3. Safeguards

Destructive analysis of safeguards samples is used to independently verify fuel cycle facility operators' nuclear material accountancy declarations and the quality of the operator's measurement systems. ID-MS is one of the most accurate analytical technique to determine the uranium/plutonium content in safeguards samples. Furthermore, the ITVs for measurement uncertainties in safeguarding nuclear materials provide state-of-practice uncertainty limits for ID-MS measurements.[24,25] The safeguards laboratories of the IAEA and the JRC-Karlsruhe use ID-MS for analysis of nuclear safeguards samples. These laboratories use ID-MS for the production of reference materials, for external verification activities in the production of LSD spikes,[84,201] for the verification of spike solutions and in-house working standards, as well as for the preparation of reference solutions that are needed for the calibration of instruments.

LSD spikes are used for fissile material control of irradiated nuclear spent fuel by operators, as well as regulatory and safeguards authorities, for instance the IAEA safeguards laboratories at the Rokkasho On-Site laboratory (OSL) and at the EURATOM OSL in the Orano nuclear fuel reprocessing facilities at La Hague. LSD spikes are provided by JRC-Geel,[84,201] the IAEA[86] and the Japan Atomic Energy Agency (JAEA)[202,203] and they are typically prepared from Pu and U metal CRMs. They are verified using independent analysis techniques and ID-MS. LSD spikes typically contain 2 mg Pu (90–98 wt% ^{239}Pu) and 10–50 mg of enriched uranium (20–93 wt% ^{235}U). The IAEA LSD spikes are prepared as glassy dried nitrates deposited on the bottom of penicillin vials. The JRC-Geel IRMM-1027 series are commercially available[84] and they are also prepared as dried nitrates deposited on the bottom of penicillin vials, although a stabilizing matrix is used to improve the mechanical stability of the spike, carboxymethyl cellulose sodium salt (CMC) or cellulose acetate butyrate (CAB).[73,204,205] The stability of spikes, which can be affected by transportation or storage conditions in the OSLs, is essential for the quality of the ID-MS analysis. In analogy to the IRMM-1027 spikes,[206] the IAEA is investigating the use of CMC to create foam-like LSD-type spike materials to increase stability and extend the life-time of the LSD spikes. For quality control and instrument calibrations for primary assay measurement techniques applied in the Rokkasho OSL (HKED or Spectrophotometry), with the current status of operations of a reprocessing facility, the Office of Safeguards Analytical Services Nuclear Material Laboratory (SGAS-NML) prepares approximately 500 units of LSD spike vials every two years. For analysis of highly active liquid waste materials, small size ^{233}U and ^{242}Pu spikes are used containing mg amounts of U and μg amounts of ^{242}Pu.

In SGAS-NML and in the safeguards laboratory at the JRC-Karlsruhe there is a wider range of spike materials available for analysis of safeguards samples. At the SGAS-NML milligram-sized dried U/Pu samples are spiked directly in the vials as received. Mono-element spike solutions, containing major isotopes ^{238}U, ^{235}U, or ^{233}U, and ^{239}Pu or ^{242}Pu, are selected, depending on the declared isotopic composition of the samples that are used for ID-MS analysis. High abundance ^{240}Pu spike solutions have been used in the past, but their use has been abandoned due to safety concerns (pressure build-up in ampoules during storage), with ^{242}Pu spikes being used instead. In general, most of the spike materials used for analysis of those samples are liquid solutions, produced in-house from metal CRMs, commercially available spike solutions, or custom-made materials provided to the IAEA through the Member States Support Programmes (MSSPs), that allow us to establish the traceability to reference materials produced by NBL, CETAMA or JRC-Geel. At the JRC-Karlsruhe small spike mono-elemental solutions containing major isotopes ^{238}U or ^{233}U and ^{239}Pu or ^{242}Pu are used for ID-MS analyses.[87] These small spikes are prepared with a concentration suitable for mass spectrometry and they are characterized against standards prepared from CRMs.[87]

For analysis of environmental samples in the environmental sample laboratory (ESL) of SGAS (mostly swipe and hot cotton swipe samples), two categories are distinguished, low-level and high-level samples, with total 10 pg Pu and 1000 ng U considered to be high-level samples. After sample digestion and pre-screening, sample splitting is done followed by spiking with enriched ^{242}Pu, ^{244}Pu, ^{233}U and ^{243}Am spikes for isotope dilution analysis, using ^{242}Pu/Pu or ^{244}Pu/Pu amount ratios between 1 and 10, and ^{233}U/U of around 100. Spike solutions used are prepared by step-wise dilutions from mother solutions, and therefore the concentration needs to be corrected for evaporation loss during storage. U and Pu analysis is performed by MC-ICP-MS following the methods outlined in ref. 45,131 and 207.

ID-MS is performed on nuclear material samples by TIMS applying the total evaporation method.[208,209] After purification when needed,[58] appropriate amounts of uranium and plutonium solutions are deposited onto a filament for each measurement of safeguards samples, CRMs and process control materials. By making duplicate analyses of both the spiked aliquots and unspiked sample aliquots the isotopic composition and elemental concentrations can be calculated and compared with defined control and warning limits.

As an alternative to traditional ID-MS when both pure and spiked sample aliquots are measured by TIMS, a combination of techniques can be used. In the OSL, High Resolution Gamma Spectrometry (HRGS) is combined with TIMS to determine the isotopic composition[210] of samples that are subsequently subjected to spiking to perform the plutonium assay in pure plutonium solutions or mixed U and Pu solutions (free of strong beta gamma emitters, U/Pu ratio greater than two). For timeliness considerations, this method has the merit of skipping the chemical separation of the {sample–spike} fractions for isotope and ID analysis. In this case, values for isotope ratios of ^{241}Pu/^{239}Pu and ^{238}Pu/^{239}Pu in the ID-MS assay equation are replaced by ones obtained by HRGS Multi-Group Analysis Software (MGA) codes. For U containing samples with complex matrices and unknown declarations (also Pu materials containing traces of U), acceptable performance is achievable by using over-spiking (high spike-to-sample amounts) with highly enriched ^{233}U spikes to determine the uranium amount and isotopic composition of the material from TIMS measurements of spiked sample aliquots. This so-called isotope stripping approach has also been used for the determination of traces of U in Pu materials.[211]

5.4. Irradiated samples

Irradiated samples, for which ID-MS is commonly applied, typically originate from the nuclear fuel cycle (definition of NFC in ref. 212). Nuclear fuels, for generation of electricity in a Nuclear Power Plant (NPP), are based predominantly on uranium (*e.g.* uranium oxide (UOX) fuels) or mixtures of uranium with other elements (*e.g.* Pu in MOX fuels). The so-called major actinide elements, U and Pu, possess fertile isotopes. These are isotopes which can be converted into a fissile isotope by neutron absorption: for example, the ^{238}U isotope can be converted into ^{239}Pu or ^{242}Pu can be converted into ^{243}Am. The major actinide elements also possess fissile isotopes, so it is possible that an actinide nucleus splits into two smaller nuclei, which are referred to as fission products: most of the lanthanides, cesium, and metallic fission products. Therefore, a nuclear fuel can contain a wide range of chemical elements once it has been irradiated. The isotopic composition of a fission product element can differ substantially from the naturally occurring isotopic composition of that same element: certain stable isotopes of an element might not be formed by fission. The amount of particular fission products (*e.g.* specific isotopes of Cs, Ce and Nd) present in an irradiated fuel can be very indicative of how much fission has taken place, and hence such isotopes can be used as fission burn-up monitors.[213] Information about the extent of fission in a particular fuel (rod) is very useful knowledge for the safe and correct operation of an NPP. In the case of non-power reactors, which are used for material testing, R&D, and training purposes for example, the trend to switch from highly enriched uranium (HEU) to low enriched uranium (LEU) fuels (an anti-proliferation measure) has involved the testing of a range of fuels that differ quite substantially, in chemical and physical form, and enrichment, from those used in NPPs. Irradiated samples received by a radiochemical analysis laboratory can therefore differ widely in terms of matrices, their chemical composition (oxide based fuels to metallic or silicide fuels) and homogeneity, their enrichment (from LEU to HEU), and their physical form (a segment from an oxide fuel or a segment from a plate fuel).

Despite the variety of irradiated samples, the determination of the U, Pu and Nd isotopic and elemental mass fractions by means of ID-MS can already provide considerable information. This is a common analysis as part of post irradiation examination. This gives information about the residual heavy metal atoms (the major actinides) and the concentration of the burn-up monitor (in this case the Nd fission product) can be used in the estimation of the fuel burn-up. Such information can be fed back into areas such as the assessment of fuel performance/qualification, validation of nuclear codes for criticality or for long-term storage of nuclear waste.[31,38,130,214,215] Crucially, these rely on the low measurement uncertainties ID-MS can provide.

The irradiated sample first has to be brought into solution, before spiking can occur. Dissolution of spent fuels for analysis is detailed elsewhere,[216–221] but in general terms an irradiated fuel is often dissolved quantitatively by heating (under reflux) under strong acidic conditions over several days inside a shielded hot cell. Only then can spikes be added to an aliquot of the dissolved sample, but crucially before any separations are started. Separations of lanthanides and actinides are discussed elsewhere.[31–33,58,222–228] Van Winckel *et al.*[220] provide a useful summary of the situations in which off-line and on-line separations are used for spent nuclear fuels.

Many practical details of the radiochemical analyses of the major actinides and Nd (amongst other actinides and fission products) to enable determination of the burn-up of an irradiated fuel are described elsewhere.[229–232] The methodology reported by Roach *et al.*[231] relies on on-line separation hyphenated to an MC-ICP-MS for isotopic vectors and Pu and Nd concentration or Davies & Gray titration for U concentration, all with calibration by ID-MS to provide results much more rapidly than off-line separations combined with an analytical technique such as TIMS.

The ASTM E321-20 method[233] uses the ^{148}Nd concentration as the fission burn-up monitor, due to the small difference between the fission yield of the two dominant fissile isotopes (^{235}U and ^{239}Pu). Govers *et al.*[234] reported that this approach works well for NPPs, but that in high-flux reactors (non-power reactors) the ^{147}Nd(n)^{148}Nd (*i.e.* short form for the ^{147}Nd + n → ^{148}Nd formula) capture reaction may no longer be insignificant. In such cases, a correction needs to be applied to avoid an overestimation of the burn-up when using the ^{148}Nd concentration. If it is not possible to correct the ^{148}Nd for such capture by ^{147}Nd an alternative is to measure the entire Nd vector. Data from the other Nd isotopes can provide estimates of the burn-up value.

The isotopic composition of stable or long-lived Nd isotopes formed during fission in irradiated fuels, including the absence of ^{142}Nd, differs from that of natural Nd. Data from almost 40 different irradiated fuel samples at the SCK laboratories indicate the isotopic abundances of ^{146}Nd and ^{150}Nd are rather similar to their natural abundances whilst those of ^{145}Nd and ^{148}Nd are approximately doubled. For ^{143}Nd and ^{144}Nd the abundances can deviate more widely from their natural isotopic abundances. Roach *et al.*[231] give examples of such data from three samples. The choice of the spike isotope for the quantification of Nd formed during fission is different than for Nd with natural isotopic composition due to their different isotopic compositions. A spike enriched in the ^{146}Nd isotope can be an alternative to ^{148}Nd and ^{150}Nd isotopes[33,38] if the entire Nd vector is to be measured. The amount of spike to be added depends on the concentration in the sample, and to some extent this depends on the laboratory's operating license. Some laboratories perform spiking inside a glovebox and others under a fumehood, the difference being the amount of U, Pu or Nd in the sample to be spiked. To perform spiking under a fumehood, an aliquot of diluted mother solution is required as the mother solution is too active, which in turn requires an appropriately lower spike concentration to avoid overspiking and to avoid spike masses with too high an uncertainty.

Cesium can also be used as an alternative fission burn-up monitor to neodymium.[235–239] After irradiation of the fuel, the sample contains ^{133}Cs, ^{134}Cs, ^{135}Cs and ^{137}Cs. Cesium is naturally monoisotopic (^{133}Cs), which makes it a good spike for such sample. The difficulties of cesium measurement by ID-MS come from the lack of reference materials to estimate the mass fractionation. Different methods can be used, such as a combination of TIMS and gamma spectrometry or intertechnique comparison.[235,240]

5.5. Biological applications

Radionuclide analysis in biological samples became important considering their intensive use in industry and medicine, and for some of them, their natural presence in the environment, such as Th and U (also named NORM, for Naturally Occurring Radioactive Material). Therefore, monitoring human exposure is crucial for evaluating the risks to the wider population and to workers. In addition, in case of a nuclear crisis or radiological exposure, such analyses are crucial to identify each individual's contamination. The most common matrices in which radionuclides are analyzed are urine and feces, but others biological tissues can also be considered in the research field.

The ICP-MS technique has become increasingly popular in recent years for measuring those radionuclides with a sufficiently long half-life ($t_{1/2}$ > 10 000 years).[241] The performance of ICP-MS, in terms of limits of detection and analysis time (several minutes), offers considerable advantages, even for complex matrices, over nuclear techniques such as alpha spectrometry.[242,243] Furthermore, in addition to activity concentration determination, the isotopic composition can be determined by means of ICP-MS, which enables the origin of a contamination to be traced.[242,244]

For urine samples, diluted samples can be measured directly by means of ICP-MS with external calibration, if their concentrations are high enough.[245,246] However, for urine samples with extremely low radionuclide concentrations and/or for other biological matrices such as feces, blood, nail and hair, a radiochemical purification and pre-concentration may be necessary before measurement by ICP-MS (urinary U,[247,248] urinary Pu[249]). The ID technique is, in this case, highly recommended: (i) to evaluate the chemical yield and (ii) to use as an internal standard to measure the concentrations accurately by means of ICP-MS. Therefore, ID coupled to ICP-MS permits proper characterization by more accurate matrix effect corrections in case of high matrix or low concentration measurements.

ICP-MS is widely used for actinide (U, Pu, Am) analyses of biological samples[241,246,247,249–270] with calibration methods that rely on an actinide isotope that is absent from the sample, such as ^{233}U for U isotopes (^{234}U, ^{235}U, ^{236}U and ^{238}U), ^{242}Pu for Pu isotopes (^{239}Pu, ^{240}Pu, and ^{241}Pu) or ^{243}Am for ^{241}Am analysis. Ni *et al.* developed a protocol for the rapid determination of ultra-trace plutonium isotopes in small volumes of urine.[249] This method is based on a chemical treatment of the urine samples (acid digestion, co-precipitation, extraction chromatography) before plutonium measurement by means of HR-ICP-MS. A ^{242}Pu spike is used as a yield tracer to characterize the Pu isotopes. The method allows a high ^{238}U decontamination factor (3.8×10^6), which is essential to limit the polyatomic interference of ^{238}UH$^+$ during ^{239}Pu measurement. An average value of 72.7 ± 5.5% was achieved for ^{242}Pu recovery for 20 mL or 100 mL urine bioassays. For 100 mL urine samples, the limits of detection (LODs) of ^{239}Pu, ^{240}Pu and ^{241}Pu were 0.003 fg mL^{-1}, 0.002 fg mL^{-1}, and 0.003 fg mL^{-1}, corresponding to 0.006 mBq L^{-1}, 0.015 mBq L^{-1} and 9.8 mBq L^{-1}, respectively. The current LODs of ^{239}Pu and ^{240}Pu by means of ICP-MS are more than 100 times lower than those usually achieved by means of the alpha spectrometry method (1 mBq L^{-1}). In another study, Wang *et al.* developed an online separation and pre-concentration method coupled with ICP-MS/MS for measurement of ^{90}Sr, ^{234}U, ^{239}Pu and ^{241}Am isotopes using ^{233}U, ^{242}Pu and ^{86}Sr tracers to correct for column recovery and matrix effects.[271] This method required small sample volumes (10 mL) and offered rapid analysis times (46 min per sample for the full process) and was applied to various liquid matrices (lake water, seawater, and urine samples). The limits of detection were 1.48 pg L^{-1} (8257 mBq L^{-1}) for ^{90}Sr, 1.75 pg L^{-1} (0.40 mBq L^{-1}) for ^{234}U, 0.65 pg L^{-1} (77.65 mBq L^{-1}) for ^{241}Am, and 0.56 pg L^{-1} (1.25 mBq L^{-1}) for ^{239}Pu. In this work, no specific spike was used for ^{241}Am analysis. The authors mentioned that high recoveries were obtained for ^{241}Am in samples analyzed by means of this protocol. Therefore, it may be suspected that no recovery correction was applied for the determination of ^{241}Am. To a limited extent, spike addition has been used to trace another radioelement, *e.g.* the use of ^{242}Pu to trace ^{237}Np, for which no suitable tracer is available, during quantification of ^{237}Np by means of ICP-MS.[254] In this study, the authors showed that ^{242}Pu can serve as the recovery monitor for ^{237}Np in the separation and pre-concentration procedure developed.

It should be noted that, in all these publications, no ID equation was detailed. Furthermore, the use of spikes is often mentioned in these papers as a yield tracer. Consequently, it may be suspected that these spikes are used more as internal tracers for recovery correction than as spikes for ID.

Clases *et al.*[272] suggested an "isobaric dilution analysis" (IBDA) method as a "new quantitative method for long-lived radionuclides" by means of ICP-MS. The technique relies on using a spike of a different element, but which contains an isobaric isotope and has similar chemical properties to those of the analyte. Demonstration of IBDA has been performed on the determination of gadolinium concentration using a certified dysprosium solution spike by measuring the ^{157}Gd/^{160}Dy ratio. The same authors applied IBDA for technetium, for which no safe standard, in terms of radioprotection, is available. They demonstrated that the IBDA technique can also be applied on an element with monoisotopic abundance such as ^{99}Tc using a ruthenium solution as a spike solution. The determination of ^{99}Tc in the ^{99}Tc-MAG3 drug is therefore obtained using the ^{99}Tc/^{101}Ru ratio. This technique could be extended to ^{41}Ca, ^{60}Co and ^{90}Sr using K, Ni and Zr, respectively and applied in various application fields such as industry, environment, cosmochemistry and medicine.[272]

Furthermore, understanding the behavior, biokinetics and excretion of radionuclides from the human body increases even more in priority due to the increase of their medical applications. Therefore, radionuclide quantification by ID-ICP-MS is a promising tool for investigating the partitioning and behavior of radionuclides in organ tissues, such as the use of ^{242}Pu and ^{243}Am spikes to determine ^{239}Pu, ^{240}Pu and ^{241}Am isotopes in brain tissues.[273]

Enriched spikes have also been used to trace specific speciation into the organism.[47] However, this technique has not yet been applied to radionuclides.

ID-MS is a promising technique for quantifying low radionuclide concentration and/or in complex matrices for radiation protection purposes and also for investigating the behavior of radionuclides in biological tissues. However, this technique has not been used widely with well-described ID equations. This is perhaps due to the limited number of laboratories performing radioisotope quantification in biological samples by means of ICP-MS. Nevertheless, developments in ID-MS can be anticipated in the coming years.

5.6. Reference material

For CRM certification, reference measurement techniques that provide metrological traceability are required. ID-MS is a very accurate technique for the determination of element mass fraction and provides results with low uncertainties: it can be applied as a primary ratio method when suitable CRMs and calibrators are available. The challenges associated with the development of reference measurement systems for clinical analytes, and in particular for ID-MS, are highlighted in ref. 274. The role of ID-MS in the certification of CRMs is presented in ref. 20 and 21. ID-MS is commonly used by nuclear CRM producers either for characterization or for verification of the assigned certified values determined by means of other techniques.[43,56,71,201] Facility operator laboratories and other laboratories performing nuclear material analyses use ID-MS for the characterization of laboratory CRMs for quality management, process or instrument control and preparation of spikes.[86,201,275] ID-MS was used in the last few years to certify several CRMs: ^{243}Am spike,[7,56,276] LSD spike,[73,201] ^{229}Th spike,[36] ^{231}Pa spike,[156] ^{242}Pu spike,[277] ^{244}Pu spike[43] or uranium oxide particle CRM.[278]

On the other hand, CRMs play a crucial role in the performance of ID-MS measurements. Using high quality CRMs in ID-MS provides accurate and traceable measurement results. For instance, in nuclear safeguards spikes are a metrological quality tool to meet the existing requirements indicated by the ITVs for reliable accountancy and verification measurements.[24,25] Considering modern instrumentation and state-of-the-practice methods, uncertainties of the CRM isotope ratios often significantly dominate the uncertainty budgets for the assay values of U and Pu. Several studies conducted by the IAEA for evaluating the fitness for purpose of CRMs in use[279] have concluded that the certified uncertainties of some CRMs were larger than the estimated intermediate precision of the TIMS measurements. Thus, the need for re-certification for better uncertainty is to be addressed by CRM producers. For this important metrology mission, the IAEA and the JRC-Geel organize technical meetings among the safeguards community to discuss the current requirements of the CRMs.

5.7. Process control

ID is a method of choice for process control applications that require an especially high accuracy, granted that appropriate spikes are available for the measured elements. ID comes with a significant advantage over almost all other methods, as it is not affected by sample losses, as long as the loss occurs after the preparation of the {sample–spike} mixture. This is a great feature of ID for trace and ultra-trace analysis that is very sensitive to any sample loss during preparation steps such as separation, dilution, evaporation, *etc.* Another actual advantage of ID is its very low sensitivity to matrix effects, because the spike and sample both share the same matrix and valency after mixture homogenization.

However, it comes with a rather complex setup that complicates and extends the sample preparation, which may be an issue for routine analysis. This is mainly due to the spiking step, where each sample is carefully spiked with an accurately weighed amount of spike. Automated systems based on highly accurate volumetric dispensers have been developed to solve this issue, helping to prepare a definite number of containers loaded with a known, accurately weighed amount of spike.[280] These automated systems are particularly effective for process control, where the analyst has generally access to a decent estimation of expected sample concentrations.

For applications where speciation is important, various reports have demonstrated the compatibility of the ID method with techniques such as laser ablation (LA)-ICP-MS, gas chromatography (GC)-MS, high-performance liquid chromatography (HPLC)-ICP-MS, gamma spectrometry, *etc.*[281–285]

6. Inter-laboratory comparisons involving ID-MS

ILCs can be divided into three categories: those involving expert laboratories participating in the certification of a CRM (such as that organized for STAM CRM ^{243}Am certification[276]), those involving laboratories validating a new measurement method, and finally those testing the proficiency of laboratories/methods for measurement (Proficiency Test, PT). These last two types of ILC are efficient tools to monitor the quality of measurement of analytical laboratories and, in particular, for those using ID-MS. Usually, PTs are organized on a regular basis to evaluate the ability of the laboratory to measure one or several quantities called measurands.[286] PTs also play an important role in a laboratory quality system and are increasingly recognized by national accreditation bodies and are part of the ISO17025 standard requirements for the competence of analytical laboratories.[287] The benefit for a laboratory of participating in PTs is to evaluate the accuracy of its measurements and to take corrective actions if necessary. The evaluation procedure consists of providing performance scores, such as the z-score or the zeta-score.

The z-score (eqn (35)) compares the difference between the laboratory measurement result (y_{lab}) and the PT assigned value (y_{PT}, certified or consensual value) to the PT standard deviation (S_{PT}, usually determined by robust statistics).

$$z\text{-score} = \frac{y_{\mathrm{lab}} - y_{\mathrm{PT}}}{s_{\mathrm{PT}}} \tag{35}$$

The zeta-score compares the same numerator to the uncertainty of the difference between the laboratory measurement value (u_{lab}) and assigned value (u_{PT}, eqn (36)).

$$\text{zeta-score} = \frac{y_{\mathrm{lab}} - y_{\mathrm{PT}}}{\sqrt{{u_{\mathrm{lab}}}^2 + {u_{\mathrm{PT}}}^2}} \tag{36}$$

According to z or zeta-score values, results are classified as:

- Satisfactory if $|z|$ or |zeta| < 2.
- Questionable if $2 < |z|$ or |zeta| < 3.
- Unsatisfactory if $|z|$ or |zeta| > 3.

The z-score indicates the number of PT standard deviations between the laboratory measurement value and the PT assigned value. The zeta-score determines whether the measurement uncertainty value claimed by the laboratory allows the laboratory's measurement value and the assigned value to be considered identical. Action is then encouraged if unsatisfactory performance is indicated.

In the field of radionuclide analysis, several international PTs are organized annually by different institutions (IAEA, CETAMA, NBL, JRC, *etc.*) in different fields ranging from environmental concerns to safeguards or nuclear mining/enrichment/reprocessing activities.

Laboratories using ID techniques are generally concerned with PTs for the measurement of radionuclide mass fractions (or amount content) in solids or solutions. For example, CETAMA offers PTs, called EQRAIN U, EQRAIN Pu and EQRAIN (U + Pu), for the determination of U or/and Pu mass fractions in solution. These PTs are typically organized every 18 months.[23] The content values lie in the ranges of 1 to 6 g kg^{-1} for Pu and 50 to 200 g kg^{-1} for U, and are designed for laboratories connected with the mining or reprocessing industries, institutions for safeguards or institutions dealing with reference materials.

The IAEA regularly organizes NMRoRo PTs and ILCs to assist the members of the IAEA network analytical laboratories (NWAL), as well as nuclear facility operators and other relevant laboratories, in the assessment of their nuclear material analyses (PTs) and environmental sample analyses (ILCs). During the last two exercises, the goal of NMRoRo was to determine uranium mass and uranium isotopic ratios in uranium oxide powder, and uranium and plutonium masses and uranium and plutonium isotopic ratios in a dried mixed Pu–U nitrate sample.[288] The goals of another ILC organized by the IAEA every two years are to measure the uranium and plutonium masses and isotopic abundances in cotton wipe samples (referred to as "swipe sample") thanks to "bulk analysis" methods (swipe dissolution, uranium and plutonium purifications and ID-MS measurements).

7. Conclusion

This article reviews isotope dilution analysis and its application for radionuclide measurements in different contexts. ID-MS is a primary ratio method that helps to measure radionuclide mass fraction, in solids or liquids, with high accuracy. The ID-MS analysis process is well understood and the ID-MS measurement uncertainty is well controlled and quantified. An uncertainty estimation is calculated considering all stages in the ID-MS process. MCM or quadratic cumulation methods can be used for uncertainty calculation: both approaches yield identical results. To obtain the most accurate measurement, implementation is needed for all stages: weighing process, mixture preparation, spike monitoring, isotopic homogenization, and mass spectrometry measurements.

The excellent performance of ID-MS for radionuclide characterization has been demonstrated in a wide variety of fields: environmental, biological analysis, irradiated sample characterization, certified reference material production, safeguards and nuclear forensics. The ability to evaluate ID-MS measurement performance by using a wide range of ILCs is essential for guaranteeing measurement reliability and demonstrates that

ID-MS has the potential to satisfy current and future needs in radioanalytical chemistry.

List of acronyms

CAB	Cellulose Acetate Butyrate
CCQM	Consultative Committee for Amount of Substance
CEA	French Alternative Energy and Atomic Energy Commission
CETAMA	Commission for the Establishment of Analytical Methods
CMC	CarboxyMethyl Cellulose sodium salt
CRM	Certified Reference Material
F	Error Multiplication Factor
HEU	Highly Enriched Uranium
HKED	Hybrid K-Edge Densitometry
HRGS	High Resolution Gamma Spectrometry
HR-ICP-MS	High Resolution-Inductively Coupled Plasma Mass Spectrometry
HU-1	Harwell Uraninite
IAEA	International Atomic Energy Agency
IBDA	Isobaric Dilution Analysis
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ID	Isotope Dilution
ID-MS	Isotope Dilution Mass Spectrometry
ILCs	Inter-Laboratory Comparisons
IRSN	French Institute for Radiation Protection and Nuclear Safety
ITVs	International Target Values
JAEA	Japan Atomic Energy Agency
JRC	Joint Research Centre
LAAT	Atalante Analysis Laboratory
LEU	Low Enriched Uranium
LOD	Limit Of Detection
LSD	Large-Sized Dried
MC-ICP-MS	Multi-Collector-Inductively Coupled Plasma Mass Spectrometry
MCM	Monte Carlo Method
MOX	Mixed OXide
MPE	Maximum Permissible Deviation
MSSP	Member States Support Programme
MGA	Multi-Group Analysis
NBL	New Brunswick Laboratory
NFC	Nuclear Fuel Cycle
NIST	National Institute of Standards and Technology
NMRoRo	Nuclear Material Round Robin
NORM	Naturally Occurring Radioactive Material
NPL	National Physical Laboratory
NPP	Nuclear Power Plant
NWAL	IAEA Network Analytical Laboratories
OSL	On-Site Laboratory
PT	Proficiency Test
R	Isotope Ratio
SCK	Belgian Nuclear Research Centre
SGAS	Office of Safeguards Analytical Services
SGAS-ESL	Environmental Sample Laboratory of SGAS
SGAS-NML	Nuclear Material Laboratory of SGAS
SI	International System of Units
SRM	Standard Reference Material
$t_{1/2}$	Half-life
TIMS	Thermal Ionization Mass Spectrometry
u	Standard Uncertainty
UOX	Uranium Oxide
u_r	Relative Standard Uncertainty

Author contributions

Alexandre Quemet: conceptualization, writing – original draft (Introduction, Theory, Optimization of the {sample–spike} mixture, Spike monitoring, and Conclusion parts) and review, supervision. Amélie Hubert: conceptualization, writing – original draft (Nuclear forensics part). Alkiviadis Gourgiotis: conceptualization, writing – original draft (Environmental applications: natural radionuclides: U-series disequilibrium part). Ana María Sánchez Hernández: writing – original draft (Weighing procedure and Reference material parts) and review. Marielle Crozet: writing – original draft (Isotope dilution uncertainty part) and review. Guillaume Bailly: writing – original draft (Process control part). Andrew Dobney: writing – original draft (Irradiated samples part) and review. Georges Duhamel: writing – original draft (Safeguards part). Joe Hiess: writing – original draft (Safeguards part) and review. Urska Repinc: writing – original draft (Safeguards part) and review. Sébastien Mialle: writing – original draft (Isotopic homogenization of the sample–spike mixture and Irradiated samples part). Béatrice Boulet: writing – original draft (Application to environmental monitoring of nuclear facilities part). Raphaelle Escoube: writing – original draft (Biological applications part). Céline Bouvier-Capely: writing – original draft (Biological applications part). Fabien Pointurier: writing – review & editing. Sébastien Picart: writing – original draft (Weighing uncertainty and Interlaboratory comparison involving ID-MS parts) and review, supervision.

Conflicts of interest

There are no conflicts to declare.

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