

**The Future of  
Reference Materials**

**Science and Innovation**

International Conference  
23-25 November 2010

Institute  
for Reference Materials  
and Measurements

Geel, Belgium

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## Welcome message

As we approach the end of the year in which the IRC's Institute for Reference Materials and Measurements (IRMM) celebrates its 50th anniversary, it is fitting that we reflect also on the future. It is very appropriate, therefore, that the conference "The Future of Reference Materials – Science and Innovation" has been arranged on the occasion of the official opening of a new reference material production building.

The title of the conference reflects our ambition to examine – together with the esteemed conference participants coming from all over the world – both the science required for developing and producing crucial measurement benchmarks and the scientific progress which can be achieved if appropriate reference materials are available. Moreover, transforming scientific knowledge into innovative products and services is certainly one of the major challenges for Europe at present and in the foreseeable future. In this respect, the conference aims at spelling which innovative developments are required for producing cutting-edge reference materials that serve the needs of our society and economy. Also innovations which rely on the provision of such materials will be envisaged.

The conference programme intentionally reflects a broad range of scientific areas and application sectors in which modern reference material activities are carried out nowadays. We are grateful that the invited speakers so willingly agreed to deliver such topical keynote lectures. We gratefully acknowledge the many proposals for oral and poster presentations from colleagues around the globe, as these contributions are a prerequisite for an interesting conference programme.

We are looking forward to a stimulating scientific event which should foster forward-looking reflections and identify the emerging demands for global measurement benchmarks. The conference should also provide plenty of opportunities to establish new contacts and to continue existing exchange and collaboration amongst the conference participants.



**Krzysztof Maruszewski**  
Director, IRC-IRMM



**Hendrik Emöns**  
Conference Chair

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# Conference programme

## Tuesday 23 November 2010

09:00-12:15 Opening ceremony of the new reference materials production building

12:15-13:30 *Buffet lunch at IRMM cafeteria*

13:30-14:00 **Chair: Krzysztof Maruszewski, JRC-IRMM**

Reference materials for material science and technology  
 Manfred Hennecke, Federal Institute for Materials Research and Testing, Germany  
 Reference materials for the nutrition community  
 Joseph M. Betz, National Institutes of Health, USA  
 Poster session

14:30-17:00 *Departure to the hotel*

17:00 *Social activity*

18:30-20:00 *Social activity*

## Wednesday 24 November 2010

09:00-09:30 **Chair: Hendrik Emons, JRC-IRMM**

Certified reference materials for environmental measurement - Think globally, act locally  
 James McLaren, Institute for National Measurement Standards, NRC, Canada  
 Reference material needs to support nanometrology and risk assessments of engineered nanoparticles  
 Martin Hasselöv, University of Gothenburg, Sweden  
 The future demand for geological reference materials  
 Thomas Weisel, University of Leoben, Austria  
 Commutability of certified reference materials at the nano-scale  
 Ilya Kuselman, National Physical Laboratory of Israel, Israel

10:40-11:40 *Coffee break*

11:10-11:40 **Chair: Yetunde Aregbe, JRC-IRMM**

Nuclear reference materials for safeguards: challenges for users and producers alike  
 Steve D. Balsley, International Atomic Energy Agency, Austria  
 Looking Forward through the Past: Status of the United States' Nuclear Safeguards Reference Material Program at New Brunswick Laboratory  
 Jon Neuhoff, New Brunswick Laboratory, USA  
 On-site laboratories of Euratom – Ten years of excellent results with nuclear reference materials  
 Peter Schwalbach, European Commission, Directorate General for Energy, Luxembourg

12:20-14:00 *Lunch at IRMM cafeteria*

14:00-14:30 **Chair: Stefanie Trapmann, JRC-IRMM**

Standardisation and reporting for nucleic acid quantification  
 Stephen A. Bustin, Queen Mary University of London, United Kingdom  
 Status and trends in in-vitro diagnostics and considerations for reference materials  
 Frank Vitzthum, Siemens AG, Germany  
 Conceptual challenges of RMs in support of multiparametric, dynamic and real time complex biomarker measurements: A changing healthcare paradigm?  
 Helen Parkes, LGC, United Kingdom

15:20-15:50 *Coffee break*

15:50-16:20 **Chair: Heinz Schimmel, JRC-IRMM**

The development of reference materials for norovirus and hepatitis A virus  
 Rachel Rangdale, Centre for Environment, Fisheries and Aquaculture Science, United Kingdom  
 Reference materials in the occupational hygiene measurement arena  
 Owen Butler, Health and Safety Laboratory, United Kingdom  
 Nuclear forensic reference materials a new direction in nuclear and radiological reference materials  
 Richard Essex, New Brunswick Laboratory, USA  
 Establishing traceability and comparability of measurement results by a limited number of well-chosen CRMs  
 Robert Kaarls, International Committee for Weights and Measures, France

17:20 *Departure to the hotel*

19:30 *Conference dinner*

## Thursday 25 November 2010

09:00-09:30 **Chair: Thomas Linsinger, JRC-IRMM**

Calibration and purity assessment in chemical analysis  
 Hun-Young So, Korea Research Institute of Standards and Science, Rep. of Korea  
 EU policy on contaminants in food and feed: An indispensable need for reliable measurements, testing and reference materials  
 Frans Verstraete, European Commission, Directorate General for Health and Consumers, Belgium  
 Uncertainty intervals in certified reference materials for nutrients in foods  
 Wayne Wolf, United States Department of Agriculture, USA  
 Allergen reference materials – the challenges  
 Adam Cryar, LGC, United Kingdom

10:40-11:10 *Coffee break*

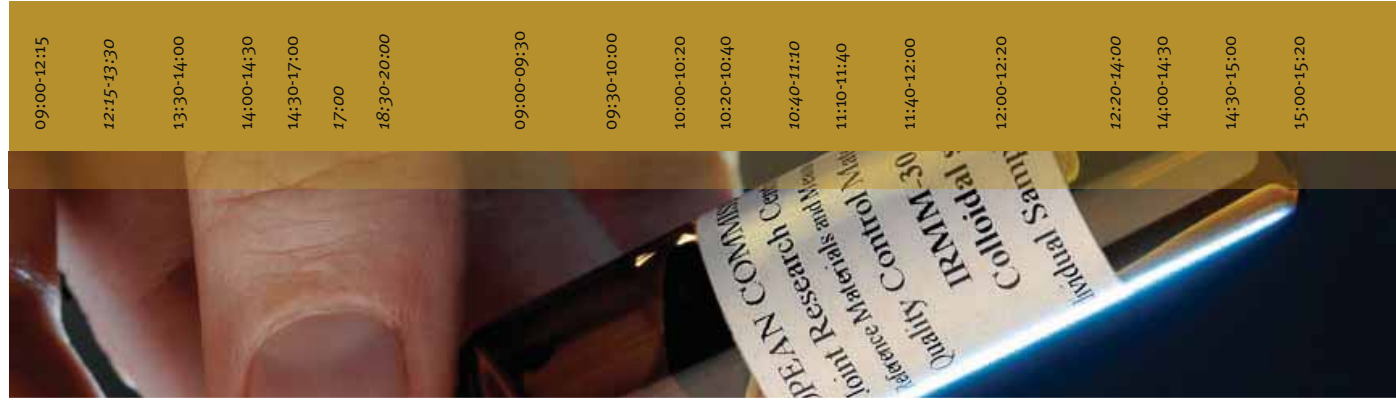
11:10-11:30 **Chair: Andrea Held, JRC-IRMM**

Reference system for somatic cell counting in milk  
 Silvia Orlandini, IIA-Laboratorio Standard Latte, Italy  
 The effective characterisation of novel, pure substance reference materials while meeting users' needs in a timely fashion  
 Lindsey Mackay, National Measurement Institute, Australia  
 Smart calibration of organic standards Proton based calibration by qNMR  
 Koichi Chiba, National Metrology Institute of Japan, Japan  
 Establishment of an universal procedure for the purity assessment of analytical standards, pharmaceuticals and peptides  
 Nacho Garcia Alonso, University of Oviedo, Spain  
 Developing benchmarks for measurements – The IRMM approach  
 Hendrik Emons, European Commission, Joint Research Centre, Institute for Reference Materials and Measurements  
*End of the conference*

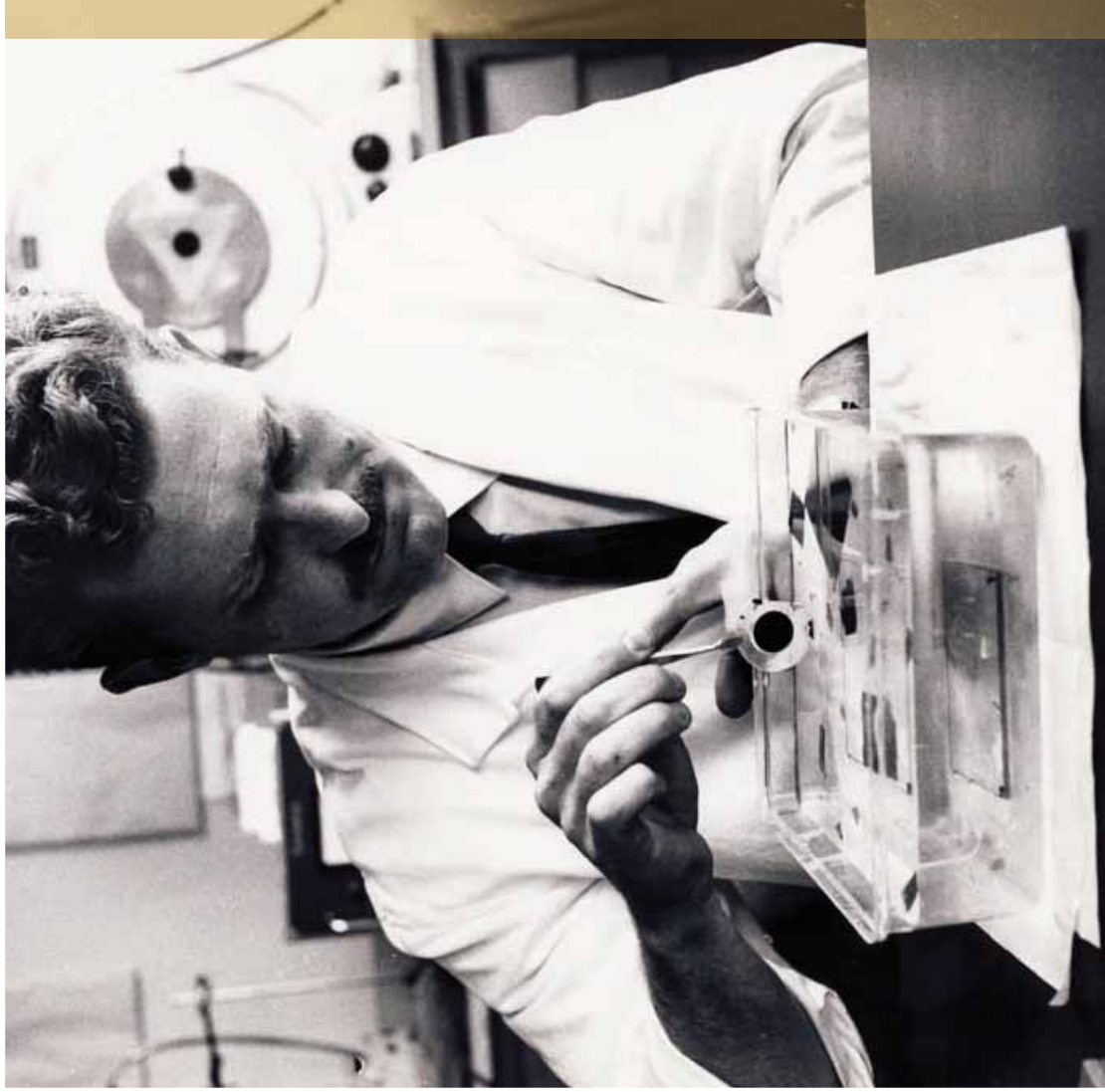
13:00 *Lunch at IRMM cafeteria*

14:30-16:00 *Laboratory visit*

16:00 *Departure*



## History of reference materials at IRMM



1957

Signature of the Treaty of Rome (EURATOM Treaty) which leads to the establishment of the Central Bureau for Nuclear Measurements (CBNM) in Geel (BE) with the mission to support nuclear industry and safeguards

1960s

Nuclear targets and other 'reference samples' are produced according to specifications of nuclear physicists at CBNM and national nuclear research laboratories, universities and other research laboratories both inside and outside of the European Community

1969

CBNM Director J. Spaepen signs an agreement to support the EURISOTOP programme by preparing special materials for international laboratory inter comparisons on gases in non-ferrous metals – the first action of IRMM in non-nuclear reference materials

1974

The Bureau Communautaire de Référence (BCR) is created by the EC with programmes for the production of industrial reference materials, later also for environmental reference materials; CBNM contributes by preparing special industrial IRMs and by storing and distributing BCR IRMs

1975

The programme management of EURISOTOP is transferred to CBNM

1978

Twelve 'EURISOTOP IRMs' prepared by CBNM are certified as BCR CRMs

1980

Full reorientation of CBNM's programme to nuclear activities; a procedure is agreed for the EC-certification of Nuclear Reference Materials (NRMs)

1981

The Nuclear Certification group is established and the first EC certificate for NRMs (purity of Pu metal) is issued by CBNM

1984

CBNM's non-nuclear activities are taken up again and increased in the 1984-1987 Multiannual Programme; decision on the construction of a dedicated building for the preparation of reference materials with professional facilities and equipment for the efficient processing of highest quality biological and environmental certified reference materials (CRMs) and centralised storage of BCR CRMs are built

1986

The 'BCR building' for the preparation of reference materials is inaugurated

1987

ca. 30 isotopic and spike EC-NRMs for nuclear safeguards and 13 EC-NRMs for reactor neutron dosimetry are available from CBNM

1989

The first non-nuclear isotopic CRM CBNM-IRM-618 Rubidium-87 spike material is released; today 23 CRMs certified for isotope amount ratios and amount fractions, respectively, and 31 CRMs certified for isotope amount content and isotope enrichment, respectively, are available



From 1989 CBNM prepares an increasing number of industrial, environmental and food CRMs for DG XII - Research (BCR candidate reference materials) and other DGs (first DG AGRI, later also DG TAXUD, DG ENV, DG SANCO, etc.), as well as for external customers

1993: In reflection of the modified mission and the increasing orientation to non-nuclear activities the name of the institute is changed to Institute for Reference Materials and Measurements (IRMM)

1994 A collaboration agreement between DG XII and the Joint Research Centre (JRC) is signed transferring major responsibilities related to the management and certification of BCR CRMs to IRMM

1995 IRMM takes over full responsibility for the storage and distribution of all BCR CRMs as well as for the renewal of exhausted reference materials; IRMM starts upgrading the BCR certification procedures and developing modern concepts on certification; these concepts have been introduced into ISO/REMCO Guides through active collaboration in the different ISO/REMCO Working Groups; since 2009 the ISO/REMCO Chair is from IRMM

1996 A collaboration agreement with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) is signed to produce joint IRMM/IFCC CRMs

1997 A collaboration agreement with Fluka AG is signed leading to the worldwide first CRM for genetic modified organisms (GMOs)

1999 IRMM/IFCC-451 Cortisol reference panel of fresh frozen human sera is released as first joint IRMM/IFCC CRM certified for hormone content; from 2000 until today this collaboration resulted in six CRMs certified for catalytic activity according to the IFCC method, a set of prothrombin CRMs for genetic testing and human serum CRMs certified for fifteen clinical relevant proteins

1999 Support of the Commission during the BSE (Bovine Spongiform Encephalopathy) crisis by evaluating the post-mortem tests on BSE; this support is still ongoing and has led to the development of a series of BSE quality control materials and the establishment of a specimen bank

1999 During the dioxin/PCB crisis IRMM has supported the Belgian Authorities by producing samples for the validation of methods and laboratories leading also to three CRMs certified for PCB content in pork fat in 2000

1999 Release of the first GMO CRMs worldwide (IRMM-410 Roundup Ready® soy bean and IRMM-411 to -413 Bt176/Bt11/MON810 maize); until now twenty sets of GMO CRMs are available certified for different maize, soybean, cotton, potato and sugar beet GM events at different levels of GMO content as well as a first plasmid CRM suitable for calibration of MON810 maize measurements

2003 IRMM assumes full responsibility for the management of all BCR CRMs and the development and certification of new reference materials in the Commission

2003: At the initiative of IRMM the ERM® cooperation (European Reference Materials) is founded between the IRMM, the German Federal Institute for Materials Research and Testing (BAM) and LGC (UK)

2004 IRMM's Reference Materials Unit is the first in Europe to obtain accreditation as producer of Certified Reference Materials according to ISO Guide 34 and ISO/IEC 17025

2005 Inauguration of a dedicated building for the storage and distribution of reference materials; this building has capabilities for controlled storage at temperatures ranging from +18 to -70 °C; moreover special liquid nitrogen containers are available for storage at temperature of about -190 °C

2007 A collaboration agreement for RM development between IRMM and the US National Institute of Standards (NIST) is signed

2008 A contract is signed for the construction of a dedicated building for the advanced production of different types of reference materials allowing parallel processing without risk of cross contamination; this building, called RMPB is inaugurated in November 2010

2009 A collaboration agreement for RM development between IRMM and the Korean Research Institute of Standards and Science (KRISS) is signed

2010 **The Institute for Reference Materials and Measurements, formerly Central Bureau for Nuclear Measurements, celebrates its 50th anniversary.**

Today IRMM is a most innovative reference material producer with world-wide recognition. It offers ca. 75 nuclear and 700 different non-nuclear high quality CRMs for calibration, method validation and quality control in areas such a food and feed analysis, clinical chemistry, environmental analysis, nuclear security and safeguards, engineered materials, bio- and nanotechnologies. IRMM's research on new materials ranges from the basic conceptual level in metrology to the technical realisation of measurement standards which are mimicking complex real-world materials. Developments are focused on crucial new reference materials to serve EU policy needs and to advance measurement sciences.

<http://irmm.jrc.ec.europa.eu/>

## KEYNOTE AND ORAL PRESENTATION ABSTRACTS

## Reference materials for material science and technology

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Our life depends on a seemingly unlimited variety of advanced materials whose safety, reliability, and availability is taken for granted for macro-, micro-, and nanoscopic building blocks. Besides broadly applied and well characterized materials, even more intangible materials will determine future needs in application areas ranging from energy to human health and from surface technology to nanotechnology. Measurement and testing of materials has always been an inherent part of materials chemistry metrology and has often been approached in a more phenomenological manner in engineering. Obviously, a full understanding of the arrangement of atoms, ions, and molecules comprise the material as well as its overall structural and physical properties is the ultimate aim in materials chemistry. Testing materials at its limits and under extreme conditions will not only require new in situ measurement and testing - e.g. to understand the dynamics of failure -, but also improved sensitivity of these methods to analyze the involved mechanism on a molecular level. Of course, all these methods will require reference materials and methods to provide a sound basis.

The talk will address new materials and methods in the broad scope of BAM, covering metals, polymers, and ceramics and including different characteristic scales of the materials building blocks.



## Reference materials for the nutrition community

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A popular reference describes Certified Reference Materials (CRMs) as “controls or standards used to check the quality and traceability of products.” This description implies that the CRM user is a manufacturer and/or the regulator charged with ensuring that quality standards are met. In the nutrition community, food manufacturers and their regulators do use reference materials, and the demand remains high for matrices with certified values provided for nutrients. Natural-matrix reference materials in newer product categories such as dietary supplements are also beginning to enter the market. Examples include NIST SRM® 3280 Multivitamin/Multielement Tablets, SRM® 3274 Botanical Oils Containing Omega-3 and Omega-6 FattyAcids, and SRM® 3278 Tocopherols in Edible Oils. Expanding the description of reference material from products to processes, CRMs useful for evaluating laboratory proficiency in biomarker measurement (homocysteine, cholesterol) and nutrients in biological fluids also exist. Going forward, recent data from national nutrition surveys such as the U.S. National Health and Nutrition Examination Survey have begun to identify newly discovered or reemerging nutrient deficiencies that may become public health issues. As people around the world reduce their consumption of iodized table salt, it is important to assess the impact of less iodine on the health of vulnerable populations. As individuals use more sunscreen to reduce skin cancer risk and cut down on dairy product consumption for health reasons, they may be compromising their vitamin D status. In order to evaluate the potential impacts of these nutrition trends, it is more important than ever to ensure that nutrient measurements in products and in people are accurate and comparable across studies and across nations. This is more challenging than it sounds as technologies for nutrient measurement proliferate and reference materials must perform well across analytical platforms that range from microbiological tests, through antibody-based assays, to LC/tandem mass spectrometry.

## Certified reference materials for environmental measurement – think globally, act locally

**J. W. McLaren**

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In the mid 1970's, the National Research Council of Canada (NRC) initiated a program to respond to needs for reliable measurement methods and certified reference materials (CRMs) that had been expressed by the oceanographic community. A high priority was an open-ocean seawater reference material certified for a suite of trace elements, many at the µg/L or sub-µg/L level. This objective was achieved in 1982, after several years of intensive R&D, with the announcement of the availability of NASS-1, the world's first reference material of this type. Since then, NRC has continued to provide successive generations of seawater CRMs to a global market. The program has expanded to include a natural freshwater material certified for trace elements as well as marine sediments and biological tissues certified for total elemental amount content. Subsequently, certified values for amount content of individual elemental “species” such as methyl mercury and tributyl tin in some of these tissues and sediments were provided. The most recent work has been directed towards certification of isotope ratios of elements of interest in these materials.

The NRC CRM program has achieved international recognition not by producing a very large number of CRMs, but instead by being the first to produce materials for which there was not just a Canadian need but also a well-recognized global need. The success of this strategy to think globally but act locally has been aided by the decision of other (and larger) CRM producers such as NIST and IRMM to avoid unnecessary duplication of CRMs of the types offered by NRC. Successful implementation requires a commitment to produce materials that are not already available and that are technically challenging; the latter requirement often involves significant research and development the costs that cannot usually be recovered through sales of the materials.

In addition to summarizing the history of the NRC environmental CRM program, the speaker will present his views on future requirements in this area, with emphasis on the need for global collaboration and cooperation.



## Reference material needs to support nanometrology and risk assessments of engineered nanoparticles

M. Hassellöv

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Nanoscience and nanotechnology have been forecasted to emerge as an industrial revolution during the coming years, and large investment in research and development is currently being put in place. Development of new nanomaterials is one important area, that has implications for almost all market segments including energy production and storage, ICT, construction, medicine, surfaces, catalysis, and consumer products such as cosmetics and food. To ensure sustainable development of nanotechnology, risk assessments of engineered nanoparticles (ENP) from various applications are required and for that it is essential to have the tools to carry out both effect and exposure assessment. Both the development of nanomaterials as well as the risk and safety studies requires thorough characterization of nanoparticles and their aggregates. The characterization needs include initial detailed material characterization and dispersion properties and exposure characterization during effect experiments. It was the consensus among 60 international experts at a workshop organized by the International Council on Nanotechnology that the need for development of nanometrology and analytical methods for engineered nanoparticles in environmental matrices is top priority.

There is a range of characterization methods available to the field of nano(eco)toxicology, that can determine relevant phys-chem properties, each with its own advantages and limitations<sup>1,2</sup>. Thus we need to agree on a suite of complementary techniques. Some harmonization and standardization of instrumentation selection and method optimization is important to produce comparable and reproducible results. Here are discussed method validations in relation to analytical chemistry, particle size analysis in ceramic and powder science, as well as nanometrology, and some suggestions for methods will be given. For such method validations availability of adequate certified reference (nano) materials is crucial. In the toxicity studies there are also high demands for reference or testing materials for comparing responses between labs or between methods.<sup>3</sup>

Finally, some potential methods for detection and analysis of manufactured nanoparticles in the complex environmental matrices will be shown, including both single particle ICP-MS and different electron microscopy methods. Results will be shown for engineered nanoparticles in highway runoff water and waste water effluent samples.

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## The future demand for geological reference materials

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Geological RMs (G-1 and W-1) were introduced in 1951 for the purpose of validating the accuracy of silicate rock analysis by dc arc spectrography. Since then the introduction of an array of other spectrographic methods have greatly enhanced research into geological processes. The range of elements that could be determined was expanded and the detection limits for measurement was lowered repeatedly through the years. The development and use of reference materials was critically important in supporting this rapid expansion of geological research. Yet national metrology institutions were largely absent from the development of these materials.

For example, NIST did certify an obsidian (SRM 278) and a basalt (SRM 688), but did not include the rare earth elements, the platinum group elements, and other trace elements of major importance to geoscience research at the time of issue in the certification. Essentially all RMs of importance to the geosciences community since G-1 and W-1 have been prepared and distributed national geological institutions, first by the USGS or the CRPG, rather than by national metrology institutions. The geological institutions are not yet certifying their RMs according to ISO Guides.

The International Association of Geoanalysts (IAG) is now meeting this higher metrological requirement. Since the inception of the IAG certification program in 2003, five powdered silicate rock materials have been issued to meet the demand with respect to calibration, method validation, traceability, etc. for whole rock major and trace element analysis.

The introduction of microanalytical techniques two-three decades ago and the more recent advent of MC-ICP-MS have become new driving forces in geochemical research. The first opened the possibility of performing in-situ elemental composition studies at the  $\mu\text{m}$  scale. The second led to the discovery of small isotope composition variations of mass and non-mass dependent processes in "non traditional" stable isotopes (e.g. Fe, Cu, Zn, Mo, W, Hg etc.) through cosmo- and geochemical processes. Coupling the two techniques expands in situ analysis to isotopic studies. These developments have created great demand for (certified) RMs for both isotope ratio and microanalytical measurements for the geochemical community that is not yet being met.

Homogeneity at a  $\mu\text{m}$  scale and unmatched matrices of the natural minerals or synthetic doped glasses hamper the progress in certification of RMs for the microanalytical measurement community. A challenge for the production of isotope RMs is to prepare an RM solution with an isotopic composition similar to the natural systems under investigation. Refined cadmium and nickel metals, for example, have fractionated isotopic compositions far above the range observed in natural systems of interest. Yet the calibration RM cannot fulfil its purpose when the uncertainty of its isotopic composition exceeds that of the unknowns being measured against it. In addition to these current and future challenges, establishing metrological traceability of geological reference materials in the absence of starting points developed by national metrology institutions is a major issue that needs attention in all future certifications.

## Commutability of certified reference materials at nano-scale

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Commutability/adequacy/match of certified reference materials (CRMs) and a material under chemical analysis is an important condition of the analysis success. A difference in the materials' matrixes and property values is the known source of the uncertainty associated with measurement results obtained using a chemical analytical measuring system calibrated against the CRMs. Therefore, a good practice is to use CRMs with the bulk chemical composition close as possible to that of the material under analysis. However, when CRMs are applied for characterization of nano-dimensional objects, adequacy of their surface compositions, rather than of their matrixes, may contribute to the measurement uncertainty. Moreover, the surface match at nano-scale can allow even use of inadequate CRMs, i.e., CRMs with another matrix than of the object under characterization.

As a case study, nanospheres containing a crystalline silicon core covered with thin silica shell were prepared by super high-frequency plasma-chemical technique and characterized in aqueous solutions by capillary zone electrophoresis (CZE). The nanospheres dispersed in phosphate buffer solutions by ultrasonication were found to be a mixture of negatively charged nanoparticles. Dependences of their electrophoretic mobility on pH were very similar to those of the silica CRMs produced by Polysciences Inc., USA. Comparison of the studied particle characteristics with those of the silica CRMs allowed to suppose that the CRMs may be used also for size estimation of the silicon particles having silica shell.

Such a "surface commutability" should be taken into account at development of CRMs for nano-particle identification and characterization.

## Nuclear reference materials for safeguards: challenges for users and producers alike

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The IAEA's ability to detect a diversion of nuclear material, or to verify the absence of undeclared activity, depends in part on the evaluation of analytical results from safeguards samples. For over thirty years, the IAEA Safeguards Analytical Laboratory has provided reliable analytical results for nuclear material accountability verification, and since 1995 for environmental swipe samples. Nuclear reference materials are essential for instrument calibration, monitoring of process control and blanks, traceability of quantitative determinations, and for establishing detection limits. Expansion of the mandate for Safeguards destructive analysis beyond conventional nuclear material accountability, and the substantial improvements in analytical instrumentation of the last decade(s), have presented many long-standing reference materials with new challenges. In some cases, safeguards laboratories and nuclear facility operators rely on certified reference materials (CRM) produced more than 30 years ago, with the result that the accuracy of the analytical results is dominated by the uncertainty on the reference material certification, especially for Pu reference materials. Recertification of the most often used of these older CRM is an important need for safeguards laboratories. Regarding new CRM, the long lead time for the preparation, purification, measurement, certification, packaging, and shipment of nuclear materials means that users must engage reference material laboratories with clear technical specifications and priorities. The recent set of IRMM standards created with high purity U-236 provided by the IAEA is a success story for this approach. There is a need to identify new sources of certain high-purity rare isotopes for future CRM, while at the same time looking for new ways to preserve the shrinking stock of existing precious CRM. In the emerging area of trace element determination in uranium materials, reference material coverage across the periodic table is restricted and the range of matrices available is limited. This highlights the need to re-certify or create new reference materials with certified amounts of metallic elements in uranium matrices. A subsidiary concern is the shelf life of certain reference materials in which radiolytic gas generation can create hazardous storage conditions; the certificates of such materials should carry appropriate guidance as to shelf life. To complete the analytical circle, interlaboratory comparisons such as the REIMEP programme run by IRMM are needed for external quality control of measurements of nuclear fuel cycle materials. Despite a world of increasingly restrictive shipment regulations, it is important to safeguards laboratories that interlaboratory comparisons utilizing uranium and plutonium samples matched to routinely analyzed materials are provided on a regular basis.

## Looking forward through the past: status of the United States' nuclear safeguards reference material program at New Brunswick Laboratory

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The New Brunswick Laboratory was founded in 1949 by the United States Atomic Energy Commission to develop uranium analytical techniques and standard materials. Headed by Dr. Clement Rodden and staffed with other scientists affiliated with the Manhattan Project, NBL added plutonium capabilities in the 1950's and operated a number of interlaboratory exchange programs utilizing standard materials developed in-house or in cooperation with other national laboratories. Beginning in the 1950's, NBL assisted the National Institute for Standards and Technology (then the National Bureau of Standards or NBS) in producing and characterizing nuclear reference materials. Beginning in 1981, NIST began to transfer the nuclear reference material program to NBL. This transfer was completed in 1987 when NIST finalized the transfer of materials and the program to NBL. NBL produced and certified a number of uranium and plutonium reference materials and operated an interlaboratory exchange program geared towards nuclear safeguards efforts. For various reasons, through the late 1990's and early 2000's the laboratory became progressively under-staffed and the aging facility was not adequately maintained. This culminated in the 2004 stand-down of nuclear operations at NBL. Beginning in 2005, Laboratory and Department of Energy Headquarters staff evaluated NBL's mission and facilities, and developed a path forward for NBL. This talk will review the history of the laboratory, discuss current accomplishments and the path forward as the nuclear renaissance impacts on NBL's mission and capabilities in the context of the needs of the international safeguards community.

## On site laboratories of Euratom – ten years of excellent results with nuclear reference materials

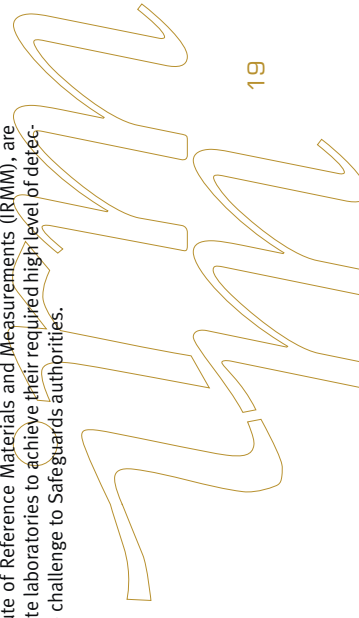
**P. Schwalbach<sup>1</sup>, F. Lipcsei<sup>2</sup>, M. Boella<sup>3</sup>, P. Chare<sup>3</sup>, K. Casteleyn<sup>3</sup>, L. Duinslaeger<sup>2</sup>,  
K. Lützenkirchert<sup>3</sup>, P. van Belle<sup>3</sup>, E. Zuleger<sup>3</sup>, Y. Aregbe<sup>3</sup>**

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Euratom safeguards was the first international safeguards organisation having to cope with nuclear material safeguards in large industrial scale reprocessing facilities. The four plants in the UK (Thorp and Magnox) and France (UP2 and UP3) were built in two sites, at Sellafield and La Hague. The regular inspections carried out by EURATOM inspectors assure that plant operator's system for material accountability is conform to Euratom regulations and matches the physical reality. The physical verification, practically measurements, are an integral part of the inspection activities. Thorough analysis concluded that sampling of major material streams would be well required but the transport of the samples to a central Euratom laboratory should be avoided. It was thus decided to establish laboratories on the site of Sellafield and La Hague and to send the analysts to the samples rather than the samples to the analysts.

The laboratories were opened roughly ten years ago and have been working continuously. They are staffed by experts of Euratom's Institute of Transuranium Elements, ITU, at Karlsruhe.

The laboratories receive samples from all the plants on the respective sites, with input solution, plutonium products (including mixed oxides) and inventory samples being the most important types of material. The criteria for selection of the measurement methods for these samples were based on a combination of highest possible accuracy and a minimum of resource consumption. The data can be used for direct comparison with the operator's results and they allow an evaluation of the material flows and material balance in a timely manner. The goal of the on-site laboratories is to deliver measurement results at a constantly high quality. In order to obtain absolute measurements of the nuclear material flow reference materials are required, which contain known quantities and isotope ratios of uranium and plutonium. The use and correct application of the certified reference materials, quality control samples, participation in external quality control schemes and rigorous data and document control are the pillars of the quality control concept implemented in the on-site laboratories. They form an essential part of the laboratories' measurement strategy. In that respect nuclear reference materials providers, mainly the Institute of Reference Materials and Measurements (IRMM), are directly supporting the on-site laboratories to achieve their required high level of detection probability, which is the challenge to Safeguards authorities.



## Standardisation and reporting for nucleic acid quantification

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The polymerase chain reaction (PCR) has matured from a labour- and time-intensive, low throughput qualitative gel-based technique to an easily automated, rapid, high throughput quantitative technology. Real-time quantitative PCR (qPCR) has become the benchmark technology for the detection and quantification of nucleic acids in a research, diagnostic, forensic and biotechnology setting. However, ill-assorted pre-assay conditions, poor assay design and inappropriate data analysis methodologies have resulted in the recurrent publication of data that are at best inconsistent and at worst irrelevant and even misleading. Furthermore, there is a lamentable lack of transparency of reporting, with the “Materials and Methods” sections of many publications, especially those with high impact factors, not fit for the purpose of evaluating the quality of any reported qPCR data. This poses a challenge to the integrity of the scientific literature, with serious consequences not just for basic research, but potentially calamitous implications for drug development and disease monitoring. These issues are being addressed by a set of guidelines that propose a minimum standard for the provision of information for qPCR experiments (“MIQE”). MIQE aims to restructure today’s free-for-all qPCR methods into a more consistent format that will encourage detailed auditing of experimental detail, data analysis and reporting principles. General implementation of these guidelines is an important requisite for the maturing of qPCR into a robust, accurate and reliable nucleic acid quantification technology.

## Status and trends in in vitro diagnostics and considerations for reference materials

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In vitro diagnostics (IVDs) are estimated to contribute up to 94% of the objective data in clinical records. They may influence 60-70% of decision making. Major healthcare cost reductions can be achieved through a more efficient use of current and novel IVDs. Despite the importance of IVDs and the essential role of the clinical laboratory, they usually account for less than 5% of the expenditures in hospitals. The proportional share of IVD laboratory costs in worldwide healthcare expenditures is even lower, accounting for around 1 to 2% of the costs. Aside cost pressure, the goal to improve patient care drives science, innovation, and developments in various fields like automation, consolidation, miniaturization, informatization technology, implementation of new technologies and the search for new biomarkers. Megatrends like urbanization, demographic change, climate change, and globalization shape our future and impact healthcare, too. Innovation will allow us to face these daunting threats. Systems Biology sciences are examples for highly innovative areas. In particular, Proteomics has gained much attention, because proteins are considered to continue to dominate IVDs. The complex nature of proteins and serum or plasma specimens often represents a challenge for accurate quantitation and standardization. Current and future protein testing will require adequate reference materials. Establishment of reference measurement systems is and will remain an integral part in the endeavours to improve healthcare. Mass spectrometry that is broadly applied in Proteomics is leveraged more and more in the establishment of reference measurement systems for IVDs. Vice versa research can benefit from the experiences of IVDs standardization and reference materials.



## Conceptual challenges of RMs in support of multiparametric, dynamic and real time complex biomarker measurements: A changing healthcare paradigm?

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The problems of an ageing population developing complex diseases such as cancer, Alzheimer's and heart disease are placing a burden on our healthcare systems and these complex, multifactor disorders are challenging diagnosis, treatment and monitoring. Advances in "omics" technologies are leading to identification of many novel putative disease related biomarkers and increasing our understanding of the mechanisms of disease.

However, these emerging clinical diagnostics and therapeutics have a number of related measurement challenges: increasingly, panels of markers or multiparametric "fingerprints" derived from multiple data types are needed to give accurate diagnosis of complex disorders. A number of novel multiple marker measurement issues have to be addressed:

- Multiple analytical platforms present issues of comparability
- The large dynamic range of putative biomarkers in blood has to be recognised
- Detection of overall shifts and trends in the datasets may be required rather than accurate quantification of individual analytes when measuring tens or hundreds of biomarkers
- A combination of genomic, transcriptomic, epigenomic, proteomic, metabolomic measurements may be required

These biomarker measurement issues increase the complexity of reference material (RM) requirements:

- RMs need to be developed to allow confidence in data produced across platforms, considering sensitivity, dynamic range, robustness etc.
- RMs should be "representative" of target analytes to give confidence that assays work within specified performance limits e.g.
  - Nucleic acids (NA) – covering a range of sequence context, length, abundance, secondary structure etc.,
  - Proteins – covering a range of size, charge, secondary and tertiary structure, modifications, abundance etc.
- Commutability – eg. does a synthetic NA target behave the same way as a naturally occurring transcript?, a pure traceable protein should represent the clinically relevant form
- How should stability be measured?
- Accurate measurement methods for full characterisation and quantification of complex nucleic acid and protein biomarker RMs are still in development
- How can measurement uncertainty be assigned to a panel of materials with different characteristics, functionality and stability?

These issues will be discussed in the context of LGC projects and studies on protein and nucleic acid biomarker measurement and RM development.

## The development of reference materials for norovirus and hepatitis A virus

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In food microbiology there is a requirement for quality assurance of test results and standardisation of methods. Most laboratories have implemented quality systems which include accreditation to internationally recognised standards. An important element of accreditation is participation in external quality assessment (EQA) schemes. EQA demonstrates that laboratory analyses are being carried out to a sufficiently high standard, and is indicative of a commitment to continuous improvement. Equally, standardisation of test methods is extremely important in the provision of uniform test results, particularly if important public health decisions are being made on the basis of those results. Accordingly standards organisations such as the European Committee for Standardisation (CEN) are actively involved in establishing international standard methods for food microbiology.

Within CEN a horizontal standard method for the quantitative measurement of norovirus (NoV) and hepatitis A (HAV) in food is under development. These viruses are important human pathogens associated with faecally contaminated foodstuffs. Worldwide norovirus is recognised as the most significant cause of acute non-bacterial food-borne gastroenteritis, Hepatitis A is the aetiological agent of an acute hepatitis transmitted by consumption of contaminated food or water. Neither virus can be grown using conventional tissue culture systems. As a result quantitative real time polymerase chain reaction (PCR) based approaches have been applied to detection of the viruses in a variety of food matrices. Of major importance to the success of method development is the availability of reference materials of known concentration and genetic character, as this enables initial calibrations and measurement of method performance. Furthermore, once a method is implemented in a laboratory reference materials are required on an ongoing basis in order to support internal and external quality assurance of results. This paper discusses the use of Lenticules™ first developed by the UKs Health Protection Agency as reference materials for viruses. Their use in EQA schemes is reviewed.



## Reference materials in the occupational hygiene measurement arena

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The health of workers in many industries is at risk through exposure to chemicals, dusts and fibres and occupational hygienists need to determine the effectiveness of measures taken to control such exposure. This is generally achieved by making personal exposure measurements, the accuracy of which relies heavily upon the use of calibrated real-time instrumentation for field measurements and the availability and use of validated measurement methods when samples are returned to the laboratory for analysis. This presentation will give an overview of current status of reference materials in this measurement arena and will provide an insight into requirements for the future.

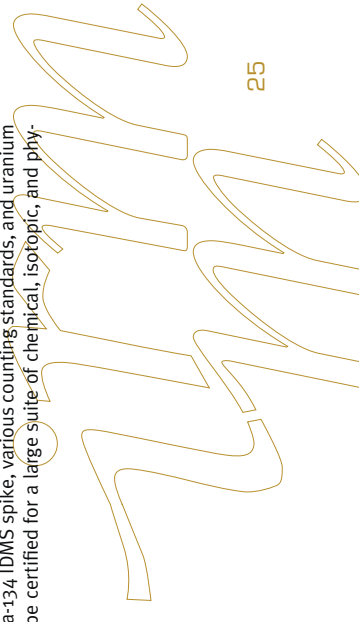
## Nuclear forensic reference materials - a new direction in nuclear and radiological reference materials

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The expanding field of nuclear forensic analysis has resulted in a need for the production and certification of a new category of reference materials. Due to the potential for profound consequences associated with an attack using an improvised nuclear device (IND) or a radiological dispersal device (RDD), the United States and the international community have been actively pursuing the development and maintenance of analytical capabilities necessary to deter the deployment of or attribute responsibility for the use of such devices. Forensic analysis of nuclear and radiological materials are likely to be an important component in the attribution process and are performed to help answer specific questions about material origin including physical condition, age, provenance, and industrial history. Considering the possible legal and punitive consequences associated with an investigation of the illegal use or trafficking of nuclear and radiological materials, any analytical evidence produced must be of the highest quality with regard to accuracy. A primary component in highly reliable analytical work is the existence of well-constrained reference materials for the purposes of instrument calibration, measurement evaluation, and method development.

The types of analyses performed to answer questions of age, provenance, and industrial history have not traditionally been targets of radiochemical, material science, and nuclear material characterization analyses. Therefore, a suite of new certified nuclear forensic reference materials (NFRMs) will be invaluable to provide the traceability, precision, and accuracy that will assure the scientific and legal integrity of existing analytical capabilities and allow for development of improved capabilities. To help address this need, the Department of Homeland Security (DHS) National Technical Nuclear Forensic Center established a cooperative program between the DHS and other US Federal agencies. New Brunswick Lab has been tasked with overseeing NFRM production and established a dedicated staff position of NFRM coordinator to assess the needs of the analytical community, determine NFRM production priorities, and facilitate NFRM production. Through surveys of the analytical communities and the specific needs of the program sponsor, necessary NFRM have been identified and production priorities have been established. The resulting projects that are in process or advanced planning include a Cs-Ba chronometric reference material, a Th-229 IDMS spike, U-Th Chronometric reference materials, a Ba-134 IDMS spike, various counting standards, and uranium NFRMs that will ultimately be certified for a large suite of chemical, isotopic, and physical attributes.



## Establishing traceability and comparability of measurement results by a limited number of well chosen CRMs

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Global comparability of chemical and bio-chemical measurements is essential for taking away Technical Barriers to Trade and for complying with Sanitary and Phyto-Sanitary measures and other regulations. Long term, credible comparability can only be established by making all measurements metrological traceable to the same long-term stable references, which are whenever possible defined in terms of the SI. The SI is the world's best long term stable measurement system, anchored on the fundamental constants of nature. Well defined, pure CRMs are essential as base, transfer and calibration standards for identification of the measurand and establishing traceability. Inasmuch as in the chemical and bio-chemical area the number of measurands and chemical matrices is almost unlimited, it is needed to develop a limited number of well chosen CRMs and related measurement procedures to establish traceability and demonstrate comparability and competence. The CCQM Working Groups are developing new approaches to realize this goal. Cooperation with all stakeholders and academia is needed to be successful.

## Calibration and purity assessment in chemical analysis

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The concept of purity is a unique one in metrology in chemistry and not so familiar with other areas of metrology. In any chemical measurements, the measurand has to be defined by its name of substance as well as its amount. When the amount of substance is known, then the question of purity of the substance follows. It is hard to imagine purity of 100 % with any substances though it depends on capabilities of separation of impurities and capability of measuring the intended substances.

Certified reference materials provided as pure substance or as solution type of calibrant are commonly used as the primary calibrators in laboratories providing measurement services. So the capability of proper purity assessment on materials is the core capability in chemical measurements. The dissemination of the pure substance could be used by external users either directly as a high purity substance CRM or as a starting materials to prepare calibration solution. It also could be characterized for internal use of the NMI as the primary calibrator for its measurement procedure.

The certified value of purity is generally reported as the mass fraction content and the value assigned to the primary calibrators underpins the hierarchy of traceability chain in a chemical measurement. The CCQM organized and planned eight of pilot studies and four of key comparisons for purity assessments since year 2002. The key comparison was intended to allow NMIs to demonstrate that their procedures used for purity assessment are suitable for the intended use of the compound.

This presentation will give introduction principles and application of some measurement method used for purity assessment, and results of CCQM activities. It will also present what KRISS is doing for the purity assessments.



## EU policy on contaminants in food and feed: an indispensable need for reliable measurements, testing and reference materials

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The EU legislation on contaminants in food fulfils two essential objectives: the protection of public health and removal of internal barriers to trade within the EU.

Council Regulation (EEC) No 315/93 of 8 February 1993 laying down community procedures for contaminants in food is the framework for the Community action on contaminants.

Based on this framework Regulation, maximum levels for the following specific contaminants have been established by Commission Regulation (EC) No 1831/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs.

Directive 2002/32/EC of 7 May 2002 of the European Parliament and of the Council on undesirable substances in animal feed is the framework for the Community action on undesirable substances in feed.

Maximum levels have been established in feed and food for a wide range of contaminants. But legislation is only effective in protecting public and animal health if the enforcement is effective and if legislation is uniformly applied across the EU. The establishment of uniform sampling and analysis procedures in that respect is of major importance.

Regulation (EC) 882/2004 of the European Parliament and of the Council of 29 April 2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules provides the regulatory framework for sampling and analytical procedures.

EU-RL/NRL networks have been established for several contaminants and are of major importance for the effective application of feed and food safety legislation. The need for co-operation, support and assistance for in many cases complex analysis is self-evident.

As regards contaminants in feed only few methods of analysis have been established at EU level. While for feed at EU level the approach of establishing specific methods of analysis has been followed, in the field of contaminants in food, the approach of establishing performance criteria has been followed.

However regardless the approach followed, there is a large need for (certified) reference materials in the field of contaminants in feed and food in order to guarantee a reliable and comparable analysis across the EU.

## Uncertainty intervals in certified reference materials for nutrients in foods

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A recent publication (1) has summarized available food matrix certified reference materials (CRM), each of which has assigned values and uncertainty intervals for a variety of food components. The specified uncertainty interval was expressed as a percentage (UIP) of the assigned value for each of 690 individual components in 63 CRMs. These UIP values vary widely, ranging from 0.2% to over 60%. Overall over 63% of the UIPs across all components and matrices were less than 10%. While the UIPs for proximates, minerals and trace elements were consistently less than 10%, the UIPs for vitamins were significantly higher. Slightly more than half of the fat soluble vitamin values and nearly 3/4 of the water soluble vitamins have a UIP greater than 10%. If the certification process involves the best possible analyses, a higher UIP (wider uncertainty range) indicates less precise methodology, higher difficulty or less homogeneity for that class of analytes. This raises the question? How good (narrow uncertainty limits) do assigned values in CRMs need to be? This depends upon the purpose of the data. The requirements for CRM uncertainty intervals for food components and specifically for vitamin content have not been significantly addressed. When assigned values for CRMs are used to assess accuracy of analytical results, the UI of the assigned value is an inherent limit. UIs of greater than 5-10% of the assigned value can limit the usefulness of the CRM. While this degree of uncertainty may be acceptable for assessing vitamin content for food labeling, users of food composition data may need to quantitatively assess the impact of this level of uncertainty in specific applications. Are the materials and assigned values of presently available CRMs for vitamin contents the best that can be produced or can materials of less uncertainty in assigned values be accomplished? The viewpoint of most producers of CRMs is directed towards what additional CRMs are needed, not how low the UIPs should be.

Over a 6.5-year period a total of 2554 values were reported by 9 laboratories for 259 certified or reference nutrient concentrations in 26 certified reference materials (CRM) submitted to contract laboratories, blinded, as part of the qualifying process for analytical contracts and in the routine sample stream as part of the NFNAP (2). Each value was converted to a Z'-score, reflecting the difference from the assigned value related to the combined expected analytical uncertainty plus the uncertainty in the CRM value. Z'-scores  $> 1/3.0$  were considered unacceptable. For some nutrients (Na, folate, pantothenic acid, thiamin, tocopherols, carotenoids),  $> 20\%$  of Z'-scores were  $> 3.0$ . For vitamin C, and niacin  $> 25\%$  of Z'-scores were  $> 1/2.0$ . Components for which CRM data were best (more than 90% of Z'-scores  $< 1/2.0$ ) were Mg, P, Mn, Se, and vitamin B12. In some cases deviations from assigned values were not uniform across laboratories and materials. For Na almost all high Z'-scores were for low-Na matrices, suggesting analytical problems related to concentration. (2) The presentation of data from the NFNAP in this paper is intended as an initial evaluation of the overall quality of production-scale analytical measurement systems for nutrients in various matrices, to focus attention on areas needing improvement. These results represent extensive "real-life" data from CRM samples of well-characterized composition that can provide insight on accuracy and variability of routine analytical data from commercial laboratories.

[1] Phillips KM, Wolf WR, Patterson KY, Sharpless KE, Amann KR and Holden JM, (2007) Summary of Reference Materials for the Determination of the Nutrient Composition of Foods, Accreditation and Quality Assurance, Vol 12 (3-6), 126-133.

[2] Phillips KM, Wolf WR, Patterson KY, Sharpless KE and Holden JM, Reference Materials to Evaluate Measurement Systems for the Nutrient Composition of Foods: Results from USDA's National Food and Nutrient Analysis Program (NFNAP), Analytical and Bioanalytical Chemistry, Special Issue on Foods and Dietary Supplements, 389:219-229

## Allergen reference materials – the challenges

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Allergen testing is a problem for the food industry. In most countries, there are no threshold levels above which a manufacturer has to declare the presence of an ingredient. This leads to precautionary labels on foods warning consumers of the possible presence of ingredients. Clearly for those individuals affected, it is important to know when there are risks, but overcautious labelling is unhelpful as it is restrictive for diet choices.

Valid measurement methods for the detection and quantification of minor ingredients in a food product are essential to forward the knowledge on the occurrence and severity of allergenic responses. The two techniques which dominate the food allergen testing area are enzyme-linked immunosorbent assays (ELISA) and a DNA based method based on the polymerase chain reaction (PCR). This presentation will discuss some of the challenges associated with these techniques and the issues for CRM production.

LGC is developing a capability for the metrologically traceable determination of allergenic proteins using isotope dilution mass spectrometry. The method of selection of indicator peptides will be described together with the analytical challenges. Combined with this approach, LGC is working closely with the food industry, researchers and test kit manufacturers to ensure any reference materials produced represent the challenges of real food samples. It is important that LGC, as the UK's National Measurement Institute for Chemical and Bioanalytical measurements, is involved at an early stage to establish action limits. Levels can then be set in legislation which are meaningful to clinicians, and enforceable through sound measurements.

Commutable certified reference materials are essential to improve measurements in this area. They will assist laboratories in the development and validation of reliable measurement methods which are essential to make informed decisions. There is a demand for materials, but the challenges of production must not be underestimated. Early work on the production of a candidate reference material will be described.

## Reference system for somatic cell counting in milk

S. Orlandini<sup>1</sup>, H. van den Bijgaart<sup>2</sup> on behalf of IDF/ICAR Project Group on reference system for somatic cell counting

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With some analytical parameters standardized reference materials are lacking and the reference method shows limited performance. It is there that a reference system approach should serve to optimally safeguard equivalence with routine testing in laboratories worldwide. A reference system is characterized as a systematically developed anchoring system that is fed by different types of information from various sources, i.e. measurements on secondary reference materials, reference method analysis and routine method results.

Somatic cell counting in milk is a clear example. It is one of the most frequently performed tests, estimated at over 500.000.000 tests/year worldwide. It serves as an indicator for the udder health status of lactating animals, is relevant in food legislation, in payment of raw milk and also has an considerable impact for farm management and animal breeding programs. However, there is lack of certified reference material and the analytical performance of nowadays fluoro-opto-electronic routine methods is superior to the reference method. Therefore, laboratories have adopted various solutions for anchoring their counting level.

A joint project group of the International Dairy Federation and the International Committee on Animal Recording has been given the task to design a workable reference system for somatic cell counting in milk with a plan for its implementation. The plan should describe the structure and the functioning of such a reference system as well as the responsibilities of the involved stakeholders. After approval in IDF and ICAR, the resulting proposal is to be offered for adoption by concerned governmental and non-governmental bodies worldwide.

In its first year, the project group with now 23 representatives from 4 continents and 16 different countries has drawn up an outline of such a reference system. Key points in its development were identified and are presently progressed:

- collection of information on available secondary reference materials and their application in practice;
- definition and description of a best suitable material for interlinking counting levels and safeguarding equivalence worldwide;
- development of a statistical model for competence scoring of laboratories contributing in the characterization of such a material;
- development of a statistical model to arrive at sound assigned values for this material based on input from both reference method analysis and routine method results;
- preparing and execution of a pilot with a limited number of laboratories;
- a plan for a gradual implementation of the reference system including proposals on organizational and financial matters.

The project is accompanied with a communication plan to keep both analytical stakeholders (laboratories, secondary reference material providers) and other stakeholders (animal health bodies, competent authorities) informed on the aims and the progress with this four year project.

## The effective characterisation of novel pure substance reference materials while meeting users needs in a timely fashion

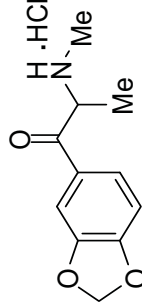
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A key component to a comparable and harmonised measurement system is the availability of appropriate pure substance reference materials. NMIA's focus in reference material production is in the area of pure substances. In many fields, particularly those related to potential prosecutions, the quality of such materials is imperative and thus NMIA produces a list of specialised materials to meet the need of the forensic and sports drugs communities. In recent times the need for appropriate reference materials for new designer drugs has been expanding and as drug profiling activities develop internationally there are also needs for precursors, intermediates and impurities. NMIA aim's to produce fit-for-purpose reference materials for this community. Our range of pure substance reference materials includes:

- Forensics (narcotics, designer drugs, drug metabolites, precursors, intermediates and profiling impurities)
- Sports drug testing (steroids, stimulants,  $\beta$ -blockers and diuretics, metabolites, labelled analogues)
- Agrochemicals (pesticides, herbicides)
- Veterinary chemicals (veterinary steroids, antibiotics, growth promotants and metabolites)

In the production of this suite of materials NMIA undertakes extensive characterisation procedures. Dealing with many of these challenging substances, such as designer drugs and drug metabolites, has highlighted the considerable challenges involved in the certification of property values for pure substance materials. In meeting the needs of the user community we need to learn to balance the effective certification of such materials with the provision of materials in a timely fashion. The technical challenges in the production of such materials with fit for purpose measurement uncertainty will be discussed.



3,4-Methylenedioxyamphetamine hydrochloride, one of the many methcathinone analogues which are now being seized internationally. NMIA produced a reference material for this in 2009 and has a suite of methcathinone analogues available.

## Smart calibration of organic standards - proton based calibration by qNMR

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National Metrology Institute of Japan (NMIJ) is responsible to disseminate the coherent and comprehensive national measurement standards throughout the nation. NMIJ has been developing the certified reference materials (CRMs) on the basis of CMCs registered in the Consultative Committee for Amount and Substance (CCQM) under the quality management system of ISO Guide 34. NMIJ is disseminating about 120 kinds of calibration standards, such as pH standard solutions, element standard solutions, standard gases and organic solvent standard solutions through Japan Calibration Service System (JCSS) under Japan Measurement Law. We have also developed more than 100 kinds of CRMs for method validation and/or quality control of measurements in various scientific and industrial fields. We are now disseminating the marine sediment CRMs, the fish tissue CRMs the rice CRMs, the water CRMs, and the Hijiki CRMs for food and environmental analyses and the clinical testing CRMs such as cholesterol, creatinine steroids, CRP and Amino acids. We mainly apply the primary measurement procedures such as ID-MS, ID-ICPMS and the freezing point depression method to characterization of CRMs in order to ensure the traceability to SI.

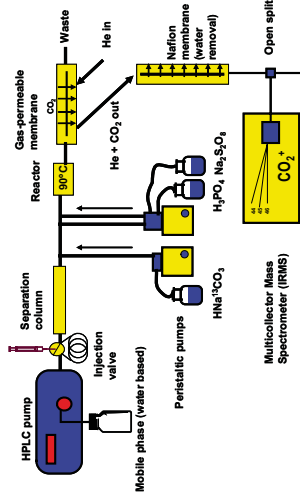
In recent years, strong demands for CRMs have rapidly been expanding to secure the reliability of measurements in a various fields, because the importance of the traceability in measurements has been understood and recognized as a crucial evidence of accuracy. For example, especially in food safety issues which every people are very nervous about, the Japan Food Sanitary Law was revised in 2003 and implemented in 2006 in order to regulate residual pesticides in food stuffs. The "positive-list" system is employed, and about 800 kinds of pesticides are permitted to be used accordingly if their residual concentration levels are below the predetermined limits (1 mg/kg). As a result, testing results of chemical residue directly impact domestic and international trades of agricultural products. The testing laboratories for food products are required to demonstrate the validity of the measurements and the accuracy of the measurement results. As a consequence, there are great demands for the proper series of reference materials of pesticides which guarantee the validity of the measurement results under the regulation. However, it is almost impossible to disseminate such a large number of reference materials in a short term. In these situations, we are now establishing a new dissemination system of CRMs on the basis of the quantitative NMR method. We will provide a proton-based calibration system, where the calibration among different chemical substances is realized by comparing their proton contents, although the amount of the chemical substance must be compared with that of the standard of the same chemical substance in a conventional calibration. Therefore, a single national standard will be a unique traceability source for a various-kinds of chemical substances in the proton based calibration, although the same numbers of the standards as the analytes measured should be prepared in a conventional one. By means of the proton based calibration with the qualitative NMR, NMIJ has already calibrated more than 100 kinds of pesticides CRMs which are disseminated as calibrants by a private chemical company. The proposed method can rapidly provide CRMs which are traceable to SI or at least to the national standard.

## Establishment of an universal procedure for the purity assessment of analytical standards, pharmaceuticals and peptides

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The purity assessment of analytical standards is the first step in the traceability chain for any analytical procedure. In most cases analytical standards are certified by their manufacturer but there are many cases in which the purity of analytical standards is not well established. For example, when new pharmaceuticals need to be measured in biological fluids a reference high purity standard may not be available. On the other hand, the use of a signature peptide for the quantification of a given protein after trypsin hydrolysis requires the use of synthetic certified peptides. The purity assessment of synthetic peptides is currently done by acid hydrolysis and amino acid analysis. Obviously this is a cumbersome and error prone procedure. So, an universal technique for the purity assessment of analytical standards, including new pharmaceuticals and peptides, which could be directly traceable to the SI would be required. In this presentation we will describe a procedure based on LC separation, post-column  $^{13}\text{C}$  addition, chemical oxidation and MS detection of carbon dioxide for the absolute quantification of analytical standards and its implementation as a universal procedure at the University of Oviedo. The experimental set-up is described in the diagram below.



The continuous measurement of the isotope ratio 44/45 in the mass spectrometer allows to build the mass flow chromatogram. The integration of the mass flow chromatogram provides directly the mass of carbon in the chromatographic peak (t). The identity of the compound will be established in parallel by LC-MS-MS with an ESI or APCI ion source. The calibration of the  $^{13}\text{C}$  post-column flow can be easily performed using a natural abundance sodium carbonate primary standard.

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## Developing benchmarks for measurements – the IRMM approach

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The increased understanding of the complexity of nature including human bodies, the identification and handling of societal challenges including globalisation, and the advancement of technologies would not be possible without sound information. Measurement data are in most cases basic components of such information and have to be tailored and reliable enough for decision making. Consequently, regulatory demands are playing an increasing role for the identification, prioritisation and quality assurance of measurement tasks, from the local to the global scale. In that context, the JRC Institute for Reference Materials and Measurements (IRMM) has focused its attention to the provision of measurement standards and quality tools for European needs since its foundation.

Benchmarking in the measurement process includes various steps, from calibration to lab-internal and external quality control. The first one comprises, at least for many chemical and biological parameters, both identification and quantification aspects, whereas the competence checks between laboratories are directed to enabling international trade and mutual recognition of measurement results. Indeed, globally accepted and used benchmarks for measurements are required for a broad range of scientific disciplines and application areas, from physics via chemistry to biology, from industrial process control via environmental monitoring to food and health surveillance. Modern measurements are performed on test samples which show an increasing level of structural and/or functional complexity on the one hand side and often a decreasing amount of the component-of-interest on the other hand side. Moreover, the relevant property to be characterized is in many cases still not sufficiently known or not clearly enough defined for performing unambiguous measurements. Consequently, the interplay between problem-tailored measurement methods, reference materials for calibration and quality control, respectively, and qualified operators in laboratories has to be understood and considered for the development and provision of adequate measurement benchmarks.

Therefore, IRMM is paying considerable attention to the identification of current and future needs for reference points and scales for measurements required by EU policy making and implementation as well as for European innovation and competitiveness. The presentation will discuss both scientific-technical and regulatory aspects for selecting new reference material projects at IRMM. Moreover, future demands on advancing the underlying science in various application sectors and challenges for reference material developments and innovative RM production technologies will be outlined. Examples from nuclear safety via environmental sciences to molecular biology and microbiology will be used to illustrate the IRMM approach.

## POSTER ABSTRACTS



## Standard reference materials for uranium analysis

# P1

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Inductively coupled plasma mass spectrometer (ICP-MS) has been widely used in a number of fields including drinking water, waste water, geology, soil and mining. One of the advantages of ICP-MS is an extremely low detection limit for a wide variety of elements like uranium. Uranium is a radioactive element and determination of uranium in low concentrations is very important for human health. Therefore ICP-MS is the most suitable method for uranium analysis. In this study total concentration and isotopic ratio of uranium was measured by ICP-MS. Experimental parameters such as dissolving techniques and ICP-MS analysis of soil sample are explained. The presented methods are applied to standard reference materials, S7, S8, and SOIL5 for total uranium analysis and from depleted to 5 percent enriched uranium for isotope ratio measurements.



## P2 Production, characterisation, and analysis of uranium reference particles for nuclear safeguards

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In support to the International Atomic Energy Agency Network of Analytical Laboratories (IAEA-NWAL), the Institute of Reference Materials and Measurements (IRMM) produces well characterized uranium reference particles that closely resemble real life particles found in nuclear facilities. These particles are produced in a specifically designed aerosol deposition chamber from the controlled hydrolysis of uranium hexafluoride (UF<sub>6</sub>) gas with certified isotopic composition and collected in-situ on graphite planchet supports. They are used as quality control samples in order to evaluate the analytical performances of the NWAL via participation in interlaboratory comparisons (NUSIMEP) and to improve the capabilities for the routine analysis of swipe samples in safeguards. Recently the environmental conditions inside the aerosol chamber influencing the particle formation and the morphology (e.g. temperature, relative humidity, UF<sub>6</sub> concentration) were optimised. These improvements enabled to prepare a well characterized test reference sample with two different uranium enrichments which will be used for the next NUSIMEP campaign.

For the particle characterization, a Scanning Electron Microscope (SEM) equipped with an Energy Dispersive X-ray (EDX) detector was used to acquire information on the particle shapes, sizes and surface distribution after deposition. In addition, an improved method was developed at IRMM for enabling the accurate determination of the isotopic composition in individual micrometer-sized uranium reference particles. This method is based on the use of the in-situ SEM micromanipulation technique and Thermal Ionisation Mass Spectrometry (TIMS) combined with filament carburization and Multiple Ion Counting (MIC) detection. Hereby individual reference particles produced from certified UF<sub>6</sub> with high, low and close to natural <sup>235</sup>U enrichment were analyzed. The advantage of this method is its high sensitivity, which is important for analysing uranium at femtomole levels. Reliable measurements with significantly smaller uncertainties were obtained, not only for the major ratio <sup>238</sup>U/<sup>235</sup>U but also for the minor isotope ratios <sup>234</sup>U/<sup>238</sup>U and <sup>236</sup>U/<sup>238</sup>U. It was shown that this technique has the potential of being a complementary technique for Secondary Ion Mass Spectrometry (SIMS), which is routinely applied for the detection of uranium signatures in swipe samples taken by safeguards inspectors in nuclear facilities. IRMM's recently established capability in the optimised production, characterisation and analysis of uranium reference particles is considered a significant support to the nuclear safeguards community.

## P3 Reference materials for age dating in nuclear forensics

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In case nuclear material (uranium, plutonium) is discovered in places out of the regulatory control of nuclear safeguards, nuclear forensic investigations are applied in addition to traditional forensics. Traditional forensics recover and analyse evidence such as fingerprints left behind by the malefactor in order to identify the individual who committed the crime; nuclear forensics focuses on the origin and the history of the seized material. Isotopic and elemental compositions as well as physical appearance give information on the production process and/or intended use of the material. Additionally the knowledge of the "age" of the material helps in reducing the number of facilities where the material has possibly been separated considerably. The "age" of a nuclear material is defined as the time that has passed since the last chemical separation of the mother and daughter isotopes. Assuming that the separation has been complete and all the daughter isotopes have been removed from the original material during this separation, the age of the material can be calculated from the ratio of daughter and mother radio-nuclides, e.g. <sup>241</sup>Am/<sup>241</sup>Pu. At a given time after the last separation and depending on the half lives of the radio-nuclides involved, a certain amount of the daughter radionuclide(s) will be present. For the determination of the unknown age of a material different "clocks" can be used. "Clocks" are pairs of mother and daughter radio-nuclides. In case of plutonium samples the isotope pairs <sup>241</sup>Am/<sup>241</sup>Pu, <sup>239</sup>Pu/<sup>239</sup>U, <sup>239</sup>Pu/<sup>235</sup>U, <sup>240</sup>Pu/<sup>235</sup>U, and possibly <sup>242</sup>Pu/<sup>238</sup>U can be used as "clocks". For the age estimation of a real sample, such as seized nuclear material, it is advisable to use more than one clock; otherwise wrong conclusions could be drawn from the measurements of a sample when it is a mixture of materials of different ages or due to incomplete separations at time "zero". Consequently, a future reference material for the separation date should be certified for more than one "clock" or several reference materials for different "clocks" should be prepared. Presently, no uranium or plutonium reference materials certified for "age" are available; although there is clearly a need for such materials in nuclear forensics and environmental measurements in view of method validation and quality control. Nuclear reference materials properly certified for their "age" would provide a more solid metrological basis for age-dating measurements and would thus increase the value of the conclusions based on these measurements. In order to meet the present needs of laboratories involved in nuclear forensics analysis the Institute for Reference Materials and Measurements (EC-JRC-IRMM) is closely cooperating with the Institute for Transuranium Elements (EC-JRC-ITU). First results from a recently started feasibility study for the development of plutonium reference materials for age dating will be presented.

## P4 The Cetama nuclear reference materials catalogue and its planned evolutions

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Measurement quality is crucial for the safety of nuclear facilities, as it is a primary requirement for the characterization of nuclear materials and for the monitoring of fissile materials. In the nuclear field, the improvement of analysis and measurement result quality is a major mission of the Commission for the Establishment of Analysis Methods (CETAMA), part of the French Atomic Energy Agency (CEA). Suitable scientific and technical developments, in particular preparation and certification of reference materials, are proposed. These materials are used either as analytical standards or as reference samples for interlaboratory comparisons organized by CETAMA: EQRAIN Proficiency Testing Schemes (PTS) and round robin validation tests.

For the nuclear industry and associated R&D laboratories, the accuracy of analysis results is of prime importance considering:

- U, Pu flow balance,
- Nuclear Materials accountability
- Effluent waste control.

The CETAMA catalogue offers about thirty different reference materials, certified either in terms of major elements, isotopic composition or impurity concentrations. It concerns uranium and plutonium materials, in oxide or metallic forms, neptunium-237 nitric acid solution, and different uranium based minerals with certified impurity contents. Four developments are currently being considered by CETAMA, the other needs being examined progressively in future years. First of all, the latest reference material we propose is a <sup>242</sup>Pu isotopic standard with a ratio <sup>242</sup>Pu/[Pu] of about 98.5%. After fabrication by the LAMMAN laboratory at CEA Marcoule, the certification, performed by five laboratories of CEA, French nuclear industry and IRMM, is in progress and is being supervised by the third CETAMA Working Group ("Plutonium analysis WG"). This standard is complementary to the other standards available, in particular those proposed by IRMM and NBL, with a higher <sup>242</sup>Pu isotope content. Secondly, elementary analysis on solids, devoted to nuclear fuel and waste conditioning matrix characterization, needs plutonium and uranium standards, certified in concentration.

The current references have to be replaced and new references produced for specific quantitative actinide determinations (U, Pu and Am). The first project concerns the production of plutonium oxide pellets at CEA Cadarache center. The certification will be organized and planned within the CETAMA WG 21 devoted to surface analysis.

Third, our metallic plutonium reference (MP2), which is a common standard for many international laboratories, will be replaced within around ten years in order to maintain the availability of this material and to cover global international needs. The production, driven by the CEA Military Application Direction division, should start in 2012.

Last but not least, in the framework of international nuclear renaissance, CETAMA will also start a re-certification program to improve the characterization of some old ores certified either for their major elements or their impurity concentration, in particular to support IAEA programs. In the future, CETAMA will also focus on different actinide based materials, solutions and solid matrices.

## P5 Development of the first certified reference material for the size of suspended silica nanoparticles

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The poster describes the preparation and certification of the equivalent particle diameter of silica nanoparticles in aqueous suspension certified reference material, namely of ERM-FD100.

ERM-FD100 is a certified reference material (CRM) and consists of colloidal silica nanoparticles suspended in an aqueous solution. The intended use is to check the performance of instruments and methods that characterize the particle diameter of nanoparticles (particle size ranging from approximately 1 nm to approximately 100 nm) suspended in a liquid medium. The CRM was prepared from commercially available colloidal silica (Koesstrosol 1530, Chemiewerk Bad Koenstritz GmbH, Germany).

Certification of the CRM included testing of the homogeneity and stability of the amplified diluted raw material as well as the characterisation using an intercomparison approach.

The CRM has been certified for its equivalent diameter of silica nanoparticles in aqueous suspension using different methods. Certified values are the Cumulant DLS intensity weighted, Line-start CLS intensity weighted, EM (TEM/SEM) number weighted and SAXS intensity weighted particle diameter.

Indicative values have been established for the equivalent particle diameter via the small angle X-ray scattering (SAXS) method and for the zeta potential via the electrophoretic light scattering method. Additional informational values are given for the particle diameter via the cumulant dynamic light scattering (DLS) method, the volume weighted particle diameter and the pH value of the ERM-FD100 suspension.

Uncertainties are expanded uncertainties estimated in accordance with the Guide to the Expression of Uncertainty in Measurement (GUM) with a coverage factor of  $k = 2$ , corresponding to a level of confidence of about 95 %.



## Development of a steel reference material certified for Charpy impact toughness at 0°C

P6

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The poster describes the development of a steel reference material certified for its KV (absorbed energy = energy required to break a V-notched test piece using a pendulum impact test machine) according to ISO 148-1 and EN 10045, at 0°C. This material will serve as Master Batch, to be used by IRMM for the certification of secondary batches, which are distributed by IRMM and its authorised distributors for the verification of pendulum impact test machines according to EN 10045-2 (Charpy impact test on metallic materials, Part 2. Method for the verification of impact testing machines) or according to ISO 148-2 (Metallic materials - Charpy pendulum impact test - Part 2: Verification of test machines).

CRMs for Charpy impact toughness at 20 °C of nominal energies between 30 J and 150 J have been available from IRMM since 1989. Recent batches of the 30 J level, however, showed an increased incidence of significant post-fracture deformation marks on the long edges of the broken samples. This suggests that the samples, after fracture, were briefly caught between the anvil and a part of the swinging pendulum, a known phenomenon called 'jamming'. Jamming induces erroneously high measured absorbed energy values, and occurs in a particular temperature range, depending on the combination of test material and test instrument. The occurrence of the problem at room temperature for a certain steel-instrument combination can be avoided by testing at lower temperatures. The new Master Batch enables IRMM to provide samples for those customers whose pendulum impact machine is affected by jamming when testing IRMM Charpy CRMs of the 30 J nominal energy level at room temperature. In addition, the new batches are expected to be of particular use for industrial laboratories without room temperature control: it is easier to cool a sample to 0 °C than to 20 °C.

## Double-phase reference materials

P7

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By means of Italy and EU-funded Research Projects, ENEA has developed real plants for the RM production, located in Casaccia (near Rome) and Trisaia (in South Italy) Research Centres. These plants were specifically designed for the preparation of Matrix-RMs of natural origin (environmental and agro-food RMs); it is possible to obtain up to 1000 homogeneous and stable aliquots and, depending on the matrix, to prepare RM in different physical-chemical forms, such as lyophilized, liquids and dry powders. As the main purpose in RM production is to achieve a lot of stable and homogeneous material closely matched to the actual products, these plants have been developed in order to control the chemical and biological degradation processes by appropriate settings of T, RH and lighting. Furthermore two homogenization steps (one at the wet and one at the dry stage) are foreseen and the contaminations occurring during the process are highly reduced by the employment of inert materials.

In 2001 ENEA took part in an intercomparison among RM producers (TRAP-LRM EU Project) to prepare a lake sediment RM. Then, as a part of national research projects, ENEA plants have been involved to prepare lyophilized agrofood RMs, such as: tomato fruit (fresh and peeled), broccoli, mushrooms and strawberry fruit. In cooperation with the Laboratory for Foods of Animal Origin – IZS\_AM, which is the Italian National Reference Laboratory for Dioxins and Polychlorobiphenyls, it was also prepared a fish feed RM to be certified for PCDDs and PCDFs. Since 2006 ENEA has been supporting the EU CRL for Chemical Elements in Food of Animal Origin c/o Istituto Superiore di Sanità in lyophilization of the RMs (bovine muscle and liver, pig meat, swine muscle, fish muscle, partly skimmed milk) to be employed in EU-NRL Proficiency Testings. Recently a feasibility study for the development of a toner RM has been carried out. One of the distinctive features of the ENEA plants is the utilisation of an industrial rotary evaporator (V=100 L) before the lyophilization phase. It allows the introduction of an additional homogenization step at low pressure in the wet stage and the significant reduction of the volume of the material to be lyophilized, with the result of a time-, energy- and cost-saving. Furthermore it permits to prepare Double-Phase RMs (DP-RMs) in which the RM is split, during the preparation procedure, into its two aqueous and anhydrous components. In fact the employment of the industrial rotary evaporator allows the extraction of a significant part of the solvent and its collection in a condensed form. After the lyophilization step, the dry powder is bottled and the condensed phase is sealed in glass vials. Therefore RMs are supplied in their two separated components (liquid and solid phases) to be re-combined before use. In addition, as these plants are equipped with an automatic press for pellet preparation, starting from lyophilized powders, there is the real possibility to prepare Single Use-RMs in Double-Phase (pre-weighed pellet plus its own solvent).

In this work we report the preparation and the characterization of Double-Phase Reference Materials, also in Single Use form. Starting from a unique homogeneous batch, ENEA has prepared both traditional RM (only lyophilized) and Double-Phase RM (lyophilized and condensed phase) of natural (environmental and agro-food)-origin: freshwater sediment, milk, strawberry fruits. Chemical characterization of raw material, lyophilized material, condensed phase and reconstructed DP-RMs has been carried out by ENEA, in cooperation with IZS\_AM. Preparation procedures are described and the results of chemical characterization are compared. Finally we discuss the application fields and the advantages of these new procedures for RM preparation.

## Proficiency testing program of sucrose measurement using refractometric method in Thailand

P8

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Proficiency testing program (PT) plays a vital function on execution of the test procedures and instrumentations, independent check on the accuracy of the analysis results and demonstrating the competency of the participating laboratories. National Institute of Metrology, Thailand (NIMT) is a sole organization responsible for production of certified reference materials. Likewise, preparation and certification of proficiency testing samples are also the major tasks. A PT program on sucrose measurement provided for domestic sugar cane industries is one of the NIMT PT programs. This PT program, with a cooperation of NIMT and Office of the Cane and Sugar Board (OCSB), Ministry of Industry, was organized. In 2008, the first round of sugar PT has been launched with only 8 laboratories participated. The second round was in 2009, the number of participants greatly increased to 44 laboratories resulting almost 90% of all existing sugar testing laboratories in the country participated. The competence of the labs was evaluated by using z-score as criteria. Target standard deviation of % Brix was calculated by applying Horwitz equation whereas the standard deviation of refractive index was obtained from the results of all participants. The evaluation of laboratory competency has shown that 93% of the participating laboratories obtained satisfactory results. This indicates a high degree of confidence on the quality of the produced sugar. However, the 7% of the participant laboratories with unsatisfactory results have individually been informed with suggestion on the investigation and improvement of the laboratory performance.

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## Novel reference materials for mycotoxin analysis

P9

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Food safety and consumer protection have increasingly gained importance during the last decade. Due to serious toxic effects caused by mycotoxins, the surveillance, determination and reduction of these compounds in food and feed is subject to the work of regulators, food business operators and researchers. In the frame of the ERM® (European Reference Materials) initiative BAM has initialized several new certified reference material (CRM) projects for mycotoxins in food.

Mycotoxins are secondary metabolites produced by several strains of fungi. Ochratoxin A (OTA), a nephro- and hepatotoxic mycotoxin, is formed by *Aspergillus* and *Penicillium* sp after the harvest under certain conditions of storage, food processing and shipment. Different kinds of food and feed commodities including cereals, coffee, wine and dried fruits are target matrices for contamination. Since coffee and wine were identified as most relevant sources for OTA exposition, EU maximum limits have been established for these foods already in 2005 [1]. With this talk, the certification process of the first reference materials for OTA in roasted coffee (ERM-BD475) and red wine (ERM-BD476) will be outlined.

Fungi of the genus *Fusarium* are the predominant mycotoxin producers in moderate climate zones. *Fusarium* toxins occur worldwide in a large variety of foods, particularly in highly consumed cereal based products. The most important *Fusarium* mycotoxins in view of adverse toxicological and economical impacts are zearalenone (ZON) as well as certain trichothecenes of type A (T-2 and HT-2 toxin) and type B (deoxynivalenol, DON; nivalenol, NIV). While for DON and ZON European maximum levels are already in effect [2,3], new levels for T-2 and HT-2 toxins are currently under discussion.

The recently completed reference material ERM®-BC600 "DON, NIV and ZON in wheat flour" as well as the candidate material ERM®-BC720 "T-2 and HT-2 in oat flakes" intend to close the current gap of available CRM for *Fusarium* mycotoxins in food. They contribute to laboratory internal quality control and facilitate method development as well as validation.

In this talk, the preparation and characterization of the wheat ERM including homogeneity and stability studies based on ISO Guide 35 [4] will be outlined. Results of the interlaboratory comparison study for certification of the mass fractions of DON, NIV and ZON are presented. Furthermore, the present status of work in production and certification of the T-2 / HT-2 material (ERM®-BC720) will be presented and discussed.

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## Brazilian rice flour candidate reference material for minor and trace elements

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Brazil is the acknowledged world leader in generating modern technology for tropical agriculture. According to the Ministry of Agriculture, Livestock and Food Supply (MAPA), the competitive performance of the Brazilian agribusiness can be attributed largely to the development of science and technology and modernization of rural activity. The adoption of food quality programs is also highlighted among the main factors that turned the country in one of the most respected global platforms of agribusiness. Nevertheless, there is a limited number of certified reference materials for food analysis, which can impose limitations on the metrological aspects of quality control. Since Brazilian laboratories rely on imported reference materials, mastering their production technology represents a strategic breakthrough for the country. In this context, a collaborating centre in agricultural defence was created for the production of certified reference materials and organization of proficiency tests on residues and inorganic contaminants. Rice flour certified for minor and trace elements is amongst the reference materials proposed to be produced by the end of 2011. The rationale for choosing this matrix material is that rice is the staple food for half the world's population. Besides, the world is facing a rice crisis with an imbalance between demand and production and concerns have been raised about levels of toxic elements like As and Cd. The producing countries are therefore being urged to provide rice in high quantity and of good quality. China is currently the only country to have set a reduced limit at 0.15 mg of inorganic arsenic per kg of food. Fifty-one rice samples of various brands, cultivation system (floodland and upland) and types (whole, polished, parboiled and organic) from 5 producing states (Mato Grosso, Paraná, Rio Grande do Sul, Santa Catarina, São Paulo) in 3 geographical regions (centre west, southeast and south) of Brazil were acquired in the consumer market in the city of Piracicaba, SP. The rice grains were then ground (Grindmix GM 200) into fine powders. The selection of the candidate reference material was primarily based on the As content in the rice samples in compliance with the limit of 1.0 mg/kg established by the Brazilian legislation for food in general. Samples were analyzed by instrumental neutron activation analysis (INAA). Both whole and polished rice from the state of Mato Grosso (upland rice) showed the lowest levels of arsenic (0.00647 mg/kg and 0.00901 mg/kg, respectively) among all samples being below the detection limit for INAA. Samples from the states of Paraná, São Paulo and Santa Catarina, with a predominance of upland rice, showed average concentrations of arsenic ranging from 0.1 to 0.2 mg/kg for all types of rice, while the samples from Rio Grande do Sul, where irrigated rice predominates, showed the highest concentrations of arsenic for all types of rice, highlighting the whole (0.2 to 0.5 mg/kg) and the parboiled rice (0.2 to 0.3 mg/kg). Taking into account the results obtained in this screening study, 3 commercial brands from Rio Grande do Sul with the highest As values were selected for the upcoming production of the rice candidate reference material. It is intended to provide certified values for as many elements as possible using INAA and ICP-MS.

## Fusarium mycotoxin CRMs - perfect tools for quality control in food analysis

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A contamination with moulds and mycotoxins may occur during the whole production chain of a food product (i.e. "from the field to the fork"). The Food and Agriculture Organization (FAO) estimates that as much as 25% of the world's agricultural commodities are contaminated with mycotoxins. Due to serious toxic effects caused by mycotoxins, the determination and reduction of these compounds in food and feed is subject to the work of regulators, food business operators and researchers. Fungi of the genus *Fusarium* are the predominant mycotoxin producers in moderate climate zones. *Fusarium* toxins occur worldwide in a wide variety of foods, particularly in highly consumed cereal based products. The toxicologically - and hence also economically - most important *Fusarium* mycotoxins are zearalenone (ZON) as well as the type A (T-2 and HT-2 toxin) and type B trichothecenes (deoxynivalenol (DON), nivalenol (NIV)). Driven by regulatory authorities (e.g., the European Food Safety Authority) extensive consumer protection efforts were made by establishing fast and reliable analytical methods for the determination of the most common *Fusarium* toxins in cereals and derived products. At the same time legally binding maximum levels were introduced for these matrices [1,2]. While for DON and ZON EU maximum levels are already in effect, new levels for T-2 and HT-2 toxins are currently under discussion. To enforce the maximum levels and thus reduce consumer risks, strict controls of food and feed are of prime importance.

For the sum of these reasons, matrix matched certified reference materials (CRMs) for trichothecenes are required. CRMs can aid in method validation and increase comparability and traceability in trichothecene analysis. In the frame of the ERM® (European Reference Materials) initiative BAM has initialised two new CRM projects for *Fusarium* mycotoxins in food.

The new candidate reference materials ERM®-BC600 "DON, NIV and ZON in wheat" and ERM®-BC720 "T-2 and HT-2 in oat flakes" intend to close the current gap of available CRMs for mycotoxins in food. They contribute to laboratory internal quality control and facilitate method development as well as validation.

The preparation and characterization of the wheat material including homogeneity and stability studies based on ISO Guide 35 [3] will be outlined. Results of the interlaboratory comparison study for certification of the mass fractions of DON, NIV and ZON are presented. Furthermore, the present status of work in production and certification of the T-2/HT-2 toxin material (ERM®-BC720) will be presented and discussed.

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ERM-BB130, a new certified reference material for reliable measurements of the prohibited veterinary drug chloramphenicol

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Chloramphenicol (CAP) is a broad-spectrum antibiotic and highly effective against many pathogenic bacteria, rickettsiae and mycoplasmas. CAP was used in veterinary practices since the 1950s, but is banned in the EU for treatment of food-producing animals since 1994 (Commission Regulation (EC) No. 1430/94), as its uptake in humans can cause serious haemotoxic effects such as leukemia. Effective consumer protection relies on accurate measurements, and certified reference materials (CRMs) are highly valuable tools for laboratories for the development, validation, and performance verification of their methods.

IRMM produced a certified reference material, ERM-BB130 - chloramphenicol in pork, designed to support the legal requirements of Commission Decision 2003/181/EC [8], which fixed a minimum required performance limit (MRPL) for testing methods of 0.3 µg/kg for residues of CAP in different matrices, including meat. Incurred pork muscle was used as raw material and converted into a lyophilised powder. Homogeneity and stability of the material was assessed by measurements with liquid chromatography tandem mass spectrometry. The relative standard uncertainty due to possible heterogeneity was found to be below 1.5 %, and no significant instability was detected during storage at -20 °C for a shelf life of two years. The certified values were established in an inter-comparison with 16 expert laboratories using different sample preparation procedures with subsequent GC-MS or LC-MS/MS methods for analysis, respectively. The certified value of  $0.230 \pm 0.021$  µg/kg (mean  $\pm$  expanded uncertainty) is traceable to the International System of Units (SI) and complies with the established MRPL.

The material shall be used for method validation (trueness determination) and method performance verification of state-of-the-art confirmatory methods based on column chromatography coupled to mass spectrometry. An additionally performed commutability study provided evidence that ERM-BB130 can also validly be used as a quality control sample for a number of commercially available ELISA and biosensors routinely used as screening methods for large sample numbers.

In-house reference material of narasin and nicarbazin in eggs: preparation and evaluation

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Coccidiostats are a group of pharmacologically active substances widely used as feed additives and veterinary drugs to protect poultry against coccidiosis. Residues of coccidiostats, especially in chicken tissues and eggs are detected relatively often in official control in many European Union countries. In recent years, the improvement of the methods applied in official control was observed. Nevertheless, the proper quality control, employing materials containing incurred residues is difficult. Unfortunately, certified reference materials of veterinary drug residues are often unavailable. Therefore, in-house reference material of lyophilized eggs containing incurred narasin and nicarbazin was produced and verified.

The eggs were obtained from hens fed with feed containing Maxiban. The homogenised eggs (without shell) were mixed with blank eggs to obtain presumed concentrations. The eggs were then freeze-dried. After lyophilisation, the loss of water was calculated. The samples of test material were placed into Falcon tubes were stored at the temperature -20±2°C. The homogeneity of the material was verified by the duplicate analysis of ten random samples and the results were interpreted with the test of sufficient homogeneity. The stability test was performed using isochronous approach within the 1 year. The assigned values of both coccidiostats (44.4 µg/kg and 7.91 µg/kg for nicarbazin and narasin, respectively) were expressed as medians of the results of inter-laboratory comparison performed by four different European laboratories using LC-MS/MS methods. It has been proved that the material is sufficiently homogeneous and stable and can be used for quality control in routine analyses. Prepared material was successfully used in the proficiency test organized by our laboratory for the routine laboratories performing national residues control plan.



## P14 Preparation and its uses of sugar reference material for determination of dissolved solid in cane and sugar industries in Thailand

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Thailand is one of the leading countries in sugar production and exportation. Recently, the demand of sucrose reference materials for quality control, and proficiency testing program in cane and sugar industries has greatly increased. The amount of sucrose in cane and sugar products can be analyzed using refractometry and polarimetry methods. Refractometry method is mainly utilized for the determination of dissolved sucrose, the refractometric solids, in solutions. The refractometric values of sugar solutions can be used as an accurate measurement of dry substance content, mainly sucrose. In 2008, National Institute of metrology, Thailand (NIMT) has launched new certified reference materials for refractometric measurement. The solutions are aqueous sucrose solutions at different concentrations. The refractive index in the range of 1.34782 to 1.4417 and mass fraction of dry sucrose in the range of 10% to 60% Brix (commercial scale for dry sucrose in solution) are characterized using refractometric technique. The traceability chain of the CRMs can be obtained through gravimetric methods. Study of homogeneity and stability including the estimation of uncertainties are described.

## P15 Matrix reference materials for the detection of genetically modified cotton

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Legislation in the European Union demands the labelling of food and feed products consisting of or containing "more than 0.9 % genetically modified organisms" (GMOs). This is the labelling threshold level for GMOs that are authorised in accordance with Community legislation (EC No 1830/2003). Consequently the availability of validated quantification methods and reference materials form, beside the safety assessment, a mandatory part of the authorisation process of GMOs in Europe. In 2008, the Institute for Reference Materials and Measurements (IRMM) was asked by Bayer BioScience to develop, produce and make available reference materials for the two cotton events GHB119 and T304-40 based on the intention to apply for authorisation of a stacked cotton event T304-40 x GHB119 in Europe.

Two sets of GMO Certified Reference Materials (CRMs) for the cotton events GHB119 and T304-40 have been produced from genetically modified (GM) seeds and non-GM seeds. The seeds were milled using a cryo-grinding vibrating mill (Palla mill, KHD, Humboldt-Wedag, Köln, DE). Beside a pure non-GM material, gravimetric mixtures of non-GM and GM cotton powder were prepared by dry-mixing, a first material by mixing non-GM and GM cotton powder and a second one by further dilution of the mixture with non-GM cotton powder. The mass fraction of events GHB119 and T304-40 cotton were certified based on the mass of GMO cotton seed powder per total mass of cotton seed powder, corrected for their respective water content and after careful investigation of the purity of the seed materials used. The measurements of the primary method used for certification were confirmed by real-time quantitative PCR.

Certified values of ERM-BF428 (GHB119 cotton) and ERM-BF429 (T304-40 cotton) are traceable to the International System of Units (SI). The traceability chain is based on the use of calibrated balances and a thorough control of the weighing procedure. The purity and the water content of the used seeds have been taken into account when calculating the certified value. The two series of CRMs are intended to be used as quality control material or calibrant in DNA-based methods for the detection of genetically modified material in food and feed.

The CRMs are currently certified for their GM mass fraction. An additional certification of the DNA copy number ratio is envisaged for the future, allowing the implementation of European Commission Recommendation (EC) No 787/2004 to express the content of GM food and feed as the percentage of transgenic DNA copy numbers in relation to target taxon-specific DNA copy numbers calculated in terms of haploid genomes.

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Real-time PCR is now a technique widely used even for qualitative tests. Most of the methods published in literature describe the cut-off value as a cycle threshold (Ct) expressed in number of cycles above which a signal is interpreted as a negative result. The parameter is presented as universal and usable whatever the PCR platform used. This way to determine the cut-off of a platform can nevertheless limit the transferability of a method considering that a Ct value can be influenced by the mastermix, the thermocycler and the operator among others.

Recently, the CRA-W proposed a protocol for the determination of the cut-off value of a PCR platform using calibrations performed with plasmids. Different parameters of the protocol such as the number of calibration points, the number of replicates per calibration point as well as the minimum number of calibrations required to calculate an accurate cut-off value were optimised and applied to a PCR method for the detection of cattle DNA in feedings. The protocol was successfully tested through an inter-laboratory study conducted by the CRA-W in the framework of the CRL-AP activities.

The preparation of the calibrants produced for these two inter-laboratory studies was a critical step. The determination of the number of copies of the target was based on the optical density (OD) measurement of a stock solution containing a very high level of plasmids. The stock solution was then diluted in an autoclaved maize DNA to obtain the different calibrants solutions at 640 copies/PCR, 160 copies/PCR and 40 copies/PCR respectively. The dilution of the plasmids in a foreign DNA makes any check impossible by OD measurement but is nevertheless mandatory to avoid any sticking effect.

In the future, the control of the calibrants will be of importance and the use of the digital PCR technology will be of a great help to determine more accurately the number of copies of the target present in the calibrants. Such calibrants with certified copy numbers of the target could be used as reference materials.

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**Background:** Hungary belongs to countries with a low selenium supply. Se was found to be essential component of the enzyme glutathione peroxidase (GPX), and this enzyme, known to participate in the antioxidant protection of cells by reducing hydroperoxides. Autoimmune destruction of pancreatic beta cells leads to insulin dependent diabetes mellitus (IDDM). Oxygen-derived free radicals play an important role in the destruction process. Defense against free radical damage include selenoenzymes, the glutathione peroxidases. Nutritional factors have great influence in the management of diabetes and early prevention of complications. An association may exist between a low intake of certain micronutrients and asthma. Individuals with asthma tend to have increased oxidative activity and lowered Se status. **Aim of the study** was to compare Se intake and blood status in healthy Hungarian (HH), healthy American (HA), diabetic (D) and asthmatic (A) children, with different eating patterns. **Patients:** Three different studies were performed. Blood samples were collected from well controlled diabetics (n=35), and age, sex matched healthy children (n=127). In the second, balance study 8 aglucosuric IDDM patients and 8 healthy controls participated. Se intake calculated from dietary records, blood status and urinary excretion (24 hours collection) were measured. In the third study duplicate food samples were collected, blood status and 24 hourly urinary Se was measured from healthy American (n=20), healthy Hungarian (n=30), IDDM patients (n=16) and asthmatics (n=25). **Methods:** Duplicate food samples were collected over 3 (HH, HA, D) and 8 consecutive days (A), recorded and individually weighed. Se content was measured by instrumental Neutron Activation Analysis (INAA). Se concentrations in blood and urine were determined by Atomic Absorption Spectrometry (AAS). **Results:** Se content (µg/l) in erythrocytes (107 ± 16 v. 89.2 ± 16), in whole blood (82.9 ± 8 v. 64.8 ± 8) and in plasma (71.9 ± 8 v. 53.7 ± 8) was higher in diabetics (n=35) compared to healthy (n=127). Se intake (range: 26-41 µg/d), blood status and urinary excretion (range: 10-25 µg Se/g creatinine/d) were significantly higher in diabetics (n=8) compared to healthy (n=8). Selenium intake (µg/d) was 33 ± 8 in HH, 62 ± 18 in HA, 54 ± 9 in D and lowest 31 ± 8 in asthmatics. **Conclusions:** Mixed food consumption provided higher Se supply in the Americans than that of diet based on solely Hungarian products. Diabetic diet provided higher Se intake in diabetics compared to healthy Hungarians. However, blood Se status was higher in diabetics, but the urinary Se excretion was not reduced in relation to glucosuria. Chronic asthmatics had the lowest Se intake.

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**Background:** Plasma (or serum) cystatin C is a marker for the glomerular filtration rate, a measure of the capacity of the kidneys to filter plasma (GFR) [1]. Several studies, as well as one meta-analysis [2], have suggested that it is superior to serum creatinine for estimation of GFR. Particularly, cystatin C could be used for tests for children, elderly, patients with low muscle mass, and the early stages of kidney problems, where creatinine measurements do not perform well. Additionally cystatin C is used as a marker for cardiovascular risk and pre-eclampsia. IRMM has certified a reference material (RM) for cystatin C, which had been prepared in collaboration with the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) working group for the standardisation of cystatin C. Here the results from a preliminary commutability study, performed in order to optimise the design of a planned large-scale commutability study, are presented.

**Methods:** Commutability studies have been performed using four assays, all employing antibodies from different sources. Thirty serum samples were measured together with dilutions of the RM (RM mass fractions of 0.1, 0.2, 0.25, 0.3, 0.6 in assay diluent) as well as the undiluted material, in one analytical run, in triplicate. The methods used were the Siemens N Latex Cystatin C Test Kit run on a BN ProSpec<sup>®</sup>, the Sentinel CH assay run on an Architect c16000, the Roche tina quant cystatin C assay run on a Cobas c501 and the Gentian cystatin C immunoassay run on an Architect.

In order to assess the commutability of the material it was investigated whether the measurement results of the dilutions and the RM were within the 95 % prediction interval of the linear regressions.

**Results:** The data were first analysed by performing linear and polynomial regressions on the means of the measurement results of the patient samples for each combination of assays. The results showed a good linear correlation for comparisons of measurements performed with the Siemens, Sentinel and Gentian assays. For comparisons of the results of these three methods with the Roche assay a better R<sup>2</sup> was obtained with a polynomial regression as there was a deviation from linearity at high concentrations. The RM and its dilutions are commutable for combinations of the Siemens, Gentian and Sentinel assays. Dilutions with a mass fraction equal to or below 0.6 are commutable for combinations of these three assays and the Roche tina quant assay.

**Conclusions:** For some combinations of the studied methods only dilutions of ERM-DA471/IFCC are commutable whereas for the other combinations also the undiluted reference material is commutable.

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#### Introduction

Within the framework of the EU funded BIOREMA (Reference Materials for BIOfuel specifications, FP7 contract grant 219081) project, reference materials for bio-ethanol and biodiesel have been examined. The aim of this project was to demonstrate the feasibility of preparing and characterizing reference materials for biofuels. The focus was on providing SI-traceable reference values for the materials studied. Furthermore, the project has established the current level of measurement capability in the end user community by means of a worldwide interlaboratory comparison using these test materials.

#### Background

With the introduction of the European Directives on renewable energies (RED 2009/28/EC) and on fuel quality (FQD 2009/30/EC), and with the increasing addition of biological products to gasoline and diesel (e.g. bio-ethanol and FAME) the quality of these products becomes more important. There is, however, up to now no international consensus on the technical specifications of biofuels. Neither is it clear what measurement standards, reference materials and measurement techniques are needed to support the legislative infrastructure.

#### Needs

Reference materials for biofuels with well-characterized property values are essential for the development and validation of measurement methods. Also, these materials are an important tool in the quality assurance of routine measurements, and in obtaining reliable, traceable measurement results.

#### Objectives

The main objective of the project was to establish whether the preparation of biodiesel and bio-ethanol reference materials with traceable reference values was feasible. To that end, test materials were prepared and tested for homogeneity and stability, followed by a value assignment procedure using high-level measurement methods. Additionally, the long-term stability of the reference values has been assessed.

Another important objective of the study was to establish the level of measurement capability of field laboratories. Information on the quality (repeatability, reproducibility, bias of measurement) has been obtained from interlaboratory comparisons that were organized using the characterized test materials.

#### Project members

- VSL (the Netherlands), project coordinator
- IRMM (European Commission)
- NPL (United Kingdom)
- INMETRO (Brazil)
- NIST (USA)
- LGC (United Kingdom)

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Isotope Dilution Mass Spectrometry (IDMS) currently stands out as the analytical technique for trace analysis providing results with the highest metrological quality in comparison to more traditional measurement methods such as external calibration or standard additions. IDMS requires the addition to the sample of an isotopically labelled form of the element or compound to be determined and the measurement of the "ratio" of labelled to unlabelled analyte by Mass Spectrometry. Based on this principle, IDMS results are not affected by analyte losses, low recoveries or matrix effects and therefore, IDMS has been considered as a primary method directly traceable to the International System of Units for the quantity "amount of substance" or mol. The theory and practice of stable isotope dilution mass spectrometry in both organic and elemental analysis has evolved during the last 50 years following a somewhat diverging trajectory. In organic IDMS a calibration graph is normally required using the labelled analyte as internal standard. This calibration graph is linear when there is no mass overlap between the labelled and unlabelled analyte and its slope is normally determined experimentally as it depends on the isotopic composition of both the analyte and its labelled analogue as well as on possible isotopic effects during sample preparation.

In the last few years we have developed a general procedure of IDMS which can be applied both to elemental and molecular Mass Spectrometry. The procedure is based on the measurement of the isotope abundance profile of the element or compound by Mass Spectrometry and the deconvolution of this profile into its constituting components by multiple least squares. This integrated approach can be applied easily to any type of mass spectrometric measurement involving one or several enriched stable isotopes such as total elemental analysis, organic analysis, trace element speciation with single and multiple spikes and trace element metabolism. So, new concepts in organic IDMS such as minimal labelling (the use of a single  $^{13}\text{C}$  for labelling) or heteroatom labelling (the use of  $^{81}\text{Br}$ ,  $^{34}\text{S}$ ,  $^{37}\text{Cl}$ ,  $^{105}\text{Sn}$ ,  $^{201}\text{Hg}$ ) can be explored. This alternative procedures will provide methodologies in which no isotopic effects should be expected and no calibration curves will need to be prepared. In this presentation we will concentrate on the synthesis, characterisation and validation of analytical methodologies using  $^{81}\text{Br}$ -labelled polybrominated diphenyl ethers and  $^{13}\text{C}$ -labelled clenbuterol for organic IDMS without resorting to methodological calibration graphs. The methods are fast, accurate, easy to accreditate and can be applied in routine analysis with lower cost in comparison to classical procedures.

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Millions of people in Bangladesh and India are threatened by an arsenic contamination caused by rice and drinking water. Because of the multitude of arsenic species and their differences in toxicity and mobility the species analysis of arsenic compounds is of special interest. In case of inorganic arsenic species a high toxicological potential is known to give rise to adverse health effects. Methylated arsenic species like monomethylarsonic acid and dimethylarsinic acid possess lower toxic effects but they are carcinogenic. Arsenobetaine and arsenocholine are the major arsenicals in seafood and seemed to be nontoxic but actual more and more hints appear that they are transformed or metabolized to more toxicological relevant species in vivo. Heavy metals like mercury or arsenic and their transformation products or metabolites can be bioaccumulated in the aquatic food chain.

For risk assessment it is essential to understand their pathways and long-term effects in vivo. To master the challenges in modern speciation analysis proper tools for a valid quantification are obligatory. Thus the development of a certified isotope labelled calibration standard for monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and arsenobetaine is necessary. Arsenic being monoisotopic is not applicable for isotopic dilution mass spectrometry (IDMS) with ICP-MS. Using LC-ESI-MS deuterated or  $^{13}\text{C}$ -labelled species can be used as internal standards. Hydrogen labels like  $^2\text{H}$  or  $^3\text{H}$  are notorious for isotope effects and for leaving the tracer. Therefore stable isotope tracers of choice are the  $^{13}\text{C}$  labelled species.

The synthesis for the unlabelled species is described by Quick et al. (MMA), Jagadish et al. (DMA) and F. Lagarde (arsenobetaine). The products are purified by ionic exchange chromatography and were quantitatively converted into a consistent form (e.g. the protonated form or the corresponding sodium salt). Purity determination was performed by using LS-ESI-MS/MS, qNMR, DSC and coulometric Karl-Fischer. These standards are a powerful tool to assist the determination, quantification and monitoring of arsenic species in several fish materials like mackerel, tuna fish or herring.

During stability tests possible degradation products can be identified by tracking the isotopic label in the corresponding metabolites. In addition the standards will help to establish an HPLC-ESI-MS method as an economic alternative for the species analysis of arsenic compounds. Finally ESI-MS/MS species can be quantified in a reliable way by using a defined multiple reaction monitoring (MRM), a standard technique for quantitative LC/MS/MS.

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## WARP: a successful approach for aquatic reference materials

P22

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In support of e.g. the EC Water Framework, the Groundwater Directives a substantial number of organic analytes have to be determined for which there are no suitable reference materials. This is to a large extent due to the fact that many of these analytes are not sufficiently stable in solution. For e.g. pesticides in water, BCR-606 could only be certified for 5 (stable) polar pesticides (in freeze-dried tap water).

In the field of reference materials for microbiological analyses the reconstitution of water samples by dissolving 'pills' is a common approach for many years. The WARP feasibility study aimed to test whether this approach would work for a series of pesticides that are routinely analysed in drinking water and for surface water monitoring.

The new approach involves the stabilisation of 24 selected pesticides (including acidic, amines, triazines, phenyl ureas and organophosphates) substantially varying in stability, were contained in a dry matrix and shaped into a 'pill'. After precise quantification of the mass of the "pill" and after dissolution in a precisely quantified mass of demineralised water, this solution can be used as reference material (RM) or quality control material (QCM).

Several test batches were prepared and preliminary tests were conducted to check on the production method (pill mass, concentration of analytes) and interferences due to changes in humic matter content, ionic strength, air humidity and pH. Homogeneity and stability tests were performed, showing that the pesticides in the 'pill' matrix remained stable for a prolonged time, and that the reconstituted water was stable at least during a working day.

European laboratories, specialised in routine analysis of pesticides in water were subcontracted to participate in an interlaboratory comparison study. Sets of pills were distributed together with a protocol for the reconstitution process. In order to study the feasibility to vary the reconstituted volume (thus concentration range), laboratories were requested to prepare a reconstituted water mass of 1,000 mg and of 100 mg.

The feasibility study and interlaboratory comparison were highly successful and demonstrated that it was possible to produce in sufficient quantity a 'reference material for pesticides in water'. The laboratories, that never used the method of reconstitution before, were able to produce analytical results to such an agreement that certification of the material would have been feasible for nearly all pesticides.

QualityConsult now aims to test the approach in parallel to their regular PT schemes. QCMs will be prepared and submitted to their clients. An additional strong argument for the WARP approach is the relative easy of shipment.

The results for of the WARP 'pesticides in water' open new ways for other – new – RMS and QCMs. This could be other organic analytes in surface/drinking water, as well as for other analytes in an aquatic matrix (clinical analyses, doping and drugs analyses, ...).

## "Just released" certified reference materials in support of the Water Framework Directive

P23

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Water is our most precious resource. The European legislative framework for its effective protection is established by the Water Framework Directive (WFD, 2000/60/EC) [1] which addresses inland surface waters, transitional waters, coastal waters and groundwater. Its primary objective is to prevent deterioration and to ensure achievement and maintenance of all waters good ecological and chemical status by 2015.

One of the steps of the WFD implementation consists in the mandatory monitoring of the Priority Substances listed in Annex X of the Directive [2] which are now regulated to respect environmental quality standards (EQSs) [3]. Four metals are present in the Priority Substances list: nickel, lead, cadmium and mercury. Besides the WFD, the Groundwater "daughter" Directive adopted in 2006 (2006/118/EC) [4] establishes a regime for the assessment of the good groundwater chemical status ensured by pollutants' concentrations not exceeding quality standards in other relevant legislation [3].

The compliance of the water with good chemical status criteria is based on a measured or predicted concentration of nitrates not exceeding 50 mg/L and on threshold values established by Member States for, among others, arsenic, cadmium, lead, mercury, ammonium, chloride, sulfate and conductivity. Three new water-base certified reference materials, ERM-CA408, ERM-CA615 and ERM-CA616 were recently released by JRC-IRMM, in response to the needs of the laboratories involved in the mandatory monitoring of water bodies as prescribed by the legislation. ERM-CA408 is a simulated rainwater certified for the mass concentration of ammonium, chloride, fluoride, magnesium, nitrate, ortho-phosphate and sulfate at the very low mg/L range.

ERM-CA616 is a natural groundwater fortified with ammonium dihydrogenphosphate and certified for the mass concentration of calcium, chloride, magnesium, ortho-phosphate, potassium and sodium at the mg/L range. pH and conductivity values are as well certified in both materials.

ERM-CA615 is a natural groundwater acidified with nitric acid to pH~2 and spiked with with Hg(NO<sub>3</sub>)<sub>2</sub>, Cd(NO<sub>3</sub>)<sub>2</sub> and Pb(NO<sub>3</sub>)<sub>2</sub> and certified for As, Cd, Fe, Hg, Mn, Ni and Pb. The mass concentrations of the four "Priority" metals (Cd, Hg, Ni and Pb) in ERM-CA615 were targeted to comply with the EQSs, very low concentration levels especially for Cd and Hg. The success of the certification exercise for all "priority" metals makes ERM-CA615 a perfect Quality Control tool tailored to meet the WFD requirements.

All values of the certified parameters in these materials are traceable to the SI.

The uncertainties for most of the major components range from 2% to 5% (ERM-CA408 and ERM-CA616), while for the trace elements span from 4% to 11% (ERM-CA615).

[1] European Commission, Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ Eur. Comm. L 327, 22.12.2000.

[2] European Commission, Decision No 2455/2001/EC of the European Parliament and of the Council of 20 November 2001 establishing the list of priority substances in the field of water policy and amending the Directive 2000/60/EC, OJ Eur. Comm. L31, 15.12.2001.

[3] European Commission, Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, OJ Eur. Union L 348/84, 24.12.2008.

[4] European Commission, Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration, OJ Eur. Union L 372/19, 27.12.2006.

## Determination of Tributyltin (TBT) at sub-ppt level in whole water samples

P24

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Tributyltin (TBT) as a compound in antifouling agents is used to protect ship hulls. This causes an increase of its concentration in sediments and surface water, especially in harbours. The toxic tributyltin species decreases the number of males in fish populations due to their estrogenic activity to organisms. Organotin compounds were taken into consideration in new federal law concerning the protection of soil and sewage sludge. In European directive related to the water contamination, the acceptable tributyltin concentration is very low and about 0.2 ng/L. So the determination of trace impurities concerning TBT in water requires a very sensitive technique like GC-ICP-MS, but basically common analytical methods do not permit the measurement of this organotin species in environmental matrices.

A preliminary step was developed for the separation of TBT from the samples mentioned above. In addition the ultra-trace amount of TBT was concentrated so that the limit of detection for common measurement techniques can be efficiently lowered. Tributyltin preconcentration procedures, like solid phase extraction (SPE) using various column packings like octyl or octadecyl reversed phase materials were established. Optimized adsorption and elution profiles for suitable recovery rates were developed and validated as well as a further concentration step using solid phase microextraction (SPME). For the accurate quantification of the preconcentrated TBT samples suitable derivatization procedures were investigated using different types of alkylation reagents.

The detection of these alkylated TBT species were carried out by using a GC-AED. Standard addition procedures using triple-distilled water and tributyltin standards are elucidated as well as real samples of contaminated water.

Finally reference materials and certified calibration standards are essential for the determination of such small amounts of TBT in water.

**Literature:** S. Mothes, R. Wennrich. *Mikrochim. Acta* 135 (2000), 91-95.  
N. Cardellicchio, S. Giandomenico, A. Decataldo, A. Di Leo, Fresenius J. Anal. Chem. 369 (2001), 510-515.  
D.S. Forsyth, C. Cleroux, *Talanta* 38 (1991), 951-957.

## IAEA MEL certified reference materials for trace elements and organic pollutants in marine samples

P25

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The IAEA Marine Environment Laboratories in Monaco (MEL) have the programmatic responsibility to provide assistance to the Member States laboratories in maintaining and improving the reliability of analytical measurement results, both in trace element and organic contaminants determinations. IAEA MEL produces and distributes certified reference materials that can be used to ensure the quality of test results in connection with numerous environmental quality standards.

The guidelines in the production of the MEL matrix reference materials are ISO Guide 35 "General and Statistical Principles for Certification" and the ISO Guide 34 "Quality system requirements for reference material producers".

Matrix reference materials produced at MEL have found widespread use in many laboratories for quality control, validation of analytical methods, assessment of measurement bias and precision, repeatability and reproducibility studies.

An overview of prepared Reference Materials (RM) / Certified Reference Materials (CRMs) for trace elements and organic pollutants in marine matrices will be presented. A new CRM for trace elements in Scallop (*Pecten Maximus*) - IAEA-452 will be discussed in more details.

One of the outcomes from the IAEA Coordinated Research Project on sea food safety was the identification of the need of producing seafood matrix CRM with elevated level of toxic elements. A preliminary intercomparison exercises using the same sample was organised with 122 worldwide laboratories. Based on the laboratory performance from this and several previous studies 15 expert laboratories were identified and invited to participate in the certification process. The reference values for methyl mercury and twelve trace elements and their associated uncertainty were established on the basis of the data from expert laboratories. Nine different analytical methods including two primary methods of measurements were employed in the certification of Scallop (*Pecten Maximus*) sample. The information values for 8 additional trace elements are also given.

MEL reference materials can be obtained from the IAEA webpage (<http://www.iaea.org/programmes/aqcs/>).



## New reference material for analysis of inorganic in agricultural soil of Thailand

P26

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Reference materials play an important role for evaluating the accuracy of analytical results, and are essential parts for quality assurance in the testing laboratory. The National Institute of Metrology (Thailand) (NIMT), in partnership with the Environmental Research Training Center (ERTC), serves to respond to the urgent needs for affordable environmental reference materials. This poster describes the preparation of an agricultural soil reference material, along with homogeneity and stability studies and the analytical work carried out for the certification of inorganic contents. The candidate soil material was collected from an agricultural area in Chaophraya River plain in the central part of Thailand. Material preparation along with homogeneity and stability testing were carried out at ERTC. Characterization of a candidate reference material was conducted by NIMT and subsequently confirmed via an inter-laboratory comparison for certification of reference material. A certain numbers of well recognized testing laboratories in Thailand participated in the comparison with satisfactory results. Further elaborative results will be discussed.

## PM<sub>10</sub> matrix certified reference materials (CRMs)

P27

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Air pollution has an increasing impact on the environment and human health. Therefore, the reduction of the air pollutants has become one of the most important issues in Europe. Ambient air quality assessment is focused on gaseous pollutants (SO<sub>2</sub>, NO<sub>2</sub>, NO<sub>x</sub>, CO, O<sub>3</sub>, benzene), PM<sub>10</sub> (particulate matter of 10 µm and less aerodynamic diameter) as well as on selected polycyclic aromatic hydrocarbons (PAHs) and elements (Cd, Pb, Ni, As) in PM<sub>10</sub>. Requirements are set in Directive 2008/50/EC and Directive 2004/107/EC. The quality of the performed measurements in the frame of the air quality monitoring have to be controlled using appropriate Certified Reference Materials (CRMs). However, at present there are no suitable CRMs which meet the requirements related to the type of matrix including particle size and the type and content of certified analytes.

The IRMM developed two candidate reference materials, which are intended to be branched after certification as European Reference Materials (ERMs), one for organic analysis and one for inorganic analysis. The starting materials came from a tunnel road in Warsaw, Poland and were collected mainly from the tunnel walls and partially from the tunnel sidewalks inaccessible to people. The collected material was processed to get a very fine dust as close as possible to the PM<sub>10</sub> matrix. Then it was tested for the homogeneity and stability for all analytes.

The results of the certification of two reference materials for selected PAHs and elements in PM<sub>10</sub> will be presented.

The reference materials will be available from the Institute for Reference Materials and Measurements (IRMM) in the near future.



## Purity certification of 2,2',4,4'-Tetrabromodiphenyl ether (PBDE-47) solid according to ISO Guide 34

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Polybrominated diphenyl ethers (PBDE's) are a major group of flame retardants, which were added to plastic/polymeric materials such as electrical equipment (e.g. casings, wiring, circuit boards), textiles etc. Increasing concerns over neurotoxicity and endocrine disruption have led to the inclusion of PBDEs in the Restriction of Hazardous Substances (RoHS) Directive (2002/95/EC) and the Waste Electronic and Electrical Equipment (WEEE) Directive (2002/96/EC). The RoHS Directive came into force in 2006.

There have also been considerable environmental concerns over these compounds which have led to the inclusion of octa- and penta-bromodiphenyl ethers in the 'dirty dozen' list of May 2009. The list is compiled by the United Nations under the Stockholm Convention on Persistent Organic Pollutants.

There are potentially 209 possible PBDE congeners, using accepted convention 2,2',4,4'-Tetrabromodiphenyl ether is known as PBDE-47. PBDE-47 is a major component of the penta technical mixture and is one of the congeners used for monitoring environmental contamination.

A detailed approach of the purity assessment will be described. Purity evaluations using HPLC-DAD, GC-FID, differential scanning calorimetry (DSC), and HPLC-ICP-MS will be described together with moisture and inorganic residue assessments. Fractions collected from a LC semi-prep system were used to investigate possible impurities formed on column. Compiled data provided a certified purity value according to the principles of ISO Guide 34. LGC is accredited to ISO Guide 34:2000 for reference material production by the United Kingdom Accreditation Service (UKAS). The approach provides traceability to the le Système international d'unité (SI) system and can be adapted for the certification of other PBDEs in the future.

## On-line isotope dilution analysis as a fast and accurate routine method for the multielemental determination of trace elements in waters and biological fluids

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During the last years, Inductively Coupled Plasma Mass Spectrometry (ICP-MS) has been increasingly used in combination with Isotope Dilution Analysis (IDA) for accurate trace and ultra-trace determinations. Isotope dilution analysis is a well-known analytical technique based on the measurement of isotope ratios in samples where their isotopic composition has been altered by the addition of a known amount of an isotopically enriched element. However, the use of IDA in combination with ICP-MS as a routine technique in testing laboratories is often judged as a costly and complicated analytical method. This "complicated" procedure can be simplified by applying on-line IDA where a mixture of enriched isotopes is mixed on-line with the sample prior to the ICP-MS nebuliser. This allows also easy automation of the procedure as samples and QC standards are supplied by an autosampler. In this presentation we describe the development and validation of an ICP-MS method for the simultaneous determination of trace elements in natural waters, seawaters and biological fluids by on-line IDA which could be immediately applied in routine testing laboratories.

In order to simplify the sample preparation the samples were spiked "on-line" with the help of the autosampler and a peristaltic pump. Sample or natural standard and spike solutions were pumped to the nebuliser and both streams were combined before the nebuliser. The concentration of the samples can be calculated directly using the on-line Isotope Dilution Analysis equation shown on the right.

In this equation  $C_s$  is the unknown concentration of the analyte in the sample (s) and  $C_{st}$  the concentration of the analyte in the natural standard (st);  $R_m$  and  $R_{st}$  are the measured isotope ratios of the mixture of the spike with the sample and the standard, respectively, and  $R_{sp}$  and  $R_s$  are the same ratios in the sample and the spike, respectively.  $R_n$  is the reverse ratio in the natural standard. The concentrations of monoisotopic elements such as Al, Mn or As were obtained using a "Pseudo Isotope Dilution" approach. The internal standards (Sc or Ga) were used as "Tracer Isotopes" and the concentrations were calculated using the same equation. For the determination of iron the correction for CaOH interferences was based on the measurement of the SrOH/Sr ratio which is related to the actual CaOH/Ca ratio. The method has been validated by the analysis of a series of reference materials of different nature and the routine procedure has been already implemented as an accredited procedure in a number of private environmental laboratories in Spain using the mixed spike solution supplied by ISC-science (photograph).

$$C_s = C_{st} \frac{R_m R_{st} - 1}{R_m R_{sp} - 1} \frac{R_{sp} - R_n}{R_{st} - R_n}$$



## Applicability of the $k_0$ -INAA for determination of elemental content in different matrix reference materials

P30

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Neutron activation analysis (NAA) has a special position among activation techniques owing to its widespread use. The use of neutrons in NAA enables determination of a relatively large number of elements (about 70% of elements of the Periodic table of elements) in macroscopic samples (to 10-12 g of element per gram of sample). The  $k_0$ -standardization method of NAA ( $k_0$ -NAA) has been launched in the mid 1970s as suitable tool for multi-element analysis. This method is a "quasi" absolute technique in which the nuclear data which are unknown are replaced by a compound nuclear constant characterising the nuclides ( $k_0$ ,  $Q_0$ ), which can be experimentally determined for all nuclides with small uncertainties. The  $k_0$ -library today contains nuclear data for 144 radionuclides, which enables the determination of 68 elements in an unknown sample. The Department of Environmental Sciences of the Jožef Stefan Institute in Ljubljana introduced the  $k_0$ -based method of NAA at the end of 1980s. Since then the  $k_0$ -method has been optimized for the determination of elemental composition in environmental samples using the 250 kW TRIGA Mark II reactor for irradiation with a neutrons and measurement of induced gamma activities using absolutely calibrated HPGe detectors. The method has been successfully used in numerous intercomparison studies and characterisation of reference materials (BCR and ERM organized by IRMM, BAM, IAEA, NIST, INCT, WEPAL, FAPAS, NESCA, APAT, etc.) for determination of macro, micro and trace elements in samples of different origin (biological, environmental, industrial, etc.). In this work, attention is focused on advantages and disadvantages of  $k_0$ -INAA when method is used for characterization of new candidate reference material. The main advantages of the method like large concentration scale of investigated elements, simultaneous determination of numerous elements, traceability and relatively small uncertainty as well as some disadvantages like high limit of detection (LOD) in the presence of interfering constituents (e.g. Na, Br, Fe, Sc, etc.) and losses due to volatilization during irradiation (e.g. Hg in biological samples) will be presented and discussed. Regardless of some minor problems, it can be concluded that  $k_0$ -INAA is an invaluable analytical technique in the certification process of new reference materials.

## Dissemination of metrological traceability for pH measurement in Thailand

P31

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The measurement of pH is one of the most common chemical measurements employed in environmental area and in production process. Many National Metrology Institutes disseminate the accurate pH measurement results in order to achieve the metrological quality for a global recognition. Therefore, the traceability on pH measurement is needed. National Institute of Metrology (Thailand), NIMT, is authoritatively responsible in providing the traceability of pH measurement. The process of dissemination the metrological traceability is through buffer solution production and value assignment for proficiency testing sample. The buffer solution production at NIMT chemical laboratory yields 4 pH values of secondary standard buffer solution, i.e. 4.01 pH, 6.86 pH, 7.01 pH and 9.18pH with uncertainty equal to 0.02 pH. Moreover, proficiency testing sample is a mean that can also provide the traceability for service laboratory. NIMT has given the assigned value service for proficiency testing sample. By closely collaborating with other government organization, Department of Science Service, a proficiency testing program for pH measurement of the water has been provided. At least 200 laboratories have participated in this proficiency testing program each year. The pH measurement capability of NIMT chemical laboratory was accredited ISO/IEC 17025 and CMC listed in the KCDB Appendix C in 2009. To complete the dissemination process NIMT also provides secondary standard buffer solutions to a manufacturer in chemical industrial sector. The manufacturer then uses the secondary standard buffers to calibrate its own pH meter for production of the working standard buffer solution which are metrologically traceable to NIMT and eventually to the IUPAC. The impact assessment and the cost-benefit-ratio are under the process of evaluation.



## Practical use of measurement capabilities – reference materials

P32

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LGC is the designated National Measurement Institute (NMI) for Chemical and Bioanalytical measurements in the UK. In this role, it develops valid procedures with the metrological rigour expected of an NMI for the determination of key analytes and takes part in high level international intercomparison studies organised by the CCQM. One of our most important roles is the dissemination of the traceability gained from these studies to practising analytical scientists in the UK and this is carried out in many ways, including peer reviewed publications, training courses, provision of reference values to PT schemes and characterisation of reference materials.

Reference materials can help analysts calibrate their instruments, validate their methods and ensure quality control of their procedures, thus enabling organisations to comply with technical regulations and provide users with confidence in the results of chemical measurements. LGC is accredited to ISO Guide 34: 2000 for the production of reference materials by the United Kingdom Accreditation Service (UKAS), and is a founder member of the ERM® cooperation, which provides an additional level of peer review for all materials released under the ERM brand.

This poster will show the coordinated approach of LGC in developing higher order measurement capabilities, comparison with peers demonstrated through CCQM studies and measurements used to characterise CRMs which are compliant with ISO Guide 34. Examples will be given in the areas of purity assessment, clinical chemistry and selenium speciation.

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## The implementation of the programme of pre-accession assistance "Improving chemical and ionising radiation metrology in Turkey"

P33

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The IPA-Project TR08209 "Improving Chemical and Ionising Radiation Metrology" part of the National Programme for Turkey under the IPA-Transition Assistance and Institution Building Component for 2008 is based on the Administrative Arrangement IPA/2009/214672 – JRC - 31331 between DG Enlargement and the Joint Research Centre, signed on the 24th July, 2009. The project acronym is EMIT meaning "Europe and Metrology in Turkey". The contracting authority for the project acting on behalf of DG ELARG is the Delegation of the European Commission to Turkey. [1]

The overall objective of the project is to contribute to the better functioning of the EU-Turkey Customs Union Agreement regarding the free movement of goods as well as to facilitate the implementation of the acquis communautaire in quality of life related areas such as environmental, health and consumer protection and food safety. To achieve this goal the project consists of an inception phase, 5 implementation phases and a final phase spanning 01.10.2009 to 30.09.2012 and totalling over 200 days of short-term training activities. The main components of the project are as follows:

**Component 1:** Institutional Capacity Building for TÜBITAK ÜME: Providing advice on the requirements for production and certification of reference materials; advising on the implementation of the ISO Guide 34 management system, providing advice on the preparation of chemistry laboratories for CRM production and providing consulting on the equipment needed for CRM production.

**Component 2:** Institutional Capacity Building for TAEK: Providing advice on the requirements for secondary standardisation at TAEK institutes; advising on what's needed for the extension of the quality management systems at TAEK institutes to secondary level standardisation activities and advising on the plans for the development of primary standardisation.

**Component 3:** Knowledge transfer and human resources development: Familiarizing TÜBITAK ÜME and TAEK researchers with metrology systems in EU member states with similar economic needs; training for TÜBITAK ÜME and TAEK researchers in matters of CRM, primary methods of measurement, secondary standardisation and applicable quality systems; organization of seminars and workshops for end users; co-operation with Turkish universities providing education in chemical and ionising radiation metrology; consulting to Turkish universities interested in joining the Euro-master Joint Degree Programme in Metrology.

**Component 4:** Networking and Raising Awareness: Promotion of TÜBITAK ÜME and TAEK among scientific and metrological community at European level; enhancement of relationships with direct and indirect users of CRM and metrology services; enhancement of relationships with universities providing a master level education in measurement science; organization of national conferences and events; support of TÜBITAK ÜME and TAEK experts participation in international events. A full list of events, which will be open to all stakeholders (i.e. the main beneficiaries; accredited laboratories, universities, other institutes and industry), as well as a poster [2] showing all EMIT events, will be presented at the conference. The details of the project's progress at the end of June, 2010 can be found in the First Interim Report [3] and via <http://ifrm.jrc.ec.europa.eu/activities/Turkey/>.

[1] McCourt J., Bickel M. Programme of pre-accession "Improving Chemical and Ionising Radiation Metrology" in Turkey. Inception Phase report, JRC 57848-2010. European Union, 2010.

[2] Gegevcicius V., McCourt J., EMIT Events Poster, 2010.

[3] McCourt J., Programme of pre-accession "Improving Chemical and Ionising Radiation Metrology" in Turkey. First Interim Report, JRC 61020, EUR 24549, ISBN 978-92-79-17080-5, European Union, 2010.

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## International Reference Material databases

Several databases exist that compile information from a multitude of reference material producers:

**COMAR:** <http://www.comar.bam.de>

Most comprehensive database worldwide containing approximately 10 000 CRMs. Quality is controlled via the COMAR Secretariat.

**ERM:** <http://www.erm-crm.org/Pages/ermcrmCatalogue.aspx>

Joint reference material database of the ERM consortium, containing also ERM Application Notes.

**AOAC:** <http://www.aoac.org/divisions/ldrm.html>

Database of the AOAC Technical Division for Reference Materials. Registration required to searching for RMs.

**VIRM:** <http://www.virm.net/>

Database of the Virtual Institute for Reference Materials. Registration required to searching for RMs.

**GeoReM:** <http://georem.mpch-mainz.gwdg.de/>

Database of reference materials and isotopic standards of geochemical and mineralogical interest. It contains about 2200 different materials. More info on <http://onlinelibrary.wiley.com/doi/10.1111/j.1751-908X.2005.tb00904.x/pdf>

## Matrix reference materials from Metrology Institutes and designated institutes of the CIPM Mutual Recognition Arrangement

National Metrology Institutes and their designated institutes which have signed the CIPM Mutual Recognition Arrangement (CIPM-MRA) aim at providing measurement tools at highest standard for disseminating metrological traceability.

**JRC Institute for Reference Materials and Measurements (JRC-IRMM), EU**

<http://irmm.jrc.ec.europa.eu/Pages/rmcatalogue.aspx>

**International Atomic Energy Agency (IAEA), UN**

<http://nucleus.iaea.org/rpst/ReferenceProducts/ReferenceMaterials/index.htm>

**Instituto Nacional de Metrologia, Normalização e Qualidade Industrial (INMETRO), BR**

[http://www.inmetro.gov.br/metricentificam/mat\\_ref\\_cert.asp](http://www.inmetro.gov.br/metricentificam/mat_ref_cert.asp)

**National Research Council of Canada (NRCC), CA**

<http://www.nrc-cnrc.gc.ca/eng/programs/imb/crpm.html> (marine toxins) <http://www.nrc-cnrc.gc.ca/eng/services/inms/reference-materials.html> (trace elements)

**National Institute of Metrology (NIM), CN**

<http://www.nim.org.cn/English/Home/Index.aspx>

**Bundesanstalt für Materialforschung und –Prüfung (BAM), DE**

<http://www.bam.de/en/fachthemen/referenzmaterialien/index.htm>

**National Metrology Institute of Japan (NMIJ), JP**

<http://www.nmi.jip/english/service/C/>

**Centro Nacional de Metrología (CENAM), MX**

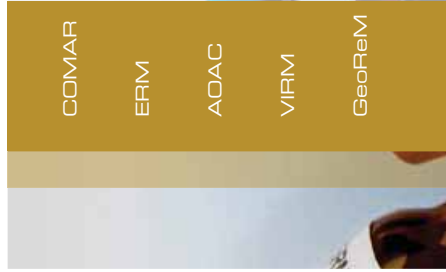
<http://www.cenam.mx/materials/busquedamrc.aspx>

**LGC Standards, UK**

<http://www.lgcstandards.com/NewAdvancedSearch.aspx>

**National Institute of Standards and Technology (NIST), US**

<http://ts.nist.gov/measurementservices/referencematerials/index.cfm>



## Guides for the selection and use of reference materials

**ILAC G9: Guidelines for the Selection and Use of Reference Materials**

[http://www.ilac.org/documents/ILAC\\_G9\\_2005\\_guidelines\\_for\\_the\\_selection\\_and\\_use\\_of\\_reference\\_material.pdf](http://www.ilac.org/documents/ILAC_G9_2005_guidelines_for_the_selection_and_use_of_reference_material.pdf)

Author: ILAC

**EA-4/14: Selection and Use of Reference Materials (2003)**

Author: Eurachem, European Accreditation (EAA)

<http://www.european-accreditation.org/n1/doc/EA-4-14.pdf>

**ISO Guide 33 (2000): Uses of Certified Reference Materials**

[http://www.iso.org/iso/iso\\_catalogue/catalogue\\_tc/catalogue\\_detail.htm?csnumber=33189](http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=33189)

Note: A complete and profound revision of this guide is currently ongoing.

Author: International Organization for Standardization (ISO)

**ERM Application Notes**

[http://www.irmm.jrc.be/reference\\_materials\\_catalogue/user\\_support/Pages/index.aspx](http://www.irmm.jrc.be/reference_materials_catalogue/user_support/Pages/index.aspx)

[http://www.erm-crm.org/ERM\\_products/application\\_notes/Pages/index.aspx](http://www.erm-crm.org/ERM_products/application_notes/Pages/index.aspx)

Note: Most application notes are available in all EU languages plus Chinese and Japanese

Author: various authors from the ERM consortium

**The APLMF Guide to The selection and use of Certified Reference Materials for legal metrological control in food safety & agricultural products**

<http://www.aplmf.org/UploadFiles/Guide/APLMF%20Guide%203.pdf>

Author: Asia-Pacific Legal Metrology Forum (APMLF)

**Guidance document on the use of Reference Materials in genetic testing**

[http://www.irmm.jrc.be/reference\\_materials\\_catalogue/user\\_support/Documents/eur3256en.pdf](http://www.irmm.jrc.be/reference_materials_catalogue/user_support/Documents/eur3256en.pdf)

Author: D. Gancberg, P. Corbisier, H. Schimmel, H. Emons, JRC-IRMM

**APLAC TC 012: Guidelines for acceptability of chemical Reference Materials and commercial chemicals for calibration of equipment used in chemical testing**

[http://www.aplac.org/documents/tc/aplac\\_tc\\_012\\_issue\\_2.pdf](http://www.aplac.org/documents/tc/aplac_tc_012_issue_2.pdf)

Author: Asia Pacific Laboratory Accreditation Cooperation (APLAC)

**The Use of Reference Materials: A Tutorial (2001)**

Geostandards and Geoanalytical Research, Volume 25, pp. 7-22,

<http://onlinelibrary.wiley.com/doi/10.1111/j.1751-908X.2001.tb00784.x/pdf>

Author: J. S. Kane

**ISO 11095 (1996): Linear calibration using Reference Materials**

[http://www.iso.org/iso/iso\\_catalogue/catalogue\\_tc/catalogue\\_detail.htm?csnumber=10660](http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=10660)

Author: International Organization for Standardization (ISO)



## IRMMI's new Reference Material Production Building

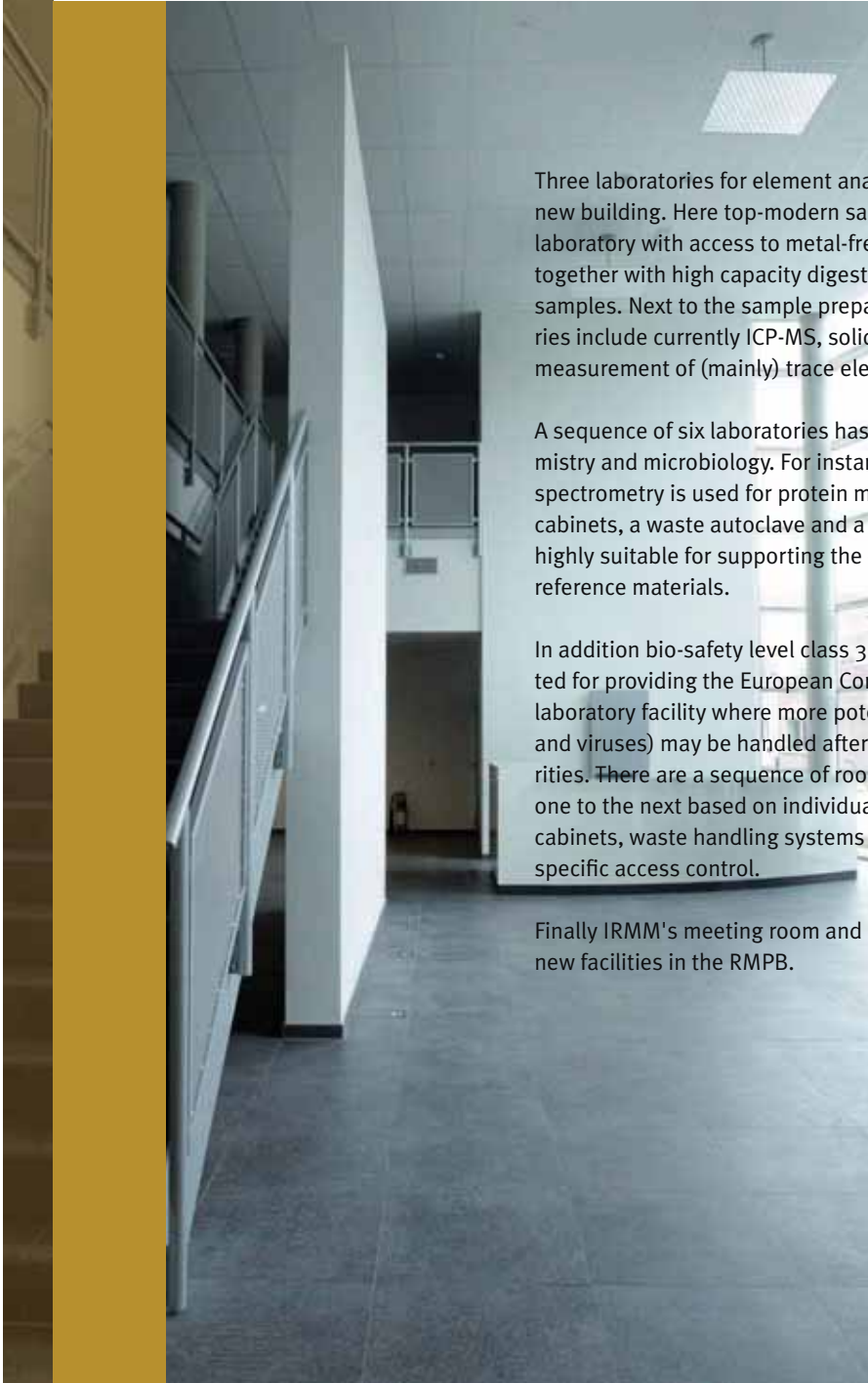


The increasing demands for new reference materials (RMs) in a broadening range of application areas result in requests to produce also a broader variety of analyte/matrix combinations with higher risks of cross-contamination during their preparation as well as to handle a wider variety of less stable materials, especially those of biological origin. Consequently, much higher technological flexibility within the RM production facilities are necessary than that existing until now. Therefore, the JRC concluded several years ago that new, flexible facilities are needed for its reference material programmes which are able to be adapted as a function of the changing requirements of research and RM production. The processing area should be such that at least four different materials can be treated at a time without any risk of cross-contamination for offering sufficient possibilities to run RM projects in parallel. Moreover, dedicated laboratories and rooms had to be foreseen for satisfying increasing needs to develop and produce various biological reference materials, including for instance various pathogens.

After intensive periods of brainstorming and planning, the construction work began in August 2008 and about two years later the building is completed now.

The end result is a truly multifunctional building with several new types of laboratories and a unique pilot plant for material processing. The RMPB is tailor-made for conducting top-level research and reference material development, enabling in particular metrology in chemistry, bio- and life sciences, through the provision of cutting-edge certified reference materials.

The pilot plant for material processing (i.e. the refinement of raw materials into candidate reference materials in their final containment) comprises of several unique features like the possibility for parallel material handling thanks to movable walls and separate air-handling systems for the main processing hall which thereby can be split into four separate areas. A new freeze dryer and equipment for manipulating and stabilising slurries and pastes for the provision of solid but wet reference materials are among the major instrumental facilities. Moreover, a number of dedicated rooms adjacent to the processing hall allow a logical sequence of activities and equipment to support the main processing areas like washing and handling of glassware, capping and labelling of vials and a process control laboratory incorporating microscopy, particle size analysis and measurements of water content. Moreover, a completely new laboratory for the processing of water reference materials has been included in the RMPB.



Three laboratories for element analysis also make up a part of the new building. Here top-modern sample preparation is housed in one laboratory with access to metal-free clean benches and fume hoods together with high capacity digestion systems for mineralisation of samples. Next to the sample preparation two instrumental laboratories include currently ICP-MS, solid sampling AAS and ICP-OES for the measurement of (mainly) trace elements.

A sequence of six laboratories has been designed to host protein chemistry and microbiology. For instance, high resolution organic mass spectrometry is used for protein measurements. Access to bio-safety cabinets, a waste autoclave and a cool-cell make these labs also highly suitable for supporting the developments in the field of clinical reference materials.

In addition bio-safety level class 3 laboratories have been constructed for providing the European Commission in-house access to a laboratory facility where more potent human pathogens (bacteria and viruses) may be handled after licensing from competent authorities. There are a sequence of rooms with reduced pressures from one to the next based on individual air-handling systems, bio-safety cabinets, waste handling systems for both liquid and solid waste and specific access control.

Finally IRMM's meeting room and office infrastructure is improved by new facilities in the RMPB.