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100 Years of radionuclide metrology

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HIGHLIGHTS

- The driving forces for the development of radionuclide metrology.
- Radium standards to facilitate trade of this valuable commodity in the early years.
- After 1950, focus changes to healthcare and industrial applications.
- National Measurement Institutes develop new techniques, standards, and disseminate the best practice in measurement.
- Challenges in nuclear medicine, radioactive waste management and nuclear forensics.

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ABSTRACT

The discipline of radionuclide metrology at national standards institutes started in 1913 with the certification by Curie, Rutherford and Meyer of the first primary standards of radium. In early years, radium was a valuable commodity and the aim of the standards was largely to facilitate trade. The focus later changed to providing standards for the new wide range of radionuclides, so that radioactivity could be used for healthcare and industrial applications while minimising the risk to patients, workers and the environment. National measurement institutes responded to the changing demands by developing new techniques for realising primary standards of radioactivity. Looking ahead, there are likely to be demands for standards for new radionuclides used in nuclear medicine, an expansion of the scope of the field into quantitative imaging to facilitate accurate patient dosimetry for nuclear medicine, and an increasing need for accurate standards for radioactive waste management and nuclear forensics.

1. Introduction

An internationally-recognised infrastructure for radionuclide metrology can be traced back to certification of the primary radium standards at national measurement institutes in 1913. To mark the centenary of the field, this article aims to give a very brief overview of the developments since then and their impact, and look ahead to the future. This article is also to acknowledge the contributions of the scientists working in national measurement institutes worldwide; the authors cannot hope to name all those involved, but refer the reader to a special edition of Metrologia (Simpson and Judge, 2007) and references therein. The authors are also indebted to comprehensive reviews of the history of radioactivity, including work by Malley (2011), Collé (2007), Allisy (1994) and Smith (1975).

The first part of the article covers the period when primary standards were samples of radium. A concise review is then given of the methods developed to replace the artefacts by more fundamental techniques. The value of the work depends on the difference radionuclide metrology has made to healthcare and industry, which is summarised in the penultimate section. The article concludes with some reflections on the future of the discipline.

2. The early years of radionuclide metrology – the Curie (Ci)

Radioactivity was discovered in 1896 by Henri Becquerel; two years later Marie and Pierre Curie had separated radium from

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uranium ore. The discoveries were made at a time of public fascination with science, and the new phenomenon was put to use very quickly – the first documented use of gamma rays from radium was reported by Dr. Danlos in the St. Louis Hospital, Paris in 1901 (Danlos and Bloch, 1901).

The Buchler company in Braunschweig started purifying and selling radium for research purposes in 1902. With many valuable applications, the cost of radium rocketed, reaching $100,000/g in the early 1920s. Laboratories working in the field had their own methods to quantify radium, but wanted to compare research results and trade radium. It was against this backdrop that the pioneers in the field, including Marie Curie and Earnest Rutherford, identified the need for an international measurement system for the new material.

The first Radium Standards Committee held its inaugural meeting at the International Congress of Radiology and Electricity in Brussels in 1910, chaired by Lord Rutherford. The committee proposed to define a new quantity named the curie as 'the amount of radon in equilibrium with 10^{-8} g of radium'. Marie Curie refused to allow the use of the name curie for such a small quantity; the committee relented and 1 Ci was defined to be the amount of radon in equilibrium with 1 g of radium (Rutherford, 1910). It was reported that Marie Curie accepted the proposal 'for the honour rendered to the memory of Pierre Curie' (although Rutherford later said it was in honour of both M. and Mme Curie).

Marie Curie was charged with realising the international primary standard and, in 1911, prepared a standard of 21.99 mg of pure radium chloride in a thin glass tube. The standard was delivered to the Bureau International de Poids et Mesures (BIPM) in Paris and it was deposited 'in the lower division of the safe located in the first vault'. Marie Curie went on to found the Institut du Radium in Paris in 1914: the Laboratoire Curie was dedicated to the study and measurement of radioactivity, issuing thousands of certificates in the following decades.

Duplicate standards of the BIPM standard were prepared at the Institut für Radiumforschung in Vienna for governments that wanted them. Standard no. 3 was obtained by the UK's National Physical Laboratory (NPL) at a cost of £354; it was received in December 1912 and certificated by Rutherford, Meyer and Curie on 2nd June 1913 with a claimed accuracy of 0.3%. Standards were also supplied to other countries: Standard no. 2 was delivered to the laboratory led by Hans Geiger at the PTR (the Physikalisch-Technische Reichsanstalt, the forerunner of the Physikalisch-Technische Bundesanstalt (PTB)) in Germany in 1912. By 1925, primary standards had been established in Paris, Brussels, London, Washington, Vienna and Berlin.

Over the next few years, there was a rapid expansion in the medical applications of radium (needles, tubes and plaques for cancer therapy and external beam radiotherapy) plus industrial applications such as luminous paint. Such was the demand that there was a public appeal for funding in the UK to purchase radium for the government. National measurement institutes faced a high demand for measurement services – NPL issued 6000 certificates in 1930 alone, the National Bureau of Standards (the predecessor to the National Institute of Standards and Technology (NIST)) issued 38,000 certificates between 1914 and 1942 – and certification of ^{226}Ra content and the determination of the ^{228}Ra impurity dominated the work.

The main scientific issues that researchers faced were self-absorption corrections and the effect of wall thickness on the gamma spectrum emitted (it had been found that radium needles tended to buckle if the walls were too thin, but increasing the wall thickness affected the results). Fragility of the original primary standards was also an issue, and new standards were prepared in 1934 by Hönigschmid (the copies were found to agree with the original standard to better than 0.3%).

3. The need for a new unit (the becquerel (Bq))

Frédéric and Irène Joliot-Curie discovered artificial radioactivity in 1934 when observing the effect of alpha particles bombarding targets made of boron and aluminium; (alpha, n) reactions were observed which produced ^{13}N and ^{30}P, the first man-made radionuclides. This was the beginning of a new era for the study, production and use of radionuclides, leading to the construction of particle accelerators and nuclear reactors (the first reactor was constructed by Fermi and Szilard at the University of Chicago in 1942). Fields such as nuclear physics, radiochemistry and radiation detectors developed rapidly, mostly as a result of the Manhattan Project.

Medical applications of the new radionuclides soon followed: the first delivery of ^{14}C from the Oak Ridge National Laboratory (USA) to a hospital occurred in 1946. Industrial-scale production of artificial radionuclides for medical and industrial applications began in the 1950s: a wide range of radionuclides became available in the 1950s and 1960s.

There were also growing concerns over the safety of using radioactivity. Worries over the health risks were growing, and the environment worldwide was contaminated with low levels of radioactivity due to both the weapons testing programme and discharges (both planned and accidental) from the expanding nuclear power industry. In response to these concerns, governments introduced stringent regulations on the use and disposal of radioactive materials to protect the general public, the workforce and patients undergoing diagnostic scans or cancer therapy using radiopharmaceuticals.

The increasing variety of artificial radionuclides and the need for accurate measurement to underpin the new regulations made it necessary to change the definition of the curie based on the radium standard. In practice, this transition was made in several steps. First, in 1950, the curie was re-defined to be the quantity of any radioactive nuclide in which the number of disintegrations/s is 3.7×10^{10} (this value had been recommended by the International Radium Standards Commission in 1930 and was used for all the early work on radionuclides). Second, the ICRU decided to replace the term 'quantity of a radionuclide' by 'mean number of nuclear transformations per unit of time', called 'activity' and the name 'curie' was kept for the unit associated to this new quantity and defined as $3.7\times10^{10}\ s^{-1}$. This was endorsed at the 12th Conférence Générale des Poids et Mesures in 1964 which defined the unit of activity to be the second to the power of minus one. Finally, in 1975, the 15th Conférence Générale des Poids et Mesures decided 'by reason of the pressing requirement, expressed by the International Commission on Radiation Units and Measurements (ICRU), to extend the use of the Système International d'Unités to radiological research and applications, by reason of the need to make as easy as possible the use of the units for non-specialists, taking into consideration also the grave risks of errors in therapeutic work, to adopt the following special name for the unit of activity (of a radioactive source): becquerel, symbol Bq, equal to one reciprocal second.' The special name becquerel was specifically introduced because of the dangers to human health that might arise from mistakes involving the unit reciprocal second, in case the latter unit was incorrectly taken to identify the different quantities involved.

4. Realising the Bq

Very soon the wide range of primary standards needed proved to be a challenge to researchers at national measurement institutes. Perhaps the first general technique for realising primary standards can be traced back to Dunworth in Cambridge in 1940

(Dunworth, 1940), who applied coincidence counting to problems in nuclear physics. The method had also been used earlier by Geiger at PTR (and his successor, Walther Bothe) to study the Compton effect.[1] Coincidence counting was in use at NPL by 1947, where it was applied to standardise ^{60}Co and a comparison exercise was organised with the National Research Council (NRC) in Canada and a medical research centre at Hammersmith in the UK. Agreement between the results was described as 'fair'.

However, there were many interesting scientific issues to address in realising the standards. Details of the solutions found to these challenges are given in the recent Metrologia publication (Simpson and Judge, 2007) and references therein, from which three main themes emerge:

4.1. *Preparing accurately weighed, thin, point sources*

The starting point for most of the standardisation techniques was a very thin (few 10s of micrograms per square centimetre) source, a few millimetres in diameter. This required depositing a 15–30 mg aliquot of a solution containing the radionuclide of interest onto a conducting foil; the mass of the aliquot had to be measured with an uncertainty of better than 0.1%. Painstaking work at national measurement institutes during the 1960s developed the technique of difference weighing still used at most institutes worldwide.

During the years that followed, many ingenious methods were developed to ensure a uniform deposit (to ensure the highest possible detection efficiency in the detectors used). As just one example, a hot nitrogen drying system was developed at IRMM to ensure the aliquot dried rapidly and evenly.

4.2. *Corrections for instrumental effects*

The results from all of the measurement techniques had to be corrected for instrumental effects such as dead time and the finite coincidence resolving time (which results in accidental coincidences in the coincidence counting technique). Mathematical models were needed for the pulse processing system so that corrections could be applied; many subtly different formulae were developed based on different assumptions. The exact formulae for correcting coincidence counting results were developed in the 1980s by two mathematicians at Imperial College, London (the Cox-Isham formulae), but other techniques and formulae are also in common use.

In recent years, digital signal processing techniques have started to replace analogue electronics but this has not changed the need for mathematical models of the systems.

4.3. *Accurate nuclear decay data for decay scheme corrections*

All of the standardisation techniques rely on (directly or indirectly) a knowledge of the decay scheme and half life of the radionuclide and any impurities. As anyone who has been involved in evaluating published nuclear decay data can testify, these data are of varying quality, due partly to the poorer resolution of early spectrometers and partly to the aim of the work being to establish the decay scheme for nuclear structure research rather than for metrology.

Over the years, techniques have improved and national measurement institutes have contributed to the data available. More recently, the Laboratoire National Henri Becquerel (LNHB) initiated a major international project (the Decay Data Evaluation Project (DDEP)) to assemble a definitive set of recommended decay data; this database is now accepted worldwide as the first point of call for decay data by radionuclide metrologists.

The culmination of this work is embodied in the current generation of systems for realising primary standards. Liquid scintillation counting (such as the CIEMAT-NIST technique and the TDCR (Triple-to-Double Coincidence Ratio) method) is used more extensively as it addresses the three challenges listed above: complex sample preparation is avoided as larger, easier-to-weigh samples are used; the complex mathematical models are avoided or built into the analysis software; decay scheme corrections are based on well known evaluated DDEP decay data and are also incorporated in the software.

There are, of course, many alternative methods for realising the standards and many other issues that the field has faced, but for these the reader is invited to consult the Metrologia Special Issue.

5. International support for the field

The previous section has hinted at the wide variety of techniques available for realizing the primary standards. This is a strength of the field, as it enables national measurement institutes to check their standards against those at other institutes to give greater confidence in the primary standards but it requires strong international collaboration. To underpin the growing field of radionuclide metrology, the International Committee for Weights and Measures CIPM of the BIPM decided in 1958 to create the Comité Consultatif pour les Etalons de Mesure des Rayonnements Ionisants (CCEMRI) (now called the Comité Consultatif des Rayonnements Ionisants (CCRI)). The Ionizing Radiation section of the BIPM was founded in 1960 to give a scientific and technical support to the realisation of international standards and comparisons.

The BIPM has therefore had a key role in ensuring international consistency through organising international comparisons and sharing best practice between laboratories. It is worth mentioning the International Reference System (SIR) which was implemented in 1975: based on a very stable and simple measurement instrument (a pressurised well-type ionisation chamber) set up at BIPM, this is a powerful permanent tool at the disposal of all national measurement institutes (NMIs) for comparing primary standards of relatively long-lived gamma emitters (further details are given on the BIPM website). So far, measurements have been carried out for 60 different radionuclides. In recent years, similar systems have started to be established for beta emitters (by liquid scintillation counting) and short-lived gamma emitters (using a transportable NaI(Tl) detector), the latter being already operational for ^{99m}Tc; an extension to other radionuclides used as radiopharmaceuticals, such as ^{18}F, is scheduled.

An important further step in the international coordination of metrology was the introduction in 1999 of the CIPM Mutual Recognition Arrangement (CIPM MRA) for national measurement standards and for calibration and measurement certificates issued by NMIs. In the context of the fast development of international trade, this was a response to the 'growing need for an open, transparent and comprehensive scheme to give users reliable quantitative information on the comparability of national metrology services and to provide the technical basis for wider agreements negotiated for international trade, commerce and regulatory affairs'. Within this framework, the NMIs have to present peer-reviewed calibration and measurement capabilities, supported by the participation in key comparisons and complying with the quality standard ISO 17025. Radionuclide metrology has the issue that a different technique has to be used to realise a primary standard of each radionuclide; the CCRI devised a methodology based on grouping radionuclides into types that can be measured using the same generic primary measurement method with the same degree of difficulty in the form of a regularly updated and revised table (Measurement Methods Matrix), to ensure that NMIs can demonstrate

[1] Rutherford et al. (1930) also refer to Geiger's ingenious coincidence method, in which human observers were used in place of detectors.

traceability to the international system without an excessive workload of comparisons.

The need for an increased and closer cooperation between radionuclide metrology laboratories and the multitude of those organisations and workers involved in applications of radioactivity was also recognised at the first International Summer School on Radionuclide Metrology held at Herceg-Novi in 1972. The International Committee for Radionuclide Metrology (ICRM) was founded to meet this need and has organised, generally, biennial conferences since that date.

6. Dissemination of the standards

Alongside the technical issues associated with realising such a wide range of standards came the problem of how to ensure the standards were adopted by the diverse user communities. In the early years, this issue was straightforward; users (hospitals, researchers and industry) sent their radium samples to the national measurement laboratories for certification.

The situation changed during the 1950s and 1960s, with expanding nuclear power industries in many countries and a wider range of reference materials needed (see Fig. 1). Secondary laboratories (such as the Radiochemical Centre in the UK) had the resources to produce the large numbers of reference materials demanded by the end-users, with the national standards institutes providing the traceability to the international measurement system (and the independence from commercial and other pressures). Some links directly to end-users remained strong though.

During the 1980s and 1990s, this traceability arrangement became more formalised, with the introduction of documentary quality standards such as ISO 17025 and ANSI N42.22-1995. In addition to providing the route to the primary standards, many experts at NMIs worked, and continue to work, as technical assessors for accreditation bodies assuring compliance with these new standards.

Globalisation of markets and fragmentation of the nuclear industry affected dissemination routes in many countries during the 1990s and 2000s. The direct link to a local supplier of reference materials weakened and national measurement laboratories looked to other mechanisms for enabling users of radioactivity to ensure the accuracy of measurements is fit-for-purpose. There are many examples of the different approaches – for example, NIST has established a system of measurement quality assurance programmes and reference materials. In the UK, NPL has set up laboratory proficiency test exercises, run user meetings, published Measurement Good Practice Guides as well as continuing to supply a range of specialist reference materials and standards of rare radionuclides. In France, LNHB has run inter-laboratory tests for users in the medical and nuclear industry fields for more than 40 years. PTB is responsible for the traceability of reference materials used for statutory proficiency test exercises for environmental monitoring laboratories in Germany. Experts from many NMIs continue to contribute to the development of national and international documentary standards (such as the ISO series).

7. The impact of the work

The fate of the radionuclide metrologist is that one's work is often hidden from the public eye and, perhaps, the true value only comes to the fore when accidents occur in the nuclear industry (Chernobyl and Fukushima being the prime examples). In such cases the international measurement infrastructure, independent of industry and of governments, enables the public to have confidence in measurements carried out on their behalf.

Apart from such crisis situations, the impact of radionuclide metrology can perhaps be summarised under three headings:

(1) *Patient safety*: Radionuclide metrology enables radiopharmaceutical manufacturers to comply with national and international regulations (for example, current Good Manufacturing Practice (cGMP)), ensuring international clinical trials are on a consistent footing, providing information for patient dosimetry calculations and providing methods, instruments and reference materials for the quality control of radiopharmaceuticals prior to administration.

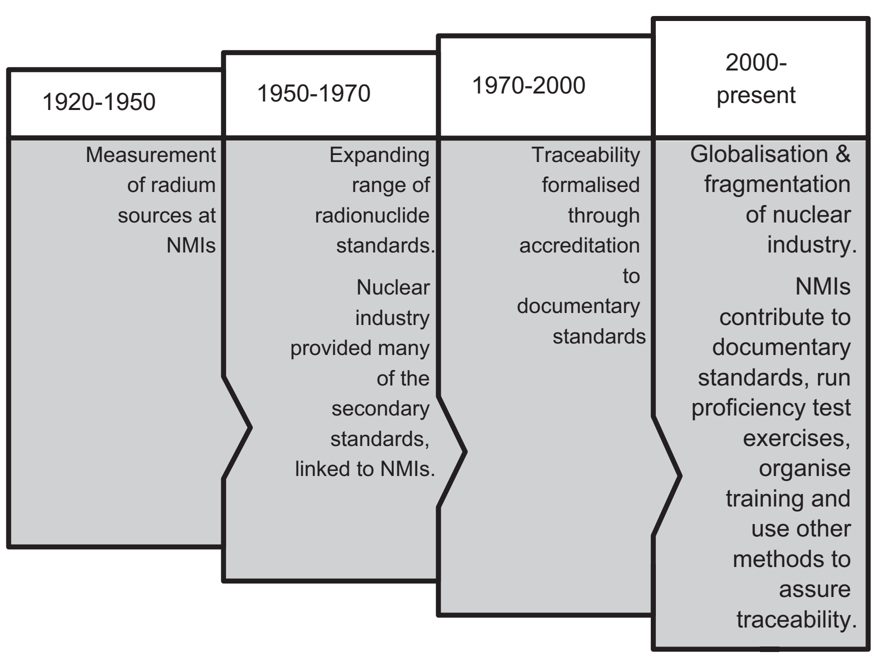

Fig. 1. Dissemination of standards over the years. In the early years of radionuclide metrology, most radium sources were calibrated at national measurement institutes (NMIs). As the range of radionuclides increased, secondary laboratories were established to provide reference materials traceable to the primary standards at the NMIs. This link was formalised by accreditation to standards such as ISO 17025. More recently, with increasing globalisation and fragmentation of the industry, NMIs have had to develop new techniques to assure traceability. (Dates shown in the figure are indicative only.)

Worldwide, this work has contributed to ensuring effective therapy and diagnostic procedures. According to the World Nuclear Association, this applies to some 18 million cases per year in the USA and 10 million per year in Europe, and radiopharmaceuticals are used in 10,000 hospitals worldwide.

(2) *Protection of the environment*: The nuclear industry is able to monitor and control discharges of radioactivity into the environment for compliance with national regulations and site licence conditions, ensuring consistent 'policing' of these discharges by laboratories acting for regulatory bodies, and providing an independent measurement system so that potentially radioactive waste materials can be checked and disposed off appropriately and with confidence.

A further benefit from the work has been the measurement of accurate nuclear decay data, which has been contributed to international databases such as the already-mentioned DDEP, presently published as a Monograph under the auspices of the BIPM and on-line on the LNHB website. These data are used in all applications of radioactivity, from estimating patient doses in the development of new radiopharmaceuticals to decay heat calculations for the long term storage of radioactive waste.

As an indication of the economic value of the work, the UK's Nuclear Decommissioning Authority estimates the lifetime cost of decommissioning the Sellafield site to be £67 billion and a significant fraction of this spend is related to accurate measurement of the radioactivity content of the waste materials.

(3) *Safety of the workforce*: In this field, radionuclide metrology contributes to ensuring that radiation protection instruments are calibrated with an accuracy that is fit for purpose, for compliance with national regulations and industry guidance. Contributions to the development of national and international documentary standards under the auspices of the ISO or IEC have impacted the procedures for testing and maintaining the instruments.

As an idea of the scale of the impact, the UK had 39,000 people classified as at risk of exposure to occupational ionising radiation (data from the Central Index of Dose Information, UK Health and Safety Executive in 2004) and France 330,000 (data from IRSN (Institut de Radioprotection et de Sûreté Nucléaire), 2010).

8. The next few years

Radionuclides continue to find new applications in medicine. The first drug for cancer therapy based on an alpha-emitting radionuclide was licensed in 2012, and other alpha emitters are being used in clinical trials. These drugs have the potential to revolutionise cancer therapy but there are measurement problems to solve in making the link between the activity and the radiation dose to the tumour and to the patient. Radio-immunotherapy is many years behind external beam radiotherapy in this respect; researchers at NIST and European NMIs are working closely with hospitals and universities to develop standards, phantoms and other methods to quantify diagnostic images and hence improve patient dosimetry.

Interest in long-lived radionuclides is also increasing as the nuclear power industry starts to decommission and the long term disposal of radioactive waste comes to the fore. Decommissioning also results in more airborne radioactivity as old buildings are demolished; the need for radioactivity in air standards is already evident. There is also increasing awareness of the problems associated with naturally occurring radioactive materials and the need to apply similar standards on radioactive materials to non-nuclear industries.

Concerns over potential terrorist attacks using nuclear materials or weapons is driving an interest in very high accuracy standards to enable security forces to identify the country of origin of nuclear materials; the accuracy needed is very difficult to meet with current techniques. Instrumentation from other fields, such as mass spectrometry, may prove to be very useful in this context and will require new types of reference material and methods.

One issue that will affect all users of radioactivity will be difficulties in obtaining raw materials, due to the impending closure of many of the nuclear facilities worldwide. There is much work to do in investigating production routes and developing the associated radiochemical separation techniques. On a practical note, radionuclide metrology on the national and international level requires the exchange of small quantities of radioactive materials to cross-check measurements and provide reference materials for instrument calibration; this exchange is becoming increasingly difficult due to stringent shipping regulations.

Finally, at a time of financial constraints, it is good to see that scientists are sharing resources and working collaboratively on international projects – whether it is those fostered informally by organisations such as the ICRM or by European initiatives such as the European Metrology Research Programme (EMRP).

9. Conclusions

Since its inception in 1913, the science of radionuclide metrology has had to respond to society's changing needs. Initially concerned with facilitating trade, the discipline has become increasingly concerned with quality of life issues and enabling all users of radioactivity to work safely and avoid damage to the environment.

There have been many scientific problems on this journey, and radionuclide metrology has called on help from nuclear physicists, radiochemists, mathematicians and scientists from other disciplines.

Perhaps the advances in mass spectrometry will eventually result in the field going full circle, and we will return to primary standards based on mass. Whatever happens, there remain interesting and challenging scientific problems to solve in the field.

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