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Action Plan for Reference Metrology in Chemistry in Denmark 2004

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Abstract

This Action Plan for Metrology in Chemistry in Denmark was initiated by The Danish Accreditation and Metrology Fund, DANAK, and produced by relevant Danish actors and stakeholders, coordinated by Danish Fundamental Metrology, DFM. The purpose is to obtain metrological traceability and thereby comparability of measurements in industry, society, and science over time and space.

The subject field of Chemistry is divided in six sub-fields: 1 Electrochemistry, 2 Products and Materials, 3 Environmental Chemistry, 4 Food Chemistry (partly covering feed, and later including plants), 5 Pharmaceutical Chemistry, and 6 Laboratory Medicine.

For each sub-field, its structure and tasks, existing resources (such as reference and primary laboratories), and metrological traceabilities are outlined. Future needs of industry and society are presented, as well as means of improving effectiveness.

In five sub-fields, many more reference materials are required. In Pharmaceutical Chemistry, uncertainty statement for values of reference materials and mutual recognition are needed. In Electrochemistry, Environmental Chemistry, and Laboratory Medicine, each sub-field proposes a centre to coordinate the national and international efforts of the laboratories and promote the creation of primary and reference laboratories. The related future resources are estimated.

Dansk resumé

Denne handlingsplan for metrologi i kemi i Danmark blev igangsat af Den Danske Akkrediterings- og Metrologifond, DANAK, og skrevet af relevante danske aktører og interessenter, koordineret af Dansk Fundamental Metrologi, DFM. Formålet er at opnå metrologisk sporbarhed og derved sammenlignelighed af måleresultater gennem tid og rum.

Hovedområdet kemi er opdelt i seks felter: 1 Elektrokemi, 2 Produkter og Materialer, 3 Miljøkemi, 4 Fødevarekemi (planter, foder, og fødevarer), 5 Farmaceutisk Kemi, og 6 Laboratoriemedicin. For hvert felt beskrives dets struktur og opgaver, nuværende ressourcer (såsom referencelaboratorier og primærlaboratorier), og de metrologiske sporbarheder skitseres. Fremtidige behov for industri og samfund opgøres, så vel som midler til at forbedre effektiviteten.

I fem felter behøves mange flere referencematerialer. I Farmaceutisk kemi er der brug for usikkerhedsangivelse for referencematerialers værdier og gensidig anerkendelse. I Elektrokemi, Miljøkemi, og Laboratoriemedicin foreslår hvert felt oprettelsen af et center til koordinering af laboratoriernes nationale og internationale tiltag og dannelsen af primær- og referencelaboratorier. De tilsvarende fremtidige ressourcer anslås.

Content

Executive summary

This Danish Action Plan is the third within the subject field *Amount of substance,* now called *Reference Metrology in Chemistry*. The work was initiated by *The Danish Accreditation and Metrology Fund,* DANAK, with the purpose of revealing the need for new reference laboratories, reference examination procedures, and reference materials within a structure for metrology in chemistry. DANAK commissioned *Danish Fundamental Metrology,* DFM, to coordinate the work of several specialists from each of six sub-fields.

The overall goal is to obtain metrological traceability of measurement results to international references, usually SI units, thereby obtaining comparability of values over time and space.

The Action Plan provides an *outline of the subject field, needs* of industry and society, and *recommendations* for national and global improvements with a Danish role. The subject field is divided into *six sub-fields,* with different structures, levels, and needs.

In general, all sub-fields obtain metrological traceability from reference materials and (except Pharmaceutical Chemistry) need production of many more. As Danish metrology in chemistry is decentralized, three sub-fields propose creation of centres for coordination and collaboration within research, development, and production of CRMs. The combined roughly estimated resources needed to implement the various recommendations concerning establishment of coordinating centres for reference laboratories are of the order of 2 MDKK and 1,5 man-years once and 8 man-years annually. The production of needed reference materials is not included in these estimates. The sub-fields of Products and Materials and of Food Chemistry have not provided such data yet.

For each sub-field, the situation is summarised as follows:

Electrochemistry has a primary laboratory for pH (at Radiometer Medical A/S) participating in highest-level international comparisons. DFM has set up a primary standard for electrolytic conductivity and performs similar functions. It is recommended to increase effectiveness by merging into a centre or primary laboratory providing research and development, dissemination of traceability, certified reference materials (CRMs) to other sub-fields, as well as publications and contacts with Danish and foreign authorities and institutes.

Products and Materials is a very diverse sub-field, which – according to preliminary investigations – seems to be adequately covered for the larger industries, but needs development of certified reference materials for the smaller industries. Examples should be presented in the near future.

Environmental Chemistry is a highly regulated sub-field, which produces measurement results involving many matrices, components, and properties. Traceability is achieved using CRMs. It is recommended to establish a coordinating centre for collaboration between four existing reference laboratories to increase effectiveness and visibility, provide research and development of CRMs, widen their applicability, and establish a model for estimating measurement uncertainty caused by sampling. Furthermore an Air-emission test centre is proposed, providing calibration services, an external quality assurance scheme (EQAS), and new measurement methods – all likely to become a good investment.

Food Chemistry (partly covering feed, and later including plants) is EU-regulated with international traceability, reference laboratory network, reference materials, inter-laboratory comparisons, accreditation, and participation in international EQAS. The sub-field provides results involving many matrices, components, and wide concentration intervals for properties that are often difficult to define. Measurement procedures are highly influenced by sample matrix and heterogeneity; consequently, funds are needed for a great number of new CRMs.

Pharmaceutical Chemistry is highly regulated with requirements stated in regional pharmacopoeias, including methods. Reference laboratories are not needed except as provided by electrochemistry (above). It is recommended that CRMs be issued with uncertainty statements to allow comparability of values; that reference materials from different pharmacopoeias be compared and mutually recognized; and that CCQM Bioanalysis Working Group create a global system for traceability and organize Key Comparisons for important products.

Laboratory Medicine encompasses a dozen disciplines, which examine many hundreds of different types of property in many materials. Research in some areas is at a high international level. It is recommended that the appointment of reference laboratories be formalized and aligned internationally; that a centre be established to coordinate the possibly large number of such reference laboratories, helping and funding them to obtain accreditation, develop reference procedures for assigning values to reference materials, and aiding Nordic and international traceability and harmonization of results – which is also a prerequisite for the electronic patient journal.

The authors are convinced that the undertakings proposed would meet current requirements of industry and society for providing chemical measurement services at an appropriate international level.

1 Introduction

1.1 Background

This Danish Action Plan is the third within the subject field *Amount of substance*, now called *Reference Metrology in Chemistry*. The work was initiated by *The Danish Accreditation and Metrology Fund*, DANAK[1], with the purpose of revealing the need for new reference laboratories, reference examination procedures, and reference materials within metrology in chemistry. DANAK commissioned *Danish Fundamental Metrology,* DFM, to coordinate the work.

The first action plan for the subject field *Amount of substance* was issued in 1992 (section 5.1). It recommended the establishment of a primary laboratory on pH measurements and resulted in the appointment of Radiometer Medical A/S as primary laboratory in 1993, so far the only Danish laboratory within the subject field. Furthermore, The Plan recommended improvements of the capabilities for international traceability by means of reference materials. A step in this direction was taken in 1993 by the establishment of DANREF (Danish Centre for Reference Materials). This centre ceased to exist due to lack of appropriations.

The second action plan was issued in 1995 (section 5.2). Here, the subject field was divided into seven sub-fields: Environmental, Clinical, Material, Food and Feed, Biochemistry, Microbiology, and pH measurements, although Biochemistry was not described in detail. This plan recommended that international traceability should be supported. Particularly the following three actions were recommended: 1) Establishment of reference laboratories for reference materials, 2) Establishment of a primary laboratory on electrolytic conductivity and 3) Definitive methods within Environmental Chemistry should be supported. Largely due to lack of funding, recommendation 1 has not been followed up, whereas recommendation 2 has been followed by setting up primary standards for electrolytic conductivity at DFM (section 2.1). Progress in recommendation 3) is described in section 2.3.

The international collaboration in metrology is rapidly increasing. Therefore, it is important to see metrology in Denmark in an international perspective. At the global level, the CCQM, Consultative Committee for Amount of Substance: Metrology in Chemistry, under the Metre Convention coordinates improvements of the quality of measurements in chemistry. The aim is to develop a global metrology structure within the frame of the Metre Convention.

In the EU, within the regulated sub-fields the European Commission has appointed Community reference laboratories, to which National reference laboratories must be traceable. In the voluntary sub-fields EUROMET and EURACHEM is operating a joint Technical Committee with a number of sub-fields. The categorisation of sub-fields varies somewhat from organisation to organisation, and is reproduced in section 6.4. It is expected that the number of primary laboratories will be reduced, and that the metrological efforts will be coordinated both to improve the efficiency and to cope with the challenge of developing traceable measurement procedures for new and complex quantities.

In the Nordic region a closer cooperation is discussed with the purpose of strengthening metrology in that region.

It has been the intention to modify the structure of reference metrology in chemistry in Denmark to comply with the current global model for structuring metrology in chemistry while remaining in accordance with Danish needs.

The subject field has therefore been divided into the following six sub-fields:

1 Electrochemistry

2 Products and Materials

3 Environmental Chemistry

4 Food Chemistry (partly covering feed, and later including plants)

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[1] Abbreviations are explained in section 6.

5 Pharmaceutical Chemistry

6 Laboratory Medicine

Each sub-field has provided an independent description, reflecting the different approaches to metrology. Common to the six sub-fields is the use of reference materials. Current praxis also means that other units than SI-units may be used.

1.2 Purpose

This Action Plan is written for public and private decision makers in order to improve their basis for decisions. Therefore we have chosen the following four purposes:

- To present the status of the subject field Reference Metrology in Chemistry in Denmark, i.e. the different ways in which measurements are treated in the six sub-fields, what the essential issues are, how metrological traceability is established, who are the major operators, and who are participating in inter-laboratory comparisons;
- To register the resources today;
- To register needs of industry and society within a five-year future;
- To give recommendations for metrology in Denmark (including allocation of resources, setting up of new primary and national reference laboratories);
- To give suggestions of specific actions that may improve global traceability and thereby support international trade, health, and safety;
- To consider how to associate Danish metrological efforts with the international structure.

1.3 Development

The content of the Action Plan is based on information and contributions from the participants listed as authors and participants in meetings in section 6.1. The new Action Plan has the same scope as the previous two action plans, namely to structure metrology as a generic discipline with common features that unites scientific, industrial, and legal metrology.

Please note the following.

- The subject field Biology including Microbiology will be treated in a separate Action Plan. It is only described in this Action Plan, when it connects naturally to some of the sub-fields.
- Laboratory Medicine extends beyond the subject field covered by this Action Plan.
- Products and Materials have only been outlined due to time constraints.

DFM invited selected persons representing various sub-fields to a first meeting at DANAK on 2003-11-10. Here, the important decision was made to divide the subject field into six sub-fields and appoint six working groups. During the following months, a meeting was held every month in order to discuss progress. 24 authors participated in writing the Action Plan. The Action Plan was submitted to a last hearing in the beginning of June 2004. The final meeting was held on 2004-06-17 at DFM. Here, the remaining details were agreed.

1.4 Structure of sub-field descriptions

Each sub-field is presented in the following sections:

1 Summary

2 Introduction

3 Description of the sub-field
(background, definitions, users, traceability, comparisons)

4 Present resources
(available standards, laboratories, equipment, personnel, economic resources)

5 Requirements
(description in general terms: research, industrial applications, legal and other applications, reference methods and materials to obtain traceability)

6 Future needs
(quantitative needs to realize the requirements above: new laboratories, centres, reference methods and materials, equipment, personnel and funds)

7 Recommendations
(actions concerning primary/reference laboratories, centres, reference materials)

8 Elements of the metrological reference system
(national standards and laboratories, accredited laboratories, contributors)

1.5 Definitions related to "reference metrology"

This Action Plan deals with Reference Metrology in Chemistry, indicating that it focuses on the higher level of traceability as maintained at officially appointed laboratories, either nationally or internationally. In this context, the following definitions are used.

1.5.1 Standardized concepts from Draft VIM 3 (section 5.3)

The following concepts of relevance for the description of reference metrology are defined in the VIM draft edition 3 (2004).

Term	Definition
primary measurement procedure **primary procedure**	measurement procedure used to realize the definition of a measurement unit and obtain the quantity value and measurement uncertainty of a primary measurement standard [draft VIM 3 – 2.7]
national measurement standard **national standard**	measurement standard designated as a national stated metrological reference [draft VIM 3–5.2]
primary measurement standard **primary standard**	measurement standard whose quantitative value and measurement uncertainty are established without relation to another measurement standard for a quantity of the same kind [draft VIM 3–5.3]
reference measurement standard **reference standard**	measurement standard used for the calibration of working measurement standards in a given organization or at a given location [draft VIM 3–5.5]
reference material **RM**	material, sufficiently homogeneous and stable with respect to one or more specified quantities, used for the calibration of a measuring system, or for the assessment of a measurement procedure, or for assigning values and measurement uncertainties to quantities of the same kind for other materials [draft VIM 3-5.13]
certified reference material **CRM**	reference material, accompanied by an authenticated certificate, having for each specified quantity a value, measurement uncertainty, and stated metrological traceability chain [draft VIM 3 – 5.14] NOTE – The sub-field of Food Chemistry distinguishes between certified reference standards, made from pure compounds, and certified reference materials having a more complex matrix.

1.5.2 Non-standardized concepts

There exist no standardized definitions for the concepts “National Metrology Institute” and “reference laboratory”. In Denmark the following two groups are recognized.

Laboratories appointed by the Ministry of Economics and Enterprise

This Ministry is responsible for general metrology and represents Denmark within the Metre Convention at the CGPM and the Bureau International des Poids et Mesures (BIPM).

According to Technical Measurement Announcement no. 170 (section 5.4), the Ministry operates with two kinds of laboratory, primary laboratories and national reference laboratories, according to the following definitions:

An appointed **primary laboratory** is a laboratory that is internationally recognized for the realization of primary standards for base or derived units at the highest attainable level, and that performs internationally recognized research within the field.

A **national reference laboratory** is a laboratory that through traceability to a foreign primary laboratory in other countries is capable of calibrating a given measurand at the highest level of performance in Denmark.

Both kinds of laboratory are considered National Metrology Institutes (NMIs), and they are appointed in the following way.

Within 10 subject fields, each Action Plan suggests a division into sub-fields (i.e. six in the present case of metrology for chemistry), and at given occasions the Ministry through DANAK will call for applications to become the Danish NMI within this sub-field. The candidates are subjected to an international evaluation against criteria set by DANAK, including a DANAK accreditation. If one or more of the candidates are qualified, the best candidate is appointed. Sometimes, several laboratories form a coordinating centre to cover, a broad sub-field.

Hence the appointment of NMIs within the Ministry of Economics and Enterprise reflects the technical competence within the metrological sub-field in question. But there are no tasks given to an NMI as a result of the appointment.

Within the context of the CIPM Mutual Recognition Arrangement (CIPM-MRA), primary laboratories represent Denmark at the highest international level and typically take part in the CIPM Key Comparisons and in the consultative committees of the CIPM. Both primary laboratories and national reference laboratories are members of the European organization EUROMET and can take part in EUROMET Key Comparisons.

Currently, there are 10 primary and 9 Danish reference laboratories working under this scheme in all ten subject fields together.

In order to stress the focus on technical competence and the fact that several institutions may collaborate in one primary or national reference laboratory, in this Action Plan they are sometimes referred to as “competence centres”

Reference laboratories appointed by other ministries

At least six other Danish ministries have appointed reference laboratories to perform specific tasks related to measurements that are relevant to the ministry in question. Such tasks may include the operation of inter-laboratory comparisons, production and certification of reference materials, and the associated provision of traceability to an internationally recognized reference standard, procedure, or reference material.

The appointment of such reference laboratories may be based on an open tender, issued by the ministry in question, and does not involve a specific technical evaluation with international participation.

Currently, there are at least 16 reference laboratories working under this scheme (section 6.2).

2 The six sub-fields

2.1 Electrochemistry

2.1.1 Summary

The sub-field description for Electrochemistry in this Action Plan comprises the quantities pH, conductivity, and redox, as well as ion analysis.

Metrological traceability for the important trans-disciplinary quantities, pH and electrolytic conductivity is established in Denmark at a level, which is comparable to that of our international partners. There are relevant relations and participation in the working groups of the Metre Convention, traceability is established to internationally recognized, primary standards, and participation in international comparisons occurs on a regular basis.

Demands for metrological traceability in ion analysis via primary reference materials exist broadly within the sub-fields of chemistry, but have not been described in detail in this part of the Action Plan as there are no Danish producers or institutions certifying such CRMs. Such activities are, however, encouraged. No significant demand by end-users for traceability for redox has been identified.

The maintenance and development of existing and future facilities is highly dependent on funding for metrology at the GTS institutes through performance contracts, as well as on financing from outside the GTS system.

2.1.2 Introduction

The sub-field of electrochemistry embraces a wide range of measurement techniques and quantities. The transformation of electric energy into chemical energy and vice versa, the exchange of charge between ions and solids, underlies a rich variety of generic and species specific effects, and may be used to provide information on chemical activation energies, electrochemical potentials, transport properties, amount of substance, etc.

This sub-field description will focus on quantities used in several sub-fields of this Action Plan, and refer the description of sector-specific needs, e.g. for certified reference materials, to the respective sub-field descriptions, e.g. Pharmaceuticals and Laboratory Medicine. Thus the heading, “Electrochemistry”, is here used to cover a few central quantities used widely over many sub-fields of chemistry, and which rely on electrochemical methods for their realization.

2.1.3 Description of the sub-field

Electrochemical measurements are used in all sub-fields of chemistry. They are usually cheap and fast to perform, equipment is relatively inexpensive, and results are fairly reproducible. Due to the strong coupling with electrical quantities (basically voltage and current) and the fundamental properties of ions, it is possible to achieve traceability in many types of electrochemical measurements to the base units of the SI.

The use of ion-selective electrodes enables a large variety of quantitative measurements on specific ionic species, reactions, etc. Due to the selectivity of the probes, the use of ion-selective electrodes for amount-of-substance measurements requires the use of certified reference materials in the form of solutions of the appropriate ions with known concentration. The most common ion-selective electrodes are pH probes.

The quantities pH and electrolytic conductivity are used widely across the sub-fields of chemistry and are important physicochemical quantities for the description of materials and solutions. They seldom give direct information on specific species, but provide summary information on materials or may be used as indicators for process events. Due to this generic nature, measurements of these quantities are performed in all industrial sectors and for numerous purposes.

Assaying of some pure substances can be made with high-accuracy coulometric titration, which is defined by the CCQM as a **primary method**. This technique derives amount of substance from direct measurement of physical quantities - in this case direct current, mass, and time - as well as the Faraday constant. The determination of purity of materials is the starting point for the traceability chain of many certified reference materials.

One further quantity is redox or reduction-oxidation potential. This quantity is increasingly used for process control, e.g. for processes requiring precipitation, or as an indicator for corrosive processes, and may even be used for quantitative measurement of for example chlorine in swimming pool water. The traceability chain is similar to that of pH, i.e. reference electrodes and a voltmeter. Some standard solutions exist, e.g. quinhydrone solutions, where the actual potential measured depends on the type of reference electrode. The quantity is very pH dependent and a pH-compensated redox scale is in use.

There is presently no significant demand by end-users for traceability of redox; however, there seems to be a future potential for this quantity.

The following will concentrate on the generic quantities pH and electrolytic conductivity, while description and needs for ion-specific reference materials and solutions are referred to the sub-field-specific chapters.

2.1.3.1 Definitions

Electrolytic conductivity is the ionic charge transport in, typically, aqueous solutions: The quantity has the symbol κ and is measured in the unit S/m. The conductivity is derived from the resistance, R, in units of Ω, of a volume of solution contained in a measurement cell characterized by a geometric cell constant, K, in the unit m^{-1}, and the relation $\kappa = K / R$.

Acidity or pH of a solution was originally defined by the Danish chemist S. P. L. Sørensen and is in modern terminology expressed in the following way:

$$\mathrm{pH} = -\log_{10} \alpha_{\mathrm{H^+}}$$

i.e. the negative decadic logarithm of the hydrogen ion activity. As the definition involves a single ion activity, which is not measurable, operational definitions have been developed, leading to conventional pH scales based on defined buffer solutions.

These measurements, as well as those involving ion-selective electrodes (which includes pH electrodes), rely on the measurement of fundamental electrical quantities, such as voltage and current, both direct and alternating, resistance/impedance, and time, as well as mass. Fundamental constants, such as the Faraday constant, the electronic charge, and ion-masses also play a direct role.

2.1.3.2 Users

Electrolytic conductivity

There are two main groups of users.

Users for measurement of very low conductivity (κ < 0,5 mS/m), mainly for measurements on purified water.

Measurement of electrolytic conductivity does not give information on any ionic species, but in the case where any ionic content acts as a contaminant, conductivity may provide a measure of purity. In the pharmaceutical sub-field, assessment of the quality of purified water has been formulated in regulatory requirements by the US, European, and Japanese Pharmacopoeias as limit values for electrolytic conductivity. For ultra-pure water or water for injection, e.g., the basic limit is 0,13 mS/m at 25 °C. There is thus a need for documented traceability of results for electrolytic conductivity obtained by the instruments mounted in the process facilities of all pharmaceutical companies. It has not been possible to quantify this need, but the number of units in Denmark is estimated in the tens of thousands.

Many other sectors also use limit values for conductivity to assess or control water purity. This need appears as soon as the quality of water may affect the quality of products or measurements.

Direct needs for traceability have been expressed for the food industry, e.g. dairies; for power generation where water quality is important to limit corrosion in turbine systems; and for the electronics industry where water is used as a solvent, coolant, for rinsing, etc., in various process steps.

In the field of environmental and chemical analysis, purified water is used in measurements for dilution and in process steps for rinsing and cleaning. In addition, in the field of physical measurements, purified water is used and affects the quality of results obtained, e.g. as reference material for flow and density, and for temperature standards (triple point of water, ice bath); in that relation, the commonly used measurement technique of freezing point depression relies on purified water for reference.

In most cases above, users require traceable measurements of conductivity for the laboratory or process instruments used, but they are often satisfied with a statement of compliance with the limit for the process instruments calibrated; absolute values and uncertainty are secondary, and relative expanded uncertainties up to 10 % (k = 2) can be tolerated. So far, users have in most cases managed with the reliability claimed by the manufacturers of measuring equipment, and the quality and maintenance of the water purification systems. However, very few manufacturers state any form of traceability of their values and have seldom performed calibrations that ensure direct traceability.

Users for the absolute value of conductivity

In situations where the composition of solutions is known, conductivity may provide a measure of concentration. For such absolute measurement, where the exact value is requested in contrast to limit assessments, users include the electroplating industry, where conductivity measurements are used to monitor and control the manufacturing process. In other industries, conductivity is used directly in process control as well, from cleaning and rinsing in the chemical industry to monitoring salt and nutrient concentrations in the food industry. The measurement interval for these applications goes up to 1 kS/m.

Absolute measurements are critical for dialysis treatment, as the effectiveness of the treatment depends on the calibration and control of the dialysis fluids used; the relevant interval here is 1–2 S/m. A dialysis apparatus measures both absolute conductivity (to control the process operating point) and differential conductivity (to monitor the dialysis process itself). Calibration is a regulatory requirement and touches upon the IVD Directive as well.

The conductivity of a solution is to a large extent proportional to the concentration of ions, and the method is thus used as a generic, non-ion-specific concentration measurement, e.g. in the analysis of drinking water and measurement of salinity, with a measurement interval in the order of 0,1 S/m. Other measurement techniques, e.g. ion-chromatography, rely partially on conductivity measurements as well.

pH

Practical pH measurements are among the most frequently performed chemical measurements. The quantity is measured in all types of laboratories and on many different kinds of samples, for example in analytical laboratories analysing environmental samples. The pH is also a very important clinical quantity measured in every hospital in connection with the determination of acid-base status of blood, for example during respirator treatment.

Ion-analysis

Again, the use of ion-specific quantitative measurements is used in almost all branches of chemical analysis, especially in diagnostic Laboratory Medicine, and for environmental analysis in the quantification of water quality and pollutants. In addition to the direct use of ion-specific electrodes, various spectroscopic methods and ion chromatography are used.

2.1.3.3 Metrological traceability

Conductivity is measured traceable to the SI units of resistance (Ω) and calibrated cell constants (m^{-1}). Primary standards rely on the calculable electric field configuration in a geometrically characterized measurement cell. Traceability is disseminated using certified reference materials, typically aqueous solutions of KCl (molality 0,01–1,0 mol/kg). Through a hierarchy of measurement cells the conductivity of the calibrant solutions and the cell constants of the measurement cells are determined.

There are several (written) standards describing recipes for standard solutions, e.g. ISO/IEC 7888, American Society for Testing and Materials (ASTM) D1125 and International Organization of Legal Metrology (OIML) Recommendation 56. The latter is probably the best one validated (National Institute of Standards and Technology (NIST), United States, in 1990); it will probably be replaced by molality-scale-based reference solutions approved by the International Union of Pure and Applied Chemistry (IUPAC). It should be noted that the reference values and recipes for standard solutions in the quoted standards are not consistent with each other and in some cases necessary reference conditions (e.g. temperature) are not specified. None of the standards specifies the uncertainties of the reference values. There are no internationally recognized standard solutions for low conductivities, i.e. below 5 mS/m (50 µS/cm). The problem is that aqueous solutions are susceptible to the dissolution of atmospheric CO_2 and thus are not stable. Development efforts for other combinations involve aqueous solutions of HCl, sucrose, ethylene glycol, glycerol, etc., but published recipes for standard solutions do not exist.

There are several accredited providers of standard reference solutions, i.e. aqueous solutions of KCl, in Europe, including Merck (Germany), Radiometer Analytical (France), and DFM (Denmark).

To achieve high accuracy, several influence factors must be specified: Temperature coefficients of the standard solutions used for calibration and for the solution under measurement, the measurement frequencies and waveforms used, and the cell constant must be shown to be independent of the measurement conditions or the dependency must be determined. There is no internationally agreed operational definition of electrolytic conductivity, hence equipment manufacturers use different methods to circumvent polarization (e.g. by using different measurement frequencies in different measuring intervals).

Two international Pilot Studies have been performed under the auspices of the Working Group on Electrochemical Analysis under the Consultative Committee for Amount of Substance (CCQM). In 2001, CCQM P22 at 1,28 S/m and 0,1 S/m, coordinated by Danish Fundamental Metrology (DFM), and in 2003, CCQM P47 was performed at 50 mS/m and 5 mS/m, coordinated by the Netherlands Measurement Institute (NMi). In 2005, a Key Comparison, CCQM K36 at 0,5 S/m and 5 mS/m, is foreseen. In 1999 DFM participated in a tri-lateral comparison with NIST and Office of Metrology in Hungary (OMH) at 1 S/m, 0,1 S/m and 10 mS/m. The results are published in Metrologia, **38 (6)**, 549 (2001).

Traceability is thus well defined at the top level, but the lack of standardized methods of calibration, including the determination of concentration dependency of the cell constant, which acts as the proportionality constant between the measured resistance and the conductivity, as well as the influence of the measurement parameters, e.g. frequency and waveform, makes traceability to the end-users less well-founded. There are no accredited providers of calibration of cell constants in Europe.

Concerning **pH**, various organizations, such as IUPAC and OIML, have given different recommendations on how to maintain the pH scale, resulting in slightly different values assigned to the pH of the Primary Standard Reference Solutions. NIST has also given its own best estimates of these values. Now, international agreement has converged on using the latest published IUPAC scale.

Important in maintaining the primary standards is the ability to use reproducible electrodes and to perform accurate chemical analysis and measurements of the electromotive force of the electrochemical cells in volt.

The highest accuracy, with the present technology, corresponds to a combined standard uncertainty of approximately $(1–3)\times10^{-3}$. This accuracy can only be obtained in a few primary laboratories in the world. In most practical pH measurements, an accuracy corresponding to a combined standard uncertainty of $(5–20)\times10^{-3}$ is acceptable.

Traceability is disseminated using Certified Reference Materials in the form of pH buffers. There are several accredited providers in Europe of such buffers.

CCQM has arranged several Key Comparisons in which the Danish Primary Laboratory for pH (DPL-pH) has participated. The results are published in the Key Comparison Data Base accessible at the BIPM homepage (http://kcdb.bipm.org/).

As mentioned in the introduction, **ion-analysis** relies on the availability of ion-selective electrodes and traceability is achieved using certified reference materials. These are commonly in the form of pure substances or diluted solutions with certified amount-of-substance content of specific ion species. There are several providers of well-characterized reference materials and solutions in Europe, primarily based on collaborations between the larger national metrology institutes and commercial producers. There are, however, also several commercial providers of reference, for which studies have shown a lack of traceability, even for simple mono-elemental solutions in simple matrices.

CCQM has performed several Key Comparisons and Pilot Studies on the measurement of pure substances and on ionic content of solutions. They have run without Danish participation.

2.1.4 Present Resources

In 1993 the Chemical Reference Laboratory at Radiometer Medical A/S was appointed by the Ministry of Industry and Trade now the Ministry of Economics and Enterprise as the national primary laboratory within the field pH, DPL-pH. The laboratory has maintained an accreditation from Danish Accreditation (DANAK) for more than ten years to perform certification of primary pH standards according to the method recommended by IUPAC.

The DPL-pH has collaborated with NIST within this field for a long period. NIST is the most active primary laboratory in the field and has been the pioneering laboratory since the 1930's. Interlaboratory comparisons between NIST and DPL-pH have been performed. In Europe a growing interest in pH measurements at the primary level has developed. The EUROMET field, Amount of Substance, has included several projects on comparison of pH at the highest level. At the Physikalisch-Technische Bundesanstalt (PTB) in Germany, a primary laboratory for pH has been active since 1992.

Radiometer presently spends annually approximately 0,5 man-year on maintenance of primary pH standards, participation in international work, and research and development projects. In addition, internal dissemination of pH is performed in the organization. This amounts to approximately 0,5 man-year annually. The turnover related to primary pH-standards equals about 180 kDKK (2003).

DFM developed a primary standard for conductivity in 1996–7 in collaboration with and based on a design of NIST. The facility was accredited by DANAK in 1999 and the accreditation scope presently covers measurement of electrolytic conductivity in the interval 0,09 mS/m to 50 S/m, and certification of standard solutions. It has not been possible to achieve an appointment as designated laboratory due to limitations expressed in the previous Plan of Action. Thus, the participation in the international work has been possible only by a relaxed application of the rules and policy of the CCQM.

DFM presently spends approximately 0,5 man-year annually on maintenance of standards, dissemination, participation in international work, and research and development projects. Turnover in dissemination of certified reference materials and characterization of standard solutions is about 150 kDKK (2003).

2.1.5 Requirements

The requirements to satisfy the present and future needs of Danish industry and various types of laboratories may be listed as follows.

Conductivity

- Availability of certified reference materials in the form of standard solutions. This is fulfilled for the high conductivity interval $\kappa > 10$ mS/m by the availability of certified reference materials from accredited sources.
- Availability of direct traceability for low conductivity.
- Availability of well-characterized reference solutions or geometrically characterized conductivity cells for the low conductivity range.
- Consistency in the written standards applicable for the users of standard solutions, as well as the availability of standardized measurement and calibration methods for conductivity cells. This concerns especially the various Pharmacopoeias, suffering from a lack of coordination of the requirements and standard methods.
- Provision of accredited calibrations of laboratory and process instruments and sensors.

pH

- Availability of certified reference materials in the form of traceable buffer solutions. This is fulfilled by the availability of certified reference materials from accredited sources.
- Provision of accredited calibrations of laboratory and process instruments and sensors.

2.1.6 Future needs

In addition to the maintenance of the activities described above, the following points must be considered for the continual access for Danish industry and laboratories to recognized traceability in the field of electrochemistry in Denmark:

- DPL-pH does not belong to the Centre for Danish Fundamental Metrology (CDFM) and hence cannot obtain government funding for maintenance of national standards, international work, including participation in comparisons, participation in the international fora, research and development projects, and general communications. The participation of DPL-pH is therefore mainly limited to activities of direct interest to Radiometer Medical A/S. There is thus an urgent need for a financing structure for such national metrology activities performed by actors outside of CDFM.
- Another possibility is to transfer the activities of DPL-pH from Radiometer to DFM and seek the additional funding needed from within the GTS system.
- Development projects on the measurement of and traceability for low conductivity must be encouraged, and international recognition sought through collaborative projects.
- Active participation in the standardization process for conductivity, including feedback to the Pharmacopoeia commissions, to ensure the fulfilment of consistent, workable, and scientifically based requirements for conductivity.
- The establishment of accredited calibration facilities for laboratory and process instruments and sensors should be furthered.
- User needs for traceability in the field of redox measurements should be monitored closely.
- User needs for and quality monitoring of reference materials for ion analysis, essential for e.g. Laboratory Medicine, should be monitored and cooperation with competent actors established.

It is estimated that the equivalent of two man-years per year is necessary to implement these developments.

2.1.7 Recommendations

To enhance the visibility of the primary facilities and to further the development efforts, a formal collaboration between the two Danish actors, DPL-pH and DFM, should be established in the form of a Centre for Reference Metrology in Electrochemistry (CRME) with responsibility for the quantities pH and electrolytic conductivity.

The purpose of this centre would be to coordinate the national and international activities: Dissemination of traceability via DANAK accredited calibrations and certification of reference materials, publications, international meetings, comparisons, and research and development projects. An important aspect is the contact with relevant authorities, e.g. the Pharmacopoeia commissions, to provide input to the standardization process and ensure the availability of rigorous calibration methods.

Instead of creating a CRME, another possibility would be to merge DPL-pH and DFM into one primary laboratory at DFM.

Although the present activities in the framework of the national metrology system in Denmark are limited to pH and conductivity, the CRME or a primary laboratory at DFM should be open to competent actors in other fields within electrochemistry. This could include parties producing or certifying pure substances or solutions and parties involved in research and development of other quantitative electrochemical measurement procedures.

2.1.8 Elements of the metrological reference system for Electrochemistry

Element	**Examples for pH**	**Examples for conductivity**
Primary standard	Reference electrodes and voltage measurement	Calculable cells and impedance measurement
Traceability dissemination	Standard reference material: Buffer solutions Several accredited labs in Europe	Standard reference material: KCl standard solutions. Several accredited labs Calibrated cells
Relevant quantity intervals and uses	pH ~ 1-12 General analysis, environmental monitoring, process control, and Laboratory Medicine	κ < 0,5 mS/m: pure water κ ~ 0,1 S/m: drinking water, salinity κ ~ 1 S/m: medical applications κ > 10 S/m: process control
Uncertainty	Expanded uncertainty (k = 2) Standards: $(1–3)\times10^{-3}$ End-users: $(5–20)\times10^{-3}$	Relative expanded uncertainty (k = 2) Primary standards: ~ 0,05 % Reference standards: 0,1–1 % End users: 1–5 %
Global fora	CCQM-WGEA, IUPAC, collaboration with NIST	CCQM-WGEA, collaboration with NIST
International comparisons	CCQM-K9, CCQM-K17	CCQM-P22, CCQM-P47
European fora	EUROMET, collaborations with PTB, SMU	EUROMET, Collaborations with PTB, OMH, IEN, NPL, LNE
Nordic fora	No facilities	Development effort on low conductivity at SP, Sweden. No facilities in Norway or Finland
Facilities in Denmark	Primary standard, DANAK Metrology appointed primary laboratory, DANAK accredited measurement facility	Primary standard, DANAK accredited measurement facility
Needs of industry	Traceable buffer solutions (fulfilled by the availability of certified reference materials from accredited sources) Accredited providers of calibration of laboratory and process instruments and sensors	Traceable standard solutions (fulfilled for the high conductivity interval κ > 10 mS/m by the availability of certified reference materials from accredited sources) Standardized methods for calibration of cells Reference solutions for low conductivity (under development by commercial sources) Accredited calibration facilities for conductivity cells, for all relevant intervals and users Accredited providers of calibration of laboratory and process instruments and sensors

2.2 Products and Materials

Due to limitations in resources and time, this sub-field was not treated in depth. Below are given the preliminary findings and thoughts produced during the course of the preparation of the Action Plan.

2.2.1 Summary

The preliminary investigations suggest, that ”large” industries are creating metrological traceability using either in-house standards and/or certified reference materials, and that these industries have drawn the conclusion that such a system is presently meeting their requirements.

The sub-field should be developed in the future to cover smaller industries.

2.2.2 Introduction

- The sub-field is covering a wide area of chemicals and materials and is not well defined.

2.2.3 Description of the sub-field

2.2.3.1 Definitions

The sub-field comprises among others:

- Industrial Chemicals and Products
  - Industrial chemicals
    - Inorganic chemicals (fertilizers, strong acids, feeds, salts, paints)
    - Organic chemicals (pesticides, oils)
    - Gases (acetylene, oxygen, nitrogen, ammonia)
  - Products
    - Polymers (PE, PVC, PP)
    - Lime, cement, surface-active agents, soap
- Materials
  - Concrete and related materials
  - Wooden materials
  - Asphalt and other road construction materials
  - Metals and alloys

2.2.3.2 Users

The industrial laboratories perform examinations during the quality control necessary for trade agreements.

2.2.3.3 Metrological traceability

In this preliminary description of the sub-field, it has not been possible to create an overview, and the information received and used in the following description has not been validated.

For all areas, metrological traceability is normally created in-house using selected pure/supra-pure analytical chemicals.

Non-certified reference materials

Traceability is created by in-house reference materials, which are used to perform company-based comparisons or for internal quality control.

Some companies have participated in the inter-calibrations arranged by the American company Magruder, which is producing reference materials.

Analytical methods

The commonly used methods are mainly from AOAC, EEC, ISO, CEN, or are national.

Reference materials (CRMs and non-certified)

Traceability is normally created using in-house reference materials, alternatively used for internal quality control purposes.

Certified reference gases for certain areas

The use of non-certified reference gases is still the dominating model for quality control.

Analytical methods

The common methods are described by AOAC, ASTM, CIPAC, DIN, EPA, ISO, VDI, and nationally.

Products: Polymers

No specific information at this moment.

Products: Lime, cement, surface-active agents, soap

Reference materials exist; some of them are CRMs.

Materials

No specific information has been received.

2.2.4 Present resources

The resources must be large compared to those of other sub-fields in Denmark, but resources are not specified for the time being.

2.2.5 Requirements

Presently not describable

2.2.6 Future needs

If the metrological investigations would cover the sub-field totally and reach a level according to the plan, the required resources are evaluated as “heavy”.

2.2.7 Recommendations

It is proposed, that the sub-field initially be treated using examples. Later an Action Plan should be developed based on interest from the organizations and companies.

This preliminary investigation indicates, that “large” companies are doing very well on their own. Therefore, the investigation in the next stage should concentrate on small and medium-size companies.

2.3 Environmental Chemistry

2.3.1 Summary

The sub-field of Environmental Chemistry covers a large number of chemical entities and properties in a diversity of matrices. The number of possible combinations of measurand and matrix is vast. Furthermore, many measurands are not well-defined chemical properties, but the result depends on the use of a prescribed method.

The area is highly regulated, and the demand for metrological traceability of measurement results for new measurands and matrices is driven by the demand from authorities. The reference laboratories at present serve as centres of excellence to ensure development according to these demands.

In practice, traceability is established through the use of certified reference materials (CRMs), definition of measurement procedures to be used for non-specific measurands, and metrological control of measuring instruments wherever possible.

Reference materials are available for a number of gases, trace elements in a number of matrices, and a limited number of other quantities. However, concentrations are often high compared to the needs in Nordic countries. Proficiency testing schemes are available for a much larger variety of measurands, but the assigned values are normally not traceable.

Sampling is expected to cause a large contribution to the uncertainty of the majority of environmental measurement results, but in many cases procedures for sampling are not well defined and recognized methods for routine determination of uncertainty are lacking.

2.3.2 Introduction

Environmental Chemistry encompasses the determination of concentrations for a number of organic and inorganic substances as well as the general properties of a sample, e.g. total residue or biochemical oxygen demand. Furthermore, the measurement of the amount of some component may only be a part of the total amount in the sample, e.g. content of leachable trace elements or chemical analysis of size-fractionated particles PM10 (particles with a diameter less than 10 µm), etc.

The matrices range from simple aqueous solutions to highly inhomogeneous materials. Matrices are for example: air (both ambient air and stationary source emissions), water (groundwater, marine water, and fresh water), soil, sediment, biota, wastewater, sludge, industrial waste, and solid waste from incineration processes. Drinking water is also handled by environmental authorities and is therefore included in the present Action Plan.

The measurand in most cases involves amount-of-substance concentration, (mol/m^3), amount-of-substance content (mole/kg), mass concentration (kg/m^3), or mass fraction (kg/kg). The majority of measurements are in the trace-component interval (e.g. 10^{-12} to 10^{-4} kg/kg), but higher mass fractions are relevant for some measurands.

2.3.3 Description of the sub-field

2.3.3.1 Background

The sub-field covers both sampling and quantitative determination of a given measurand, but also qualitative determination and identification are relevant. In sampling, one major problem is to ensure that the sample taken is representative for the situation. Thus, sampling is an important factor, which often is the source of the largest contribution to uncertainty.

For air measurements, samples may be taken by passive sampling or by suction through, e.g., different types of filter, coated glass tubes, solid sorbents; or through devices containing water or chemical solutions.

For air measurements some quantities are measured with on-line monitors. Such monitors require extraction of gases through a sample system and in some cases a conditioning (drying, filtration, cooling, dilution, heating) is necessary. Monitors have to be calibrated against certified reference gases. The following are examples of principles or methods used for on-line monitors:

- Chemiluminescence
- UV, IR, FTIR, NDIR
- FID, GC PID
- Paramagnetism
- Semiconductor sensors
- Electrochemical cells
- Nephelometry

For air measurements, a set of influence quantities have also to be measured: the sample flow, the flow of gases in stacks or ventilation ducts, dynamic pressure, static pressure, barometric pressure, temperature, and gas density. Correct measurements are therefore dependent on traceability in a number of physical sub-fields.

On-line monitors are also increasingly used for monitoring of constituents in, e.g., wastewater treatment processes or monitoring of streams and marine waters. Some of the detection principles as applied in conventional laboratory equipment are available for monitors in on-line equipment.

For water, the sampling equipment range from, e.g., a bottle mounted on a handle of a suitable length to advanced equipment that allows a continuous sample or a series of samples to be collected automatically. Two types of automatic equipment are primarily available, namely time-proportional (time-weighted composite samples) and flow-proportional (flow-weighted composite samples).

Analyses of solid matrices are in most cases performed on discrete or composite samples taken to the laboratory. For solid matrices, the problem of obtaining representative data is not only related to the ability to take a representative primary sample, but also to ensure homogeneity of this sample, from where the measurement portion is drawn. For soil, waste, and sediment, several sub-samples are often taken to give a composite sample from where a laboratory sample is taken.

Laboratory instrumental methods are used in the majority of cases, often preceded by a preparation to liberate the measurand of interest from the matrix. The following methods are used separately or in combination:

- Gravimetry,
- Titrimetry,
- Spectrometry (UV/VIS, fluorescence, X-ray fluorescence, infrared, atomic absorption, atomic emission, mass), including turbidimetry and nephelometry,
- Chromatography (gas or liquid), and
- Electrochemistry (pH, conductivity, ion-selective electrodes, etc.).

Gravimetry is a primary method. However, if the measurand has a procedure-dependent component, the procedure is an integral part of the definition of the measurand.

The use of pre-treatment for liberation, e.g. extraction, of the substance of interest means that one reference material may in principle be assigned a number of different "conventional true values", one for each pre-treatment method.

Certified reference gases are available in high concentrations and it is often necessary to use a calibrated dilution system for dilution of the reference gas to a concentration useable for calibration. Reference materials and certified reference materials are available for trace elements and certain stable organic substances in various types of water sample and in solid matrices, e.g. soil, sediment, sludge, mussels, and other biological material, and for certain types of waste. For most organic as well as for inorganic analyses other than trace elements, very few reference materials are available internationally. Furthermore, each type of sample is highly diverse in many cases and therefore a reference material for, e.g., one soil may not be relevant to secure traceability for all soil analyses for the measurand. In addition, reference materials in concentrations relevant to the low pollution level in the Nordic countries are often difficult to find.

Environmental measurements are often performed for unstable measurands for which reference materials are difficult to produce.

2.3.3.2 Users

A large part of samples and analyses within Environmental Chemistry are seen in connection with legislation and regulation by authorities. The field is heavily regulated by EU directives, national legislation, and in environmental permits. In addition, national monitoring programmes account for considerable activity. The users of environmental data are:

- Industrial enterprises
- Energy-producing enterprises
- Wastewater and drinking water treatment plants
- Authorities
  - Danish Environmental Protection Agency
  - Danish Energy Authority
  - Counties
  - Municipalities
  - Customs and Tax Administration
- Other (swimming pools, bathing water, etc.)

Industrial enterprises, energy-producing enterprises, wastewater and drinking water treatment plants, as well as other users of environmental chemical data have their main demand driven by legislation. The requirements are data for control of air emissions, ambient air quality, and effluents (wastewater), as well as control of drinking water quality to be provided as part of the authorities' surveillance. These analyses are required by legislation to be performed by accredited laboratories.

Wastewater and drinking water treatment plants in addition need data for the operational control of the plants. Such analyses may be performed by the plants themselves (self-monitoring or operational control) or by accredited laboratories.

The authorities' need for data is driven by the legislation to control the enterprises and treatment plants mentioned above, in many cases to estimate taxes and duties based on emissions, and needs for monitoring of the state of the environment. These analyses are required by legislation to be performed by accredited laboratories.

Research and image nursing for enterprises form a small part and is not regulated by legislation.

2.3.3.3 Metrological traceability

Most environmental analyses deal with traceability of values from quantitative chemical measurements, i.e., measurements of concentration or content, but there are several problems associated with establishing traceability. The problems are related, among other things, to the indirect calibration of instruments and to the necessity in many cases of liberating or extracting a component from the matrix.

The traceability of measurements within Environmental Chemistry is primarily obtained by the use of certified reference materials. For most measurands related to environmental management, it is difficult to establish traceability to an SI unit. Instead, one must rely on the precision and trueness of analytical methods, supported by the absolute metrological control of measuring instruments wherever possible. The "calibration"/control of analytical capability ensures that the instrumental measurements produced by individual laboratories working within a system of laboratories are comparable. By these means, within the science of environmental management and control, a kind of traceability of measurements, analyses, and tests is achieved. However, traceable or comparable calibration is not sufficient to ensure that measurements are comparable, especially for solid samples and complex water matrices. The reason is that the larger part of measurement uncertainty is associated with isolation of the component from the sample matrix.

Certified reference materials are produced for a limited number of measurands within the environmental field. Of these, traceability to a primary standard is only secure for a few measurands, e.g. some trace elements. CRMs exist for a number of measurands and matrices for which traceability to an SI unit can only be secured by specifying the prescribed measurement procedure, e.g. biochemical oxygen demand (BOD) and chemical oxygen demand (COD). The certified value in such a case relies on comparable measurement results and the use of a given standardized procedure. For these measurands, the comparability is strictly depending on the availability and the use of well-described analytical procedures.

A major problem in Environmental Chemistry is the variety of matrices included and the variety of interferences that may compromise trueness if not correctly addressed during the procedure. Having proved traceability in one matrix does not guarantee that the demand for trueness is fulfilled for other matrices.

Furthermore, there is the complex of problems concerning representative sampling. It is a challenge to create traceability within environmental sampling.

2.3.4 Present resources

The field is comprehensively standardized though standard reference methods although many measurands still lack sufficient reference procedures that cover both sampling in and extraction from the relevant matrix.

2.3.4.1 Proficiency testing schemes

Ring tests or proficiency testing schemes are available, but only for some measurands and matrices, and generally not for sampling.

- Drinking water, fresh water, and wastewater
  - PAH, phthalates, softeners, pesticides, halogenated aromatic compounds, aromatic hydrocarbons, phenols, trace elements, organic matter, nutrients, other inorganic components, etc.
- Soil, sludge, sediment
  - Oil, PAH, nutrients, trace elements, etc.
- Air emission
  - Fly ash (trace elements) – none exist on filters (and sampling is not included).
  - Some organic and inorganic gases in pressurized gas cylinders (but not in the correct matrix)
  - Solid sorbents (primarily activated carbon) with organic substances (but sampling is not included)
- Ambient air quality
  - Synthetic rainwater samples containing inorganic measurands (international)
  - Synthetic prepared filters for measurement of sulphate concentration (international)

- Solutions for analysing nitrogen dioxide (international)
- Organic and inorganic gases; sampling from a common manifold (international)
- Possibilities for comparison with an ozone photometer, which is traceable to the primary NIST standard (USA) (A photometer is available in Stockholm and in Paris.)

Most of these proficiency testing schemes are available from Danish providers. For the more specialized measurands it is difficult to establish national schemes due to the low number of potential participants. For the marine environment an international proficiency testing scheme, QUASIMEME, is available. In other areas, international proficiency testing schemes are available; however, for many measurands it can be difficult to find schemes with concentration levels that are sufficiently low for the needs according to monitoring and surveillance programmes in Denmark. It is important to strengthen national proficiency testing programmes for the majority of measurand/matrix combinations.

The level of traceability in the schemes varies. Since traceability is not well established in the environmental sub-field, the assigned values (conventional true values) are only rarely traceable. When assigned values are traceable, the matrix in most cases does not represent the environmental samples well since traceable assigned values are only established for samples prepared from pure chemicals and clean water.

2.3.4.2 Reference materials

Certified reference materials are available in some areas, but certainly not covering every substance and every matrix. During the last five years the number of available CRMs has increased, primarily for the well-known pollutants, such as inorganic constituents, polycyclic aromatic hydrocarbons, and polychlorinated biphenyls. However, as the field is heavily regulated there is an increasing need for new CRMs for a number of matrices and measurands in order to fulfil demands from the authorities and ensure confidence. Similarly to the situation for proficiency testing, the reference materials available internationally are often at high concentrations compared to the needs for Danish monitoring and surveillance.

The European Coordinating centre for Reference Materials (VIRM) is established with participation from Denmark. The aim of VIRM is to facilitate communication between stakeholders in the area of Reference Materials.

2.3.4.3 Laboratories

The Danish laboratories are well equipped, and have skilled and highly educated personnel. All laboratories operating in areas covered by legislation or public monitoring networks are accredited, and must be so according to legislation for quality of measurements. In addition, a number of non-accredited sampling and analyses are carried out. The laboratories produce high-quality work, even though the fact that the users often focus on price rather than the quality of the result poses a risk of a downward tendency in the quality of the results from this field. The total annual revenue of sampling and analyses carried out is estimated in the table below. The estimates include both sampling and analyses, and also activities carried out as part of process control.

Estimated total annual revenue of environmental sampling and measurement

Sector	Estimated total annual revenue / MDKK
Air emission	55
Ambient air quality	13
Water, soil, sludge, sediment, biota, and waste	400 – 500

2.3.4.4 Reference laboratories

The following laboratories function as reference laboratories in the sub-field of sampling and environmental chemical analyses in Denmark:

- Water, soil, sludge and sediment - organic micropollutants: National Environmental Research Institute (NERI) (name: the Danish Environmental Protection Agency's Reference Laboratory for Xenobiotics)
- Water, soil, sludge, sediment and waste - other environmental chemical measurands: Eurofins A/S (name: the Danish Environmental Protection Agency's Reference Laboratory for Environmental Chemistry)
- Air emissions: FORCE Technology (in collaboration with Eurofins Denmark) (name: The Danish Environmental Protection Agency's Reference Laboratory for Air Emission Monitoring)
- Ambient air quality: National Environmental Research Institute (NERI), Department of Atmospheric Environment

However, only Eurofins A/S produces certified reference materials (water and solid matrices) on a regular basis. Other functions of the reference laboratories are to carry out method evaluations, contribute to international standardization, develop quality assurance instruments, and to function as advisors for the Danish EPA within their area of expertise. These activities are performed in collaboration with similar institutions in other countries and international bodies to ensure international comparability and harmonization. The reference laboratories also organize proficiency testing.

2.3.5 Requirements

Even though the number of certified reference materials have increased over the last few years, the number is still far from sufficient to cover all necessary matrices and compounds. The number of possible matrices is large and the diversity within each type of matrix considerable. Regarding the measurands, their number is also large. In principle every chemical invented, including its by-products and degradation products, may prove hazardous to the environment and therefore need to be analysed in one or more matrices. However, in practical terms the measurands needing frequent analysis number in the order of 200 different measurands each of which is measured in one or more matrices.

It is therefore evident that the number of possible matrix/measurand combinations is very large. Furthermore, for several compounds and matrices it is not possible to prepare stable reference materials. It is therefore necessary to establish a connection between standards of pure compounds and reference materials.

There is a need for strengthening the role of the national reference laboratories by ensuring that capability for traceable analyses and ambitions for monitoring and surveillance programmes coincide, nationally and internationally.

2.3.5.1 Certified reference materials

Reliable and comparable measurements are especially important where data are used for legal purposes. In the field of drinking water, the Drinking Water Directive (Directive 98/83/EF) includes a variety of inorganic as well as organic properties. For the Water Framework Directive (Directive 2000/60/EF), the number of parameters as well as matrices is even larger. Reference materials are available for most inorganic constituents, including a number of trace elements, but very few are available for organic micro pollutants. It would therefore improve the application of the Drinking Water Directive, the Water Framework Directive, as well as the resulting national legislation, if new reference materials for organic micro pollutants relevant to the directives were available.

2.3.5.2 Widening the applicability of reference materials

In order to cope with the insurmountable number of possible combinations of matrix and measurand, especially for solid matrices, knowledge on the possibilities for extrapolation from a reference value in a specific certified reference material to other matrices within the same type of matrix or to similar matrix types could potentially reduce the number of reference materials needed. Similarly, it is probably possible to extrapolate from a reference value for a measurand to another measurand of similar chemical structure. This option is only relevant for organic pollutants, but since the large number of measurands is in this field, the possibility may prove attractive.

2.3.5.3 Uncertainty of sampling

Investigations of the uncertainty due to sampling are needed. An operational method of sampling of wastewater is relatively well described in an International Standard from ISO. However, very limited data are available on the uncertainty of sampling of wastewater as well as for other matrices. Furthermore, the establishment of uncertainty estimates in each sampling situation is not considered feasible for routine sampling. It is therefore recommended that a model for estimating the uncertainty of sampling of wastewater be set up and tested on well-described and representative sampling situations. The aim is to provide standard uncertainties for unit operations related to sampling. A model would promote the establishment of similar models for other matrices.

2.3.5.4 Air-emission test centre and proficiency testing schemes

An increasing use of on-line monitoring for air measurements demands facilities for calibration of on-line monitors, either by certified reference gases at the same level of concentration as the measurements, or more concentrated reference gases and a laboratory with a documented gas-phase dilution system.

Invitations to ring tests should be issued on a regular basis. Within air emissions it could be relevant to have one to two rounds of ring tests a year with selected measurands and matrices either in a test centre or at relevant industrial enterprises. Ring tests at enterprises can only be performed at very large plants with sufficient space and sampling ports in the stack. One major problem with ring tests at enterprises is that a reference value is not available.

Only one or two test centres for hot and wet flowing gases containing particles (flue gases) are available in Europe and none in Scandinavia. There is one test centre in Denmark for inorganic and organic gases in dry, cold (20 °C) flowing air (Eurofins Denmark A/S). A test centre with possibilities for hot and wet gases (flue gases) and dosage of particles and chemical substances (all traceable) could prove a very good investment. It will increase the quality of sampling and analysis and also provide a basis for development of new methods and validation of methods. It could make Scandinavia the North European alternative.

2.3.5.5 Coordinating centre

As described in previous sections, there are at present four reference laboratories active in the subfield in Denmark. A formal collaboration between these laboratories would improve development efforts and would increase international influence. The primary aim of this collaboration could be dissemination of traceability to Danish accredited laboratories. The collaboration could be established as a coordinating centre with joint projects and a joint user interface.

2.3.6 Future needs

2.3.6.1 Certified reference materials

It is estimated that development of reference materials covering the organic micropollutants mentioned by name in the directives as well as 10-15 of the most important pesticides would require the equivalent of five man-years in total. International cooperation is called for, and it is recommended that Denmark participate with focus on those measurands for which the conditions in relation to concentration level and matrix require special consideration. It is estimated that there is an annual requirement for Danish contribution equivalent to two man-years.

2.3.6.2 Widening the applicability of reference materials

A pilot project to investigate the feasibility of extrapolation of certified reference values is estimated to require the equivalent of one man-year.

2.3.6.3 Uncertainty of sampling

It is estimated that the equivalent of half a man-year plus cost for analyses equivalent to 0,3 MDKK is required to establish and test a model for uncertainty of sampling.

2.3.6.4 Air-emission test centre and proficiency tests

Establishing a test centre is estimated to require in the order of 1,5 MDKK expenses (hardware, facilities, etc.) plus 0,7 man-years annually. In addition there will be annual costs for proficiency testing to be covered by participating laboratories.

2.3.6.5 Coordinating centre

It is estimated that one man-year annually will be necessary to establish the formal collaboration.

2.3.7 Recommendations

It is recommended to establish a coordinating centre comprising the present reference laboratories within Environmental Chemistry. The activities of the coordinating centre are described below. It is possible to perform these activities without establishing a coordinating centre, but formal collaboration is recommended to increase effectiveness and visibility. The coordinating centre will furthermore allow improved coordination among the reference laboratories, for example regarding advisory functions to authorities in matters general for Environmental Chemistry.

The reference laboratories are presently required to be centres of excellence, capable of improving, developing, and testing methods for analysis, sampling, and tools for quality assurance according to the needs in EU directives and national legislation. It is recommended that these activities be continued and even developed as needed:

- Research and development of certified reference materials

  It is recommended to increase the number of certified reference materials, especially in relation to the Drinking Water Directive and the Water Framework Directive. This task should be carried out by international cooperation.

- Widening the applicability of reference materials

  It is recommended to implement research with the aim of widening the applicability of reference materials, thereby contributing to reducing the need for different materials. The aim is twofold: testing the possibility for widening applicability and developing procedures to be used by laboratories to demonstrate applicability of a reference material. It is recommended to use one or more trace elements (for example copper) in a solid matrix as a model. Trace elements are suggested because a number of reference materials already exist and trace elements are stable compounds. The research would cover the following points:

  - gathering and processing existing information from production of available reference materials and the international literature;
  - developing a procedure to be used in investigation of the range of applicability of a reference material; and
  - testing of the procedure on the model measurand(s), and as required amending the procedure.

- Establishing a model for estimation of the uncertainty of sampling. The research on establishment of a model will include:

  - selection of strategy for estimating uncertainty;
  - selection of sites for testing the strategy on actual wastewater sampling, as a pilot project; and
  - experimental investigations.

- Establishment of an air-emission test centre providing:

- facilities for hot and wet gases (flue gases), dosage of particles, and chemical substances; and
- inter-laboratory comparison (ring tests) on air emissions.

2.3.8 Elements of the metrological reference system for Environmental Chemistry

Element	**Examples**
Primary standard	Only available for a limited number of measurands
Traceability dissemination	Certified Reference Materials
Relevant interval and uses	Amount of substance (10^{-9} – 10^{6} mole), mass (10^{-2} - 10^{5} kg) Amount of substance concentration approx. 1 mol/m^3 mass fraction approx. (1-10 000) mg/kg mass concentration (1-1000) µg/l main component > 10^4 mg/kg 10^2 mg/kg < secondary component < 10^4 mg/kg 10^{-4} mg/kg < trace component < 10^2 mg/kg Amount of substance (air emissions) Dioxins, PAH, PCB: 0.001-30 ng/m³ Trace elements: 0.05-100 µg/m³ Other parameters: 100 µg/m³ - 1 g/m³
Relevant written standards	Standards according to DS, EN, ISO, DIN, USEPA, National Standard Reference Methods, etc.
International fora	CEN, ISO, DIN, USEPA, Standard Methods, etc. IUPAC, Eurachem, Eurolab, EuroAirlab
International comparisons	May be found in the database: www.eptis.bam.de
European fora	CEN, DIN, Helcom/ICES, Eurachem, Eurolab, EuroAirlab, VIRM
Nordic fora	Collaboration between Baltic countries Nordtest Collaboration among Nordic Reference laboratories
Facilities in Denmark	Reference laboratories and accredited (commercial) laboratories
Needs of industry	Comparability and trueness (Certified Reference Materials)

2.4 Food Chemistry

2.4.1 Summary

Food Chemistry within EUs legislation has been a well-regulated area for many years compared to some other areas of chemical analysis. Quality assurance including metrological traceability has been subject to international activities for a long period. The establishment of EU Reference Laboratory networks in specific control areas made it possible to establish appropriate methods for analysis, reference standards, and comparison between national reference laboratories. The use of accreditation of laboratories, proficiency testing, and reference materials have been implemented several years ago.

Food Chemistry is a complex subject covering a large number of different sample matrices, analytes, and a wide interval of concentration levels of the individual analytes. As a result, the number of needed certified reference materials is staggering and consequently there is an ongoing need for establishing supplementary reference materials. Due a lack of certified reference materials, participation in proficiency testing programmes is an important activity for food control laboratories in order to assure an acceptable quality of analytical results. However, as the number of laboratories in Denmark in the sub-field of Food Chemistry is limited, the Danish reference laboratory has concluded that proficiency testing programmes exclusively with Danish participants would in most cases be of poor quality. It has therefore been decided, that Danish laboratories should predominantly use international, well-established (preferably accredited) proficiency testing programmes, such as, FAPAS.

2.4.2 Introduction

In the area of food related analysis in general, important questions, such as quality assurance including traceability, have been subject to international activities.

Codex Alimentarius Commission (CAC)

With the purpose to develop written standards for Food Chemistry, The Codex Alimentarius Commission (http://www.codexalimentarius.net) was created in 1963 under FAO/WHO.

The main purpose of this Programme was - and still is - to protect the health of the consumers, to ensure fair practice in the food trade, and to promote coordination of all food-standards work undertaken by international governmental and non-governmental organizations. Activities on quality assurance of analytical results are carried out by different Codex Committees, i.e. Codex Committee on Pesticide Residues (CCPR) and Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF). However, the most important committee for horizontal subjects is the Codex Committee on Methods of Analysis and Sampling (CCMAS). Major tasks of this committee are to define criteria appropriate to Codex Methods of Analysis and Sampling, and to serve as a coordinating body for Codex with other international groups working on methods of analysis and sampling, and quality assurance systems for laboratories. Recently guidelines on requirements for laboratories carrying out analysis in the field of import/export control of food have been adopted by the CAC. A major requirement of these guidelines is that the laboratories have to be accredited in accordance with an internationally accepted standard and have to join ILC's (Inter-Laboratory Comparisons).

EU Reference Laboratory networks

Within the framework of EU legislation, various EU Reference Laboratory networks have been established. Each network consists of a Community Reference Laboratory (CRL) and National Reference Laboratories in individual member countries (NRL's). The CRL is responsible for activities such as coordination of development of appropriate methods of analysis, establishing of reference materials, and comparisons between the NRL's. Activities of the NRL's are directed towards national control laboratories in order to ensure comparability between analytical results obtained by different control laboratories within each country.

Nordic Committee on Food Analysis (NMKL)

NMKL is a Nordic organization, founded as early as 1947, consisting of food analysts - microbiologists, chemists, and sensory analysts - from Denmark, Finland, Iceland, Norway and Sweden. The committee's primary objective is to select, validate, approve, and publish methods for the analysis of foods. Performance characteristics are initially assessed in collaborative studies, arranged by NMKL or other cooperating international organizations. In recent years, the establishment of procedures and guidelines regarding quality assurance has been added to NMKLs working programme.

2.4.3 Overview and definitions

Food Chemistry covers qualitative and quantitative determinations of food constituents, such as, proximates, vitamins, minerals, food additives, inorganic impurities, organic impurities, mycotoxins, pesticides, veterinary drug residues, together with determination of metabolites and reaction products. Furthermore, analysis in relation to identity and purity of materials added to food are included.

The sub-field is regulated partly through EU directives and/or regulations and partly by national rules. While, with respect to EU food standards, in many cases specific reference methods have been drawn up, the tendency for other relations is to draw up performance criteria that methods have to comply with.

Analyses are performed by official laboratories, commercial laboratories, and laboratories at individual manufacturers.

Laboratories carrying out analyses in relation to official control have to be accredited in accordance with ISO/IEC 17025.

Sample matrices cover all kinds of food material ranging from raw materials, such as meat, fruit, vegetables, and milk, to processed food, such as meat products, fats and oils, beverages, and ready-to-eat dishes.

The levels of individual analytes in different matrices often cover an interval of several decades. Furthermore the samples received at laboratories are often complex and have poor homogeneity.

Analytical techniques used in the field include both organic and inorganic analyses, including:

- spectroscopy (IR, UV/VIS, ICP-OES, ICP-MS, AAS),
- chromatography (HPLC, GC, TLC with various detectors, such as FID, EC, MS, RT),
- titrimetry,
- microbiological procedures,
- ELISA, and
- PCR.

2.4.3.1 Problems of defining the measurand (exemplified by fish analysis)

Stating an analytical result as the value and measurement uncertainty of **system-component-quantity** is highly recommended within the field of food analysis, but definition problems often arise regarding all three elements. The system often comprises one or more highly heterogeneous entities, e.g. a barrel of fish, where severe sampling problems arise. Even considering a single fish the “system” poses a problem as analysis often is made on a part of the fish only. Most chemical and physical properties of the fish muscle are unevenly distributed, causing another contribution to sampling uncertainty.

The component may be a well-defined chemical substance, but often reports on protein or fat content are asked for. The result of analysis for such components is highly dependent on the method used, e.g. Kjeldahl degradation/titration or staining with coomassie blue, and/or the extraction procedure. Results are dependent on the amino acid composition of the protein or the polarity of the lipid, and comparison of results is only meaningful when similar measurement procedures have been used.

The quantity most often has to be relative in order to be useful, but relative to what? Sometimes a quantity, e.g. amount of substance, is related to the sample mass of dry material, sometimes to the so-called wet weight, sometimes to the protein mass). Definition and determination problems regarding this “denominator quantity” obviously present serious obstacles to obtaining traceability. For better-defined, more homogeneous systems than solid food matrices, e.g. liquids such as milk, a concentration may be appropriate.

Classes of methods used by laboratories working with fish-food and research

- Standard methods published by organizations like NMKL, IUPAC, AOCS and AOAC.
- Local methods, often modified versions of former standard methods and used traditionally for many years.
- Instrumental, calibrated methods based on, e.g., spectroscopic signals and a (multivariate) calibration model, which in many cases is managed by an independent company.

The classes Local methods and Instrumental methods also encompass methods developed as research projects or part of research projects. Such methods may have been tested in a collaboratory trial programme (a ring test) but are often published in international journals based on the work in the developing laboratory only.

Few international stable measurement standards exist. Most calibrations are done by the use of solutions with distilled (or demineralized) water, mixture of water and organic substances, or so-called pure organic solvents. Batches of analytical grade chemicals are often used, but seldom purified further or checked for impurities, e.g. water absorbed from the air. Laboratory balances are checked by service personnel, using certified weights. Some common quantities such as dry matter content, drip loss, liquid holding capacity, and total lipid content make use of weighing only or weighing combined with extraction.

Quantitative chromatographic methods most often use peak areas of external and/or internal standards for quantification. In addition to the uncertainty in the concentration of these standards, the peak-area calculations contribute to the total uncertainty and sometimes also introduce a bias. Often, the uncertainty in peak-area values is by far the highest.

Sensory analysis is unique to the sub-field of Food Chemistry. For calibration of the assessor panel, standardized methods and procedures are used. Standard solutions are most often made locally in the sensory laboratory from dry batches of analytical grade chemicals and distilled water by the use of a calibrated balance and volume apportion equipment. The fundamental attributes salt, sweet, acidic, and bitter are calibrated by aqueous solutions of sodium chloride, sucrose, citric acid, and quinine (or caffeine), respectively.

2.4.3.2 Users

- Public control organizations
- Industry and trade
- Research laboratories

2.4.3.3 Metrological traceability

Traceability of measurement results is obtained by means of certified reference standards (pure substances) and/or certified reference materials (preferably food matrices) where possible. Certified reference standards and certified reference materials are obtained from a variety of suppliers, such as IRMM (EU), National Institute of Standards and Technology (USA), National Research Council Canada, National Institute of Environmental Studies (Japan), and CPI-International (Netherlands).

2.4.4 Present resources

Resources are included in the total resources for the quality systems in the individual laboratories, but cannot be specified.

2.4.5 Requirements

Certified reference standards exist for a major part of analytes, but certified reference materials are lacking for a wide range of combinations of analytes, matrices and concentrations levels.

2.4.6 Future needs

Additional resources should be provided for production of new reference materials.

2.4.7 Recommendations

As described above, the sub-field of Food Chemistry is very complex with respect to analytes, matrices and concentration levels. It is therefore impossible to cover the total need for acceptable certified reference materials. CRMs from pure substances exist for the major part of analytes, but are lacking for a wide range of combinations of analytes, matrices, and concentration levels. International suppliers should be urged to develop more reference materials with a wider range of combinations of analytes, matrices, and concentration levels.

Reference (matrix) materials in most cases are easier to handle than normal food samples. The use of reference materials is therefore often not sufficient to ensure that a laboratory obtains correct results on food samples. For this reason, food laboratories in addition to using CRMs must also participate in proficiency testing. Acceptable proficiency testing schemes exist for a major part of the food chemistry sub-field, but still some analytes are only partly covered. The schemes should be urged to cover the deficient areas.

It may be concluded that funds are needed for a great number of new CRMs, since measurement procedures are highly influenced by sample matrix and heterogeneity. There is also an ongoing need for Danish experts to have the possibility of influencing the decision making of schemes in proficiency testing (such as FAPAS, BIPEA), and the production of CRMs.

2.4.8 Elements of the metrological reference system for Food Chemistry

Element	**Examples**
Primary standard	Only available for a limited number of analytes
Traceability dissemination	Certified Reference Materials
External quality assurance	Proficiency testing schemes
Relevant interval and uses	From 1 µg/kg to 10 g/kg All kinds of chemical compounds present in food
Relevant standards	EU directives, Codex standards, NMKL methods, DS, ASTM
International fora	Codex
International comparisons	FAPAS (UK), Livsmedelsverket (Sweden), Bipea (France)
European fora	EU Commission, CEN
Nordic fora	NMKL
Facilities in Denmark	The Danish Food and Veterinary Research is appointed as Danish reference laboratory for a major part of food analysis
Needs of industry	Comparability and trueness

2.5 Pharmaceutical Chemistry

2.5.1 Summary

Pharmaceutical Chemistry covers the qualitative and quantitative analyses provided for marketing drug products. The sub-field is highly regulated by the authorities. The requirements are in general stated in regional pharmacopoeias, which must be followed in order to get a marketing authorization for the products.

In order to develop the metrology in Pharmaceutical Chemistry, uncertainty statements for certified reference materials are needed. Furthermore, mutual recognition of reference materials between the regional pharmacopoeias is recommended.

2.5.2 Introduction

Pharmaceutical Chemistry encompasses qualitative and quantitative determination of specific substances in active pharmaceutical ingredients (API), degradation products, and excipients (auxiliary substances, e.g. additives) as well as properties of the drug product, e.g. pH. Furthermore, analyses of raw-materials are covered by this sub-field.

The sub-field is highly regulated, i.e. authorities prescribe the analyses for raw materials, for intermediate products, and for the finished drug products. The requirements are stated in the regional pharmacopoeias, e.g. the European Pharmacopoeia (Ph. Eur.), the United States Pharmacopeia (USP) or the Japanese Pharmacopoeia (JP). Correspondingly, certified reference materials are provided by the regional pharmacopoeia commissions.

2.5.3 Description of the sub-field

2.5.3.1 Background and definitions

In Pharmaceutical Chemistry analyses are performed by internal laboratories in the pharmaceutical companies or by external, commercial laboratories. A number of the external laboratories are accredited for this purpose. Furthermore, the Danish Medicines Agency is accredited for analyses of active pharmaceutical ingredients and drug products.

The sample matrices are ranging from aqueous solutions, e.g. solutions for injection, to solid preparations, e.g. tablets. The size of the molecules determined ranges from small (e.g. steroids) to very large (e.g. proteins).

The qualitative determinations cover identification of active pharmaceutical ingredients and known impurities. The analytical techniques used cover, e.g.,

- physical tests (melting point, boiling point),
- general chemical identification reactions of ions and functional groups,
- infra-red spectroscopy, and
- chromatography (TLC).

The quantitative determinations of content are generally referred to as assays. The analytical methods in use are in the majority of cases dedicated to the determination of a specific measurand, e.g. concerning the active pharmaceutical ingredient. Sample preparations may be more or less extensive ranging from simple dilutions of the sample to extractions of the substance from the matrix.

The analytical techniques used in the field include both organic and inorganic analyses. The instrumental methods include, but are not limited to:

- titrimetry,

- spectroscopy (UV/VIS, fluorescence, NIR, AAS, mass),
- chromatography (GC, HPLC), and
- electrochemical methods (for the quantities pH and conductivity).

2.5.3.2 Users

Measurement results obtained in Pharmaceutical Chemistry are typically used for quality control purposes during the development, production, and final assessment of active pharmaceutical ingredients and drug products. Furthermore, authorities request continuous assessment and documentation of the stability of a drug product throughout the shelf life in order to ensure patient safety.

2.5.3.3 Metrological traceability

Traceability of measurement results is obtained by means of reference materials or reference spectra (for identification purposes only). The reference materials are mainly available as pure substances or as formulated products. In situations where the measurand is not related to an active pharmaceutical ingredient, commercial reference materials are used.

The U.S. Pharmacopeia (USP) and the European Pharmacopoeia (Ph. Eur.) certify and distribute a large number of reference materials. The chemical reference materials certified by USP are denominated Reference Standards and chemical reference materials certified by Ph. Eur. are denominated Chemical Reference Substances. Furthermore, WHO issues a number of reference materials with assigned values for the biological activity. Some reference materials, e.g. protein substances, were formerly certified on the basis of their biological potency. However, these reference materials are now used for chemical analyses with the same certified value but with a different purpose of the analyses, i.e. determination of the chemical properties of the substance instead of the biological potency of the substance.

Reference materials are available for substances for which a quantitative determination of content is described in the relevant pharmacopoeial monograph.

The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of the European Union, Japan, and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects in developing new pharmaceuticals for human use. However, there is no tradition for coordination of the availability and certification of reference materials between the pharmacopoeias.

The reference materials are distributed without certificates and without stated uncertainties. The uncertainty is not stated due to a note in the ISO Guide 34 saying that: "... the uncertainty of their assigned values is not stated since it is negligible in relation to the defined limits of the method-specific assays of the pharmacopoeias for which they are used". As a consequence of this, the uncertainty of the stated values of the in-house reference materials used in the pharmaceutical industry can not be evaluated properly.

The reference materials distributed by USP are supposed to be used as 100 % pure substances after drying. Protein substances have certified values stated as content per vial or content per mg "as is" (without drying).

2.5.4 Present resources

The resources needed to obtain the metrological level expected by the authorities today are realized by the pharmaceutical companies and the regional pharmacopoeia commissions. The pharmacopoeia commissions are responsible for elaboration of monographs and certified reference materials. Generally, this is made in cooperation with the pharmaceutical companies.

2.5.5 Requirements

Requirements regarding conductivity measurements are covered by section 2.1.

For determination of the identification or the potency of a drug product approved by the local authorities for sale in a specific geographical area, it is required to use the reference substance certified by the Pharmacopoeia covering that area. The number of reference substances issued by the pharmacopoeias increases with the number of registered active pharmaceutical ingredients.

In order to ensure comparability of measurement results over time and space it is required that the uncertainty of the certified values is estimated according to the internationally accepted guidelines and that the uncertainty is stated on a certificate.

2.5.6 Future needs

The resources needed to develop the sub-field can be realized by means of representatives from the industry and the Danish Medicines Agency working with special focus on metrological issues in relevant working groups, scientific committees, and pharmacopoeial expert groups.

It is estimated that the equivalent of at least one man-year per year is necessary to obtain the implementation of the recommendations.

2.5.7 Recommendations

Active pharmaceutical ingredients are usually produced by a limited number of companies and the analytical methods used for quantifying the content of active pharmaceutical ingredients are dedicated to the specific substance. Therefore, establishment of reference or primary laboratories within this field is not relevant.

Of the more generally used analyses, pH measurements are covered by the present primary laboratory. The sub-field will, however, benefit from the establishment of a primary laboratory for conductivity.

There is a need for uncertainty statements of certified values for the reference materials in order to improve the comparability of measurement results for drug potency and stability.

Mutual recognition of reference materials and comparison between existing reference materials from the different pharmacopoeias would support the development of metrology in the area.

Proposal

In accordance with the recommendations in Resolution 11 at the 21st Conférence Générale des Poids et Mesures (1999) it is proposed that the CCQM Bioanalysis Working Group consider the need for a global system for traceable measurements in the field of pharmaceutical products. In particular it is proposed that the global acceptance of reference materials issued by national or regional pharmacopoeias could be facilitated by the organization of a key comparison of the content of active substance in representative products of economic importance.

A table of elements of the metrological reference system is not applicable to this sub-field.

2.6 Laboratory Medicine

2.6.1 Summary

Laboratory Medicine in Denmark annually provides many millions of results for a great number of different properties of various systems and consequently incurs large public expenses. The diversity and scattered sites are the reasons for the need of another structure of metrology in Laboratory Medicine than in some other metrological sub-fields.

Denmark has the experts, the interest, and the enthusiasm within the laboratories, and their scientific research is internationally recognized, but the appointment of reference laboratories has to be formalized and organized in order to be internationally recognized.

Therefore the establishment of a centre for coordination of reference laboratories is recommended.

If this is achieved, we can sell our know-how and fulfil legal and regulatory demands within Denmark and strengthen the harmonization of Laboratory Medicine in the Nordic countries as well as globally.

A prerequisite is that laboratories get funding to obtain accreditation or an analogous recognition to develop the metrology in their research area, for instance in the form of reference procedures, and to assign reference values to reference materials.

If the recommendations in this part of the plan are followed, the improvements will have great impact on laboratory outcome and patient care, not least because they are prerequisites for comparability of results in the electronic patient journal.

2.6.2 Introduction

Currently, higher levels of metrology in Laboratory Medicine are not organized nationally, but coordinated within the Nordic countries on a voluntary basis to obtain metrological traceability and comparability.

Participation in international committees or working groups takes place more or less sporadically. Denmark has a key position in producing reference materials with a native matrix, but assigning reference values for selected properties is done elsewhere.

In order to obtain and maintain common traceability for values of properties being analysed in Laboratory Medicine, reference materials are needed for:

- internal quality control,
- external quality assurance, and
- calibration.

All of these materials need values assigned by reference measurement procedures.

2.6.3 Description of the sub-field

Laboratory Medicine encompasses several disciplines. In this description the following are included: Clinical biochemistry, clinical genetics, clinical haematology, clinical immunology, clinical microbiology, clinical pharmacology, clinical physiology, nuclear medicine, forensic medicine, including forensic chemistry and forensic genetics, laboratories in occupational health, pathology, and veterinary laboratory medicine.

2.6.3.1 Background and definitions

Laboratory Medicine is characterized by the examination of many different properties in various systems, for instance:

In *clinical biochemical laboratories* blood, plasma, urine, faeces, saliva, cerebrospinal fluid, and hair from humans are investigated. Usually 100 – 150 types of quantities are being analysed on a daily basis, while 500 ore more quantities are being regularly analysed.

In *microbiological laboratories* a huge number of pathogenic micro organisms, bacteria, vira, fungi, prions, etc. are being identified.

In *forensic laboratories* all kinds of human material are systems for investigation, including identification of an enormous number of DNA sequences and a huge number of legal or illegal drugs. In addition, drugs themselves as well as all environmental material are systems for investigation.

In *veterinary medical laboratories* many systems from all kinds of domestic and some wild animals are being investigated.

For many of the clinical biochemical properties, primary reference procedures of examination could in principle establish traceability to SI units or to other approved metrological references.

Globally, for the vast majority of these properties, there are no primary or reference laboratories offering measurement capabilities and there are no nationally or internationally recognized reference procedures.

For some of the clinical properties, international reference materials have been produced and categorized as such by WHO, NIST, or IRMM.

For a few of the clinical biochemical properties, agreement has been reached upon international reference procedures, as for instance in IFCC.

The introduction of the IVD Directive, through its requirement for traceability, should bring many measurement results to agree better.

The concept of reference laboratory is under discussion by a working group under JCTLM preparing draft requirements for being recognized or nominated as either a primary or a reference laboratory.

The demands may be that such a laboratory follows a quality manual; is able to work according to ISO/IEC 17025 (calibration level), or ISO 15195; and possesses scientific skills to fulfil the requirements of metrological traceability to a recognized stated reference, usually a measurement unit, and to obtain a suitably low measurement uncertainty in the determination of the property.

2.6.3.2 Users

Reference laboratories are needed by several types of user for assigning reference values to reference materials because these are prerequisites for

- the standardization and harmonization of clinical laboratory examinations of individual patients (whether human or animal),
- epidemiological studies (whether human, animal or environmental),
- laboratories documenting their analytical quality in order to obtain accreditation,
- laboratories tracing the reason for odd (unexpected) examination results,
- industry to fulfil demands of the IVD Directive in the production of reference materials, including calibrators, and
- organizers of external quality assurance.

Furthermore, for legal or regulatory purposes, health authorities, the court, sports organizations, or employers directly or indirectly may ask for investigations performed at medical reference laboratories.

2.6.3.3 Traceability

See 2.6.4 Present resources and 2.6.8 Elements of the metrological reference system.

2.6.4 Present resources

Thanks to a well established Nordic cooperation within NFKK and the Nordic EQAS organizers, a common Nordic certified reference material has been produced, which is the basis for the recently (2003-2004) established common Nordic biological reference intervals for 24 properties in serum and some in blood.

Essential for the project is that the reference material has a matrix of human serum.

Scientific and technical skills are in most cases adequate or can be established. Equipment is in many cases adequate or can be brought up to date with suitable investment.

2.6.5 Requirements

2.6.5.1 General problems

For many reasons, there is an increasing need for site- and time-independent comparability of results through metrological traceability.

Specifically, a prerequisite for the establishment of the electronical patient journal, comparability of patient results is needed.

Legal demands in the IVD Directive force the manufacturers of equipment and reagents supplying routine medical laboratories to document traceability of assigned values.

The main problem is the lack of higher-level reference material with a suitable matrix and the lack of reference measurement procedures for most of the properties being determined by the medical laboratories.

Denmark is a key contributor in the production of suitable external quality control materials, ensuring comparability between results from different routine measurement procedures. External quality control materials produced by DEKS has for instance been used in the interlaboratory comparison called IMEP 17, arranged by IRMM for medical laboratories in collaboration with BIPM.

Other external quality control materials produced by DEKS have been two control materials (Cal and NFKK reference serum X), which were used as anchors for the trueness of all determinations in all laboratories participating in the establishment of the Nordic common biological reference intervals for 24 properties.

Continuing production of this kind of high quality control material is crucial in maintaining the obtained harmonization as well as for further development of the Nordic cooperation.

The closing of some of the production facilities at the SSI for human blood products is a setback for DEKS and the production of reference materials.

A problem for the research laboratories is to find resources for the specific task of assigning reference values to reference materials.

2.6.5.2 Industrial applications

Producers of calibrators, reference materials, and control materials, as well as EQAS organizers all need reference values assigned to their materials.

2.6.5.3 Legal and other regulatory applications

The examination of properties at the forensic laboratories has judicial impact.

The determination of drugs used for revealing doping has an impact on health in sports and a positive outcome can have serious personal consequences. Due to lack of funds, there is no longer any Danish laboratory recognized as an anti-doping laboratory by the Olympic Committee. This is inconvenient for the organization “Antidoping Danmark”.

2.6.5.4 Reference measurement procedures and materials to obtain traceability

There is a need for development of reference measurement procedures for the main part of properties being investigated within medical laboratories.

International reference measurement procedures allowing traceability to SI units are claimed to exist for

- inorganic ions,
- simple organic molecules, such as glucose, cholesterol, and steroids, and
- enzymes.

International reference materials exist for some peptides and proteins, but their validity are questionable, their stability is unknown, and no uncertainty is provided.

Denmark has several reference laboratories in various areas appointed by Danish ministries or international organizations (EU Commission, EULAR, IFCC, IUIS, OIE, and WHO), as listed in 2.6.8 Elements of the metrological reference system.

The scientific techniques have been improved recently, making assignment of reference values to native reference materials more reliable. It would be natural to utilize the expertise in Denmark and to ensure international coordination and collaboration for such components as drugs, steroids, amino acids, peptides, proteins, and genes.

There is a serious discrepancy between those few properties for which reference procedures or certified reference materials exist to the unsupported 100 – 150 most common properties being examined at clinical biochemical laboratories plus the common properties being examined in other disciplines of Laboratory Medicine.

2.6.5.5 Research

The scientific and technical skills are available in several medical and other laboratories. The existing techniques need to be developed so that they can be applied to the investigation of specific medical properties.

New updated equipment is needed in some cases, as for instance to obtain an adequately low uncertainty in the examination of a property.

2.6.6 Future needs

Medical laboratories have already shown an interest in being recognized as reference laboratories within their specialized area, such as amino acids and related compounds, therapeutic drugs, veterinary properties, as well as in new areas, which for instance utilize gene techniques. In addition, there are laboratories at the periphery of clinical biochemistry with scientific know-how of great interest.

Economical resources are needed in order to utilize the already existing know-how. Due to many years of decreasing budgets, there are no longer neither time nor economical resources to develop reference procedures or to assign certified reference values to reference materials.

All categories of laboratories need economic subvention to obtain accreditation or a status equivalent to that. The scientific research laboratories have no incentive to be accredited.

To demonstrate their academic skills and capability in a global context and in order to gain international acceptance as a reference laboratory, accreditation according to ISO/IEC 17025 (calibration level) or ISO 15195 may be required.

The workload for the coordination of reference laboratories in a centre is estimated to be annually equivalent to one man-year.

2.6.7 Recommendations

Because of the huge number of properties in clinical chemistry, no single laboratory has or can obtain knowledge to be reference laboratory for all properties.

There is a great need to coordinate and govern the future medical reference laboratories in a centre. Each of the reference laboratories covers special knowledge on single properties or on a group of related properties.

Internally, the centre should guide the medical laboratories to obtain international reference laboratory status, and the centre should encourage the laboratories to be accredited.

Externally, the centre should facilitate the requisition of reference values to reference materials for both international and national customers.

The international customers would be the IVD industry, WHO, NIST, and IRMM as producers of certified reference materials.

Denmark has the experts, the interest, and the enthusiasm within the laboratories, but the appointment of reference laboratories has to be formalized, to be structured, and to be organized in order to be internationally recognized.

If this is achieved, Denmark can sell its know-how, fulfil national legal and regulatory demands, and strengthen the harmonization of Laboratory Medicine in the Nordic countries.

2.6.8 Elements of the metrological reference system

Because of limited time, rather few laboratories and relatively few properties are mentioned in the tables below. The tables are meant as examples to illustrate the complexity of the field.

The lists are thus preliminary lists of laboratories having shown an interest in being nominated or appointed as reference laboratories. Laboratories can be removed or added as the sub-field becomes more organized and requirements for inclusion are agreed.

The lists are meant as an illustration of the huge potential in Denmark for reference laboratories in the Nordic, the European, and the Global development towards an agreement on traceability to SI units (alternatively other units) and/or common measurement procedures within the sub-field.

Some of the scientific societies have not provided examples to the lists, but not being mentioned does not mean lack of interest, rather lack of time for clinical immunology, clinical pharmacology, clinical physiology and nuclear medicine, laboratories in occupational health, and pathology.

It should be noted, that if a laboratory has been appointed as a Reference Laboratory, it is specifically mentioned.

Clinical biochemistry

Matrix: Unless otherwise stated, the matrix is blood (plasma or serum).

Component (analyte)	Laboratory	Contact	Comment
Enzymes	Clinical biochemical laboratory at Odense University Hospital	Poul Jørgen Jørgensen	Appointed by IFCC as a Reference Laboratory for enzymes.
Properties primarily associated with auto-immune diseases	SSI	Allan Wiik or Niels Heegaard	Appointed by IUIS as a Reference Laboratory for anti-neutrophilocyte-cytoplasma antibodies and appointed by EULAR, a Standing Committee on Inventive Rheumatology within the European Autoantibody Standardization Initiative, as a Reference Laboratory and organizer of key comparison studies in Europe.
Homocysteine and methyl malonate	Clinical biochemical laboratory at Vejle Hospital	Anne Schmedes	Measurement by LC-MS-MS is established.
Cortisol	Clinical biochemical laboratory at Vejle Hospital	Anne Schmedes	Matrix includes urine.
5-Hydroxy-indolylacetate (HIAA) and vanillyl mandelate (VMA)	Clinical biochemical laboratory at Vejle Hospital	Anne Schmedes	Matrix includes urine.
Calcifediol (25-hydroxy-vitamin D3)	Clinical biochemical laboratory at Vejle Hospital	Anne Schmedes	
Complement C3d	Clinical biochemical laboratory at Vejle Hospital	Ivan Brandslund	Double-layer rocket immunoelectrophoresis
Calcifediol (25-hydroxy-vitamin D3) and Calcitriol (1,25-dihydroxy-vitamine D)	Clinical biochemical laboratory at Aarhus hospital	Lene Heickendorff	ELISA and radio-immuno assay (RIA) respectively
Collagen metabolites	Clinical biochemical laboratory at Aarhus hospital	Lene Heickendorff	ELISA and RIA
5-Hydroxy-indolylacetate (HIAA) and Vanillyl mandelate (VMA)	Clinical biochemical laboratory at Aarhus Hospital	Carsten Schriver Højskov and Holger Jon Møller	HPLC Matrix is urine
Adrenalin and noradrenalin	Clinical biochemical laboratory at Aarhus Hospital	Carsten Schriver Højskov and Holger Jon Møller	Measurement by LC-MS-MS or HPLC Matrix is urine

Component (analyte)	Laboratory	Contact	Comment
Cyclosporin			Measurement by LC-MS-MS
Therapeutic drugs			Components: Tacrolimus, levetiracetam, tiagabin, gabapentin, mycophenolate, sirolimus and topiramat Measurement by LC-MS-MS
Therapeutic drugs			Components: Lamotrigen and oxcarbazepin Measurement by HPLC
M-component			Matrix includes blood and urine measured by CE, IEF and turbidimetry, IEF respectively.
M-component, free kappa and lambda string			Measurement by turbidimetry
Fractionated alkaline phosphatase			Measurement by gel electrophoresis
Fractionated haemoglobin and haemoglobin A1c			HPLC
Steroid hormones		Frode Engbæk and Ebba Nexø	Components: Corticotropin, androstenedion, cortisol, dehydro epiandrosterone sulphate, estradiol, progesterone and testosterone Measurements by competitive and two site immunometric methods
Peptide and protein hormones			Components: Chorionogonadotropin, ferritin, follicle stimulating hormone, luteinizing hormone, prolactin; sexual hormone binding globulin, thyroxin, thyreoidea stimulating hormone, and triiodine thyronin Measurements by competitive and two-site immunometric methods
Antibodies, cancer markers and others	Clinical biochemical laboratory at Aarhus Hospital	Frode Engbæk and Ebba Nexø	Components: Alpha-fetoprotein (*Matrix is blood and amnion fluid), acetylcholin receptor antibody, cancer antigen 125, DNA antibody, immunoglobulin E Measurements by competitive and two-site immunometric methods
Cobalamines and folate			Measurements by competitive protein binding methods

Component (analyte)	Laboratory	Contact	Comment
Cobalamin-binding proteins		Ebba Nexø	Transcobalamine, total and holo, haptocorrin, total and holo, and intrinsic factor auto-antibody Measurement by sandwich ELISA and ELISA
Epidermal growth factor (EGF) system			Epidermal growth factor, tissue growth factor (TGF), alpha, amphiregulin, betacellulin, heparin-binding EGF, HER1, and HER2 (Human epidermal growth factor receptors) Measurement by ELISA and real-time PCR (Polymerase Chain Reaction) Matrix includes blood, urine, and tissue biopsies.
T-tau, P-tau, beta-amyloid and sCD163 (Hemoglobin (Hb) scavenger receptor)		Holger Jon Møller	Measurement by ELISA Matrix includes cerebrospinal fluid for the 3 components and blood for sCD163.
Androgens/estrogens	SSI	Paul Bennett	Measurement by MS will be introduced
Proteins		Niels Heegaard	Measurement by MS
Glucose and haemoglobin	Clinical biochemical laboratory at Odense University Hospital	Ole Blaabjerg	A reference measurement procedure has been developed for haemoglobin, and a reference measurement procedure will be developed for glucose.
Homocystein and methyl malonate	Clinical biochemical laboratory at Skejby Hospital	Jan Møller	Measurement by mass-spectrometry will be introduced.
Cyclosporin	Clinical biochemical laboratory at Rigshospitalet	Anders Holten Johnsen	Measurement by LC-MS-MS
Tacrolimus			
Leukocyte type		Linda Hilsted	Measurement by microscopy
M-component		Lars Bo Nielsen	Measurement by agarose electrophoresis Matrix includes blood and urine.
M-component, separated in class and type			Classes are: IgG, IgM, IgA, IgD and IgE, and types are kappa and lambda. Measurement by agarose electrophoresis

Component (analyte)	Laboratory	Contact	Comment
Hormones		Linda Hilsted	Components: Chromogranin A, gastrin, progastrin, somatostatin and glucagons, pancreas type Measurement by RIA
Pro-Brain natriuretic peptide		Jens Peter Gøtze	Measurement by electrochemiluminiscense and a processing independent method
Protein C and protein S, free		Sixtus Thorsen	Measurements: Two independent methods, enzymatic and ELISA for protein C and latex ligand immuno assay for protein S
Coagulation properties	Clinical biochemical laboratory at Roskilde Hospital	Karin Kynde	The reference measurement procedure for INR has been established.
Porphyrins	Clinical biochemical laboratory at Viborg Hospital	Axel Brock	Matrix includes blood, faeces and urine.
Rheumafactor, IgM	Clinical biochemical laboratory at Sygehus Fyn, Svendborg	Susanne Nielsen	Measurement by ELISA.

Clinical microbiology

The matrix is blood.

Component (analyte)	Laboratory	Contact	Comment
Microbiological examinations	SSI	Helle Bossen Konradsen	Appointed by WHO as Reference laboratory within some areas of microbiology
Parasites		Maiken Cavling Arendrup	Appointed by WHO as Reference Laboratory within some areas of parasitology
Virology		Claus Nielsen	Appointed by WHO as Reference Laboratory within some areas of virology

Clinical biochemistry and genetics

Matrix: Unless otherwise stated, the matrix is blood (plasma or serum).

Disease or component (analyte)	Laboratory	Contact	Comment
Specific DNA tests	Clinical Genetic Laboratory at Skejby Hospital	Lillian Gryesten Jensen	
	Clinical Biochemical Laboratory at Hvidovre hospital	Anne Charlotte Jäger	
Hemochromatosis, hereditary hypercholesterol-aemia and calcium sensing receptor	Clinical Biochemical Laboratory at Aarhus Hospital	Peter Nissen and Lene Heickendorff	Measurements: DNA sequencing, single-strand conformation polymorphism (SSCP), and restriction fragment length polymorphism (RFLP)
Antithrombin, protein C and protein S DNA-sequenation	Clinical biochemical laboratory at Rigshospitalet	Sixtus Thorsen	
Specific DNA and RNA tests		Anne Tybjærg Hansen	Measurements: dHPLC, DNA sequencing and analysis for deletions/duplications by MLPA (multiple ligation-dependent probe amplification). Matrix includes blood and bone.

Forensic medicine

Matrix: Systems of human origin

Examination or component (analyte)	**Laboratory**	**Contact**	**Comment**
Short Tandem Repeat (STR) DNA-tests, forensic genetic investigations	Institute of Forensic Medicine, University of Copenhagen	Niels Morling	Forensic genetic investigations in crime, paternity and immigration cases Appointed by the Danish Ministry of Justice as National Reference Laboratory
Variable Number of Tandem Repeat (VNTR) DNA-tests, forensic genetic investigations			Forensic genetic investigations in paternity and immigration cases Appointed by the Danish Ministry of Justice as National Reference Laboratory
Single Nucleotide Polymorphism (SNP) DNA-tests, forensic genetic investigations			
Mitochondrial DNA (mtDNA) DNA-tests, forensic investigations			
Ethanol in blood		Henning Willads Petersen	Appointed by the Danish Ministry of Justice as reference laboratory (national)

Veterinary laboratory medicine

Matrix: Blood and others

Discipline and component (analyte)	**Laboratory**	**Contact**	**Comment**
Haematology, clinical chemistry, endocrinology, and cytology	Central laboratory, Department for clinical studies at the Royal Veterinary and Agricultural University	Asger Lundorff Jensen	Matrix includes blood from domestic animals (dog, cat, horse, cattle, pig and goat) and wild animals (rat and mouse) plus specified wild animals from the Zoo.
Epidermal growth factor	Clinical biochemical laboratory at Aarhus Hospital	Ebba Nexø	Measurement by sandwich ELISA Matrix includes blood and urine from rat.
Virology, fish diseases	Danish Institute for Food and Veterinary Research	Niels Jørgen Olesen	Appointed by the EU Commission as EU Community Reference Laboratory for Fish Diseases and OIE Reference Laboratory for Viral Haemorrhagic Septicaemia (VHS)
Bacteriology		Frank Aarestrup	Appointed by WHO as Collaborating Centre for Antimicrobial Resistance in Food Born Pathogens
Zoonoses		Dorthe Lau Baggesen	Appointed by the Danish Ministry of Food, Agriculture and Fisheries as National Reference Laboratory in relation to the EU Zoonose Directive and the statute concerning zoonoses

3 Major recommendations

3.1 Reference materials

Electrochemistry and some other sub-fields, e.g. Pharmaceutical Chemistry, need *reference solutions with low conductivity*. It will be one of the research activities in the proposed Centre for Reference Metrology in Electrochemistry.

In Products and Materials, large industries obtain metrological traceability using their own standards or certified reference materials. The sub-field should be developed, so that small and medium-size industries are also covered. It is proposed, that the sub-field be described by a few examples. It is proposed that *an activity plan be developed based on interest and need from the organizations and companies*.

In the sub-field Environmental Chemistry, it is recommended to *increase the number of certified reference materials in relation to the Drinking Water Directive and the Water Framework Directive*. This task should be carried out by international cooperation. It is also recommended to implement research with the aim of *widening the applicability of reference materials*, thereby contributing to reducing the need for different materials. It is recommended that a *model for estimating the measurement uncertainty caused by sampling* is set up and tested on well-described and representative sampling situations, e.g. wastewater.

In the sub-field Food Chemistry, it is recommended to *develop more reference materials with a wider range of combinations of analytes, matrices, and concentration levels*. The use of reference materials is however not sufficient to ensure correct results on normal food samples. Support by quality systems is also necessary.

One of the main problems within Laboratory Medicine is the lack of reference material with a suitable matrix and the lack of reference measurement procedures for most of the properties being determined by the medical laboratories. Denmark is a key contributor in the production of external quality control materials, ensuring comparability between results from different routine measurement procedures. External quality control materials produced by the Danish Institute for Quality Assurance for Laboratories in Health Care, DEKS, has for instance been used in the inter-laboratory comparison called IMEP 17, arranged by IRMM for medical laboratories in collaboration with BIPM. Continuing production of this kind of high quality control material is crucial in maintaining harmonization as well as for further development of the Nordic cooperation. *It is recommended to allocate economical resources to develop reference procedures and assign reference values to certified reference materials*.

3.2 Centres for reference metrology

Establishment of a competence centre is recommended within three of the six sub-fields where laboratories are spread geographically. This will enhance the visibility of the primary and reference facilities, make it possible to coordinate the national and international activities, and increase the effectiveness by collaboration.

It is recommended to set up requirements and procedures for nominating and appointing *a national primary laboratory or a national reference laboratory*. The framework of the Metre Convention requires, that a participating laboratory has the status of being officially ‘designated’. This also influences export of know-how and reference materials.

It is recommended that the two laboratories within Electrochemistry at primary level in Denmark concerning pH and electrolytic conductivity be combined in a Centre for Reference Metrology in Electrochemistry or merged into one primary laboratory at DFM. The purpose of such a centre would be to coordinate the national and international activities, certification, development of reference materials (especially for low conductivities), research and development projects, publications, international meetings, and comparisons. An important aspect is the contact with relevant authorities, e.g. the pharmacopoeia commissions, to provide input to the standardization process and ensure the availability of rigorous calibration methods. The centre should also monitor the user needs for development of techniques within other disciplines of electrochemistry, e.g. needs for redox measurements.

In Environmental Chemistry, it is recommended to establish a centre to coordinate a formal collaboration between the present reference laboratories. Activities of the centre should include establishing of an air-emission test centre, and coordination of research into development of certified reference materials and models for estimation of the uncertainty of sampling.

It is recommended to establish a centre of reference laboratories within Laboratory Medicine to coordinate the efforts from the many skilled laboratories in Denmark. The sub-field has a laboratory working with haemoglobin at the highest scientific level and it should be possible to nominate this laboratory as a primary laboratory. A centre of reference laboratories would make it possible to sell know-how and fulfil legal and regulatory demands. It would maintain the Danish key position in producing external quality control materials and strengthen the harmonization of Laboratory Medicine in the Nordic countries. It would also have a great impact on laboratory outcome and thereby on patient care, by providing comparable laboratory results for the electronic patient journal. The centre should:

- guide medical laboratories in obtaining international reference laboratory status and encourage laboratories to be accredited,
- make it easier to obtain reference values for reference materials,
- provide income from exporting know-how,
- fulfil legal and regulatory demands within Denmark, and
- strengthen the harmonization of Laboratory Medicine in the Nordic region.

3.3 Other recommendations

Pharmaceutical Chemistry: *The pharmacopoeia commissions are strongly encouraged to establish uncertainty statements of certified values for their reference materials*. This will improve the comparability of measurement results for drug potency and stability. Mutual recognition of reference materials and comparison between existing reference materials from the different pharmacopoeias will support the development of metrology in the sub-field. It is proposed, that *Denmark encourages the CCQM Bioanalysis Working Group to consider the need for a global system for traceable measurements in the field of pharmaceutical products*. In particular, the working group should *propose global acceptance of the reference materials issued by national or regional pharmacopoeias*. It could be facilitated by the organization of key comparisons for representative products of economic importance.

3.4 Costs

The table given below gives the estimated costs of establishing and operating a national structure for reference metrology in chemistry as recommended in this Action Plan. The costs are estimated as costs that must be added to the current level of funding. They are separated into costs of establishing facilities (personnel and expenses) and operating costs (personnel only)

Sub-field	**Sub-field**	**ESTABLISHMENT personnel (person-year)**	**OPERATION personnel (person-year)**	**ESTABLISHMENT, Expenses (MDKK)**
Electrochemistry	Centre for Reference Metrology in Electrochemistry		2	
Products and Materials	No data			
Environmental Chemistry	Increasing the number of certified reference materials in relation to the Drinking Water Directive and the Water Framework Directive in international cooperation	5	2	
	Research with the aim of widening the applicability of reference materials, thereby contributing to reducing the need for different materials	1		
	Model for estimating the measurement uncertainty from sampling, tested on well-described and representative sampling situations, e.g. wastewater	0,5		0,3
	Air-emission test centre		0,7	1,5
	Centre for the present reference laboratories		1	
Food Chemistry	No data.			
Pharmaceutical Chemistry	Estimating measurement uncertainties for reference materials and obtaining mutual recognition		1	
Laboratory Medicine	Centre of reference laboratories		1	
TOTAL		6,5	7,7	1,8

4 Conclusion

In Denmark, the metrology in chemistry is decentralized. The sub-fields are dissimilar, and - to some extent - uncoordinated and isolated from each other. The work with the Action Plan has brought people from the different sub-fields together and allowed sharing of experience.

The global metrological traceability to the International System of Units (SI) is insufficient. In some cases, other units than SI units are in use. During recent years, however, there has been an increasing awareness of the importance of having traceability to the SI.

It is characteristic of the subject field that traceability is mostly obtained by using reference materials. It is therefore an important issue for all of the sub-fields to have enough reference materials to meet the demands from industry, society, and science.

It is also characteristic that some of the analytical methods are used within several sub-fields. This is the case for titrimetry, spectroscopy (UV/VIS, fluorescence, NIR, mass), chromatography (GC, HPLC), and electrochemical methods (pH, conductivity).

In some of the sub-fields, there is a need of forming a centre to coordinate the efforts from the sub-field laboratories.

Reference materials

It is concluded, that most of the sub-fields need more reference materials.

In the sub-fields Environmental Chemistry and Electrochemistry, research and development of certified reference materials is recommended.

Although Food Chemistry is an established area, there is a need for more reference materials (and quality systems) to assure traceability and high accuracy.

It was not possible to develop Products and Materials in detail for this Action Plan. Preliminary investigations have shown that small and medium-size industries need reference materials. It is intended to present some examples in the near future.

The sub-field Pharmaceutical Chemistry has enough reference materials, but uncertainty statements are needed. The sub-field also needs mutual recognition of reference materials and comparison between existing reference materials from the different pharmacopoeias. The CCQM Bioanalysis Working Group should consider how to make a global system for traceable measurements in the field of pharmaceutical products. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of the European Union, Japan, and the United States, but there is no tradition for coordination of the certification and availability of reference materials between the pharmacopoeias.

Laboratory Medicine needs a large number of reference materials with assigned values and uncertainties.

Centres for reference metrology

Three of the six sub-fields need a centre to enhance the visibility, coordinate the efforts, and increase collaboration of the geographically spread laboratories, both nationally and internationally.

The two laboratories at primary level in Denmark concerning pH and electrolytic conductivity should be combined in a Primary Laboratory or a Centre for Reference Metrology in Electrochemistry.

The reference laboratories within Environmental Chemistry wish to form a centre to coordinate comparisons, research, and development of certified reference materials.

Likewise, laboratories within Laboratory Medicine recommend establishment of a centre coordinating the future medical reference laboratories.

It would be useful to provide a standing mechanism for nominating and appointing a primary or reference laboratory irrespective of previous mention in a current Action Plan.

About the work process

This Action Plan is not a modification of the former Action Plan; it is a new and more comprehensive treatment of the subject field. Five of the six sub-fields were detailed in this Action Plan. The sub-field Products and Materials should be developed before the work with the next Action Plan is started.

The authors are convinced that the undertakings proposed would meet current requirements of industry and society for providing chemical measurement services at an appropriate international level.
The work with the present Action Plan was performed with enthusiasm by all participants in the working groups and the whole team worked very well together.

5 References

5.1 First action plan

Plan of action for the subject field of metrology: Amount of substance (Danish text) DFM-1992-R5.

Authors

Ole Bjørn Jensen, Cimpexco Scandinavia A/S;

Mogens Bergstrøm-Nielsen; Levnedsmiddelstyrelsen;

Kaj Heydorn, Forskningscentre Risø;

Jytte Molin Christensen, AMI;

Flemming Boisen. MLK Fyn I/S;

Elisabeth Gade Nielsen, DFM

5.2 Second action plan

Plan of action for the subject field of metrology: Amount of substance. DFM-1994-R23.

Authors

Ulla Lund, Vandkvalitetsinstituttet;

Ole Siggaard-Andersen, Københavns Amts Sygehus, Herlev;

Ole Petersen. FORCE instituttet;

Flemming Boisen. MLK Fyn I/S;

Hans Bjarne Kristensen. Radiometer Medical A/S;

Mogens Bergstrøm-Nielsen; Levnedsmiddelstyrelsen

Elisabeth Gade Nielsen, DANAK;

Carl Aage Dahl Winther, DFM

5.3 Draft VIM 3

International Vocabulary of Basic and General Terms in Metrology (VIM), Draft 3. ed. April 2004

Published in the names of: BIPM, IEC, IFCC, ILAC, ISO, IUPAC, IUPAP, OIML

5.4 Technical Measurement Announcement no. 170

Måleteknisk Meddelelse 170,

Primærlaboratorier og Nationale Referencelaboratorier, DANAK, 2002-12-06

6 Appendices

6.1 Participants at the meetings

The following persons participated in at least one of the six meetings concerning this work. Sub-field coordinators are indicated by *.

Kirsten Jebjerg Andersen, Eurofins A/S, Environmental Chemistry

Marianne Tambo Andersen, H. Lundbeck A/S, Pharmaceutical Chemistry

Paul Bennett, Statens Serum Institut, Laboratory Medicine

Henriette Bergen, H. Lundbeck A/S, Pharmaceutical Chemistry

Anne Cathrine Bollerup, DANAK - The Danish Accreditation and Metrology Fund, Laboratory Medicine

Helle Bruhn-Rasmussen, Statens Serum Institut, Laboratory Medicine

*Kirsten Byrialsen, Novo Nordisk A/S, Pharmaceutical Chemistry

Kim Carneiro, DFM - Danish Fundamental Metrology, Coordination

Niels-Ebbe Dam, DFM - Danish Fundamental Metrology, Coordination

René Dybkær, Copenhagen Hospital Corporation, Department of Standardization in Laboratory Medicine, Laboratory Medicine

Klaus Ennow, National Institute of Radiation Hygiene, Laboratory Medicine

Mia Flinta, Danish Medicines Agency, Pharmaceutical Chemistry

Lars Kristian Gram, FORCE Technology, Environmental Chemistry

Lone Grundahl, NERI - National Environmental Research Institute , Environmental Chemistry

Kaj Heydorn, Department of Chemistry, Technical University of Denmark, Pharmaceutical Chemistry

Jesper Høy, DANAK - The Danish Accreditation and Metrology Fund, Coordination

*Keld Palner Jacobsen, DANAK - The Danish Accreditation and Metrology Fund, Products and Materials

Asger Lundorf Jensen, The Royal Veterinary and Agricultural University, Department of Small Animal Diseases, Laboratory Medicine

*Hans Dalsgaard Jensen, DFM - Danish Fundamental Metrology, Electrochemistry

Bo Jørgensen, Danish Institute for Fisheries Research, Department for Seafood Research, Food Chemistry

Pia Lassen, NERI - National Environmental Research Institute , Environmental Chemistry

*Lisbeth Lund, DANAK - The Danish Accreditation and Metrology Fund, Food Chemistry

*Ulla Lund, Eurofins A/S, Environmental Chemistry

Inge Meyland, Danish Institute for Food and Veterinary Research, Food Chemistry

Henning Willads Petersen, University of Copenhagen, Dept. of Forensic Chemistry, Laboratory Medicine

*Inger Plum, Danish Institute for Quality Assurance for Laboratories in Health Care, DEKS, Laboratory Medicine

6.2 National primary and reference laboratories

Criteria for appointment are given in section 1.5.

6.2.1 Laboratories appointed by the Ministry for Economy and Enterprise

Radiometer Medical A/S
Sub-field: Electrochemistry, (pH measurement, primary laboratory)
Contact person: Hans Bjarne Kristensen, Radiometer Medical A/S, Åkandevej 21, DK-2700 Brønshøj
Telephone: +45 3827 3827. Telefax: +45 3827 2727. www.radiometer.com

6.2.2 Laboratories appointed or recognized by other ministries

A number of laboratories outside DANIAmet work for ministries and governmental agencies.

The list below includes laboratories with a formal status as reference laboratory as well as laboratories doing similar work without a formal appointment or recognition.

Danish Institute for Fisheries Research
Sub-field: Food Chemistry
Contact person: Maike Timm Heinrich, DTU, Søltofts Plads, Building 221, DK-2800 Kgs. Lyngby
Telephone: +45 4588 3322. Telefax: +45 4588 4774
Ministry of Food, Agriculture and Fisheries

Danish Institute for Food and Veterinary Research
Sub-field: Food Chemistry (Food Chemistry/Food Microbiology)
Contact person: Inge Meyland, Mørkhøj Bygade 19, DK-2860 Søborg
Telephone: +45 7234 6000. Telefax: +45 7234 7001
Ministry of Food, Agriculture and Fisheries

Danish Institute for Food and Veterinary Research
Sub-field: Food Chemistry (Microbiology[2])
Contact person: Conny Wolstrup, Bülowsvej 27, DK-1790 København V
Telephone: +45 7234 6000. Telefax: +45 7234 6001
Ministry of Food, Agriculture and Fisheries

Danish Institute for Quality Assurance in Laboratories in the Health Care, DEKS
Sub-field: Laboratory Medicine
Contact person: Inger Plum, 54M1, University Hospital Herlev, DK-2730 Herlev
Telephone: +45 4488 3454. Telefax: +45 4453 5369
Ministry of the Interior and Health

Danish Institute of Agricultural Sciences
Sub-field: Environmental Chemistry (soil and water)
Contact person: Niels Henrik Spliid, Forsøgsvej 1, Flakkebjerg, DK-4200 Slagelse
Telephone: +45 5811 3300. Telefax: +45 5811 3301.
Ministry of Food, Agriculture and Fisheries

Danish Medicines Agency, Medicines Control Division
Sub-field: Microbiology[2], Biology[2], Chemistry, Radiopharmacy[2]
Contact person: Finn H. Clemmensen, Axel Heides Gade 1, DK-2300 København S
Telephone: +45 4488 9595. Telefax: +45 4488 9599
Ministry of the Interior and Health

Danish Plant Directorate
Sub-fields: Food Chemistry / Environmental Chemistry

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[2] The sub-field is not included in this Action Plan, but is mentioned here because of the connection to some of the sub-fields in the present Action Plan.

Contact person: Mogens Nagel Larsen, Skovbrynet 20, DK-2800 Kgs. Lyngby
Telephone: +45 4526 3600 Telefax: +45 4526 3610
Ministry of Food, Agriculture and Fisheries

Eurofins A/S
Sub-field: Environmental Chemistry (Water, soil, sludge and waste)
Contact person: Ulla Lund, Agern Alle 11, DK-2970 Hørsholm
Telephone: +45 7022 4230 Telefax +45 7022 4255
Ministry of Environment

Eurofins Denmark A/S
Sub-field: Environmental Microbiology2
Contact person: Vibeke From Jeppesen, Frydendalsvej 30, DK-1809 Frederiksberg C
Telephone: +45 7022 4233. Telefax: +45 7022 4255
Ministry of Environment

FORCE Technology, Division of Energy and Environment
Sub-field: Environmental Chemistry (Air emission monitoring)
Contact person: Lars Gram, Gladsaxe Møllevej 15, DK-2860 Søborg
Telephone: +45 3955 5999 Telefax: +45 3969 6002.
Ministry of Environment

Institute of Forensic Medicine, University of Copenhagen
Sub-field: Laboratory Medicine (Forensic genetic investigations in crime, paternity and immigration cases)
Contact person: Niels Morling, Dept. of Forensic Genetics, Institute of Forensic Medicine, 11 Frederik V's Vej, DK-2100 Copenhagen Ø
Telephone: +45 3532 6113. Telefax: +45 3532 6270.
Ministry of Justice

Institute of Forensic Medicine, University of Copenhagen
Sub-field: Laboratory Medicine (Ethanol analysis in blood)
Contact person: Henning Willads Petersen, Dept. of Forensic Chemistry, Institute of Forensic Medicine, 11 Frederik V's Vej, DK-2100 Copenhagen Ø
Telephone: +45 3532 6109. Telefax: +45 3532 6085
Ministry of Justice

National Environmental Research Institute,
Department of Atmospheric Environment
Sub-field: Environmental Chemistry (Ambient air pollution measurements)
Contact person: Lone Grundahl, Frederiksborgvej 399, DK-4000 Roskilde
Telephone: +45 4630 1134. Telefax: +45 4630 1214
Ministry of Environment

National Environmental Research Institute,
Department of Environmental Chemistry and Microbiology
Sub-field: Environmental Chemistry (Environmental Chemistry and Microbiology)
Contact person: Pia Lassen, Frederiksborgvej 399, DK-4000 Roskilde
Telephone: +45 4630 1200 Telefax: +45 4630 1114
Ministry of Environment

The National Institute of Occupational Health
Sub-field: Environmental Chemistry
Contact person: Jesper Kristiansen, Lersø Parkallé 105, 2100 København Ø
Telephone: 3916 5200. Telefax: 3916 5201.
Ministry of Occupation

6.3 Laboratories accredited by DANAK

Further information: see www.danak.dk

Accreditation no.	Name
2	Teknologisk Institut (Murværk)
25	Teknologisk Institut (Tekstil)
26	DHI - Institut for Vand og Miljø
37	Teknologisk Institut (Træteknik)
48	R. Dons' Vandanalytiske Laboratorium
51	FORCE TECHNOLOGY
65	FORCE Technology
90	Teknologisk Institut
92	Teknologisk Institut (Emballage og Transport)
119	Radiometer Medical A/S
153	Eurofins Danmark A/S
160	Capio Diagnostik a.s.
168	Eurofins Danmark A/S
172	NORDLAB A/S
179	PC-Laboratoriet A/S
221	Odense Universitetshospital, Sporstoflaboratoriet
222	Steins Laboratorium Sp.z o.o.
242	Højmarklaboratoriet A/S
255	DFM - Dansk Fundamental Metrologi
265	William Hansen og Co A/S
294	Fødevareregion Vejle
300	Teknologisk Institut (Energi)
303	Heilsufrødiliga Starvsstovan, Færøerne
315	Fødevareregion København
324	ROVESTA Miljø I/S
330	Plantedirektoratet
338	ROVESTA Miljø I/S
339	Fødevareregion Nordjylland
343	A/S AnalyCen
344	Miljøcentre Vestjylland I/S
346	House of Prince A/S
348	Elsam A/S Enstedværket

Accreditation no.	Name
349	Miljøcentre Vendsyssel I/S
350	Danmarks Fødevare- og Veterinærforskning, Afd. For Kemiske Fødevareundersøgelser og Afd. For Toksikologi og Risikovurdering
358	Teknologisk Institut (Træ)
361	MILANA-A/S
362	Lægemiddelstyrelsen
365	Miljølaboratoriet StorKøbenhavn I/S
375	Fødevareregion Esbjerg
383	Danmarks Miljøundersøgelser
392	Slagteriernes Forskningsinstitut
393	Retsmedicinsk Institut, Retsgenetisk Afdeling
397	Statens Serum Institut
401	AnalyTech Miljølaboratorium ApS
405	Fødevareregion Ringsted
408	Danmarks Fødevare- og Veterinærforskning, Afd. For Veterinær Diagnostik og Forskning
411	Danmarks Miljøundersøgelser
412	Danmarks Fødevare- og Veterinærforskning, Afd. For Veterinær Diagnostik og Forskning og Afd. For Mikrobiologisk Fødevaresikkerhed
413	Danmarks Fødevare- og Veterinærforskning, Afd. For Fjerkræ, Fisk og Pelsdyr
417	Enmaco Motorer A/S
423	Københavns Energi
424	Fødevareregion Århus
428	Højvang Miljølaboratorium
430	Rolls-Royce Marine A/S
432	Danmarks Miljøundersøgelser
434	Københavns Praktiserende Lægers Laboratorium
435	Danmarks Miljøundersøgelser
439	Amager Hospital, Klinisk biokemisk afdeling
442	Rigshospitalet, Klinisk biokemisk afdeling
450	Århus Sygehus, Klinisk biokemisk afdeling
456	Odense Universitetshospital, Klinisk Immunologisk Afdeling
457	NNE's Laboratorium
1001	Amtssygehuset i Gentofte, Klinisk-biokemisk afdeling (DS/EN ISO 15189)

6.4 CCQM, Euromet, and previous Danish divisions of chemistry into sub-fields

There is no unique way of dividing the subject field, as shown by the following three pertinent schemes for metrology in chemistry.

CCQM working groups

Gas analysis

Organic chemistry

Inorganic chemistry

Electrochemistry

Bioanalysis

Surface Analysis

Euromet

Gas analysis

Organic chemistry

Inorganic chemistry

Electrochemistry

Danish Action Plan for Metrology in Chemistry 1995

Environmental Chemistry

Clinical chemistry

Materials chemistry

Feed and Food Chemistry

Biochemistry

Microbiology

pH measurement

6.5 Abbreviations

Abbreviation	Name
AAS	Atomic Absorption Spectrometry
AOAC	Association of Official Analytical Chemists
AOCS	American Oil Chemists' Society
API	Active pharmaceutical ingredient
ASTM	The American Society for Testing and Materials
BIPEA	Bureau Inter Professionnel d'Etudes Analytiques
BIPM	Bureau International des Poids et Mesures (The International Bureau of Weights and Measures)
BOD	Biochemical Oxygen Demand
CAC	Codex Alimentarius Commission
CCM	Consultative Committee for Mass and related quantities. Established 1980
CCMAS	Codex Committee on Methods of Analysis and Sampling
CCPR	Consultative Committee for Photometry and Radiometry. Established 1933
CCQM	Consultative Committee for Amount of Substance: Metrology in Chemistry
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CDFM	Center for Dansk Fundamental Metrologi
CE	Capillary Electroforesis
CEN	Comité Europééne de Normalisation. European standardisation organisation
CGPM	General Conference of Weights and Measures
CIPAC	Collaborative International Pesticides Analytical Council
CIPM	Comité Internationale des Poids et Mesures
COD	Chemical Oxygen Demand
CRL	Community Reference Laboratory
CRM	Certified Reference Material
CRME	Centre for Reference Metrology in Electrochemistry
DANAK	The Danish Accreditation and Metrology Fund. Den Danske Akkrediterings- og Metrologifond
DEKS	Danish Institute for External Quality Assurance for Laboratories in Health Care
DFM	Danish Fundamental Metrology (the National Metrology Institute of Denmark). Dansk Fundamental Metrologi
DIN	Deutsches Institut für Normung e.V.
DKK	Danish crown

Abbreviation	Name
DPL-pH	Danish Primary Laboratory for pH
DS	Danish Standards Association is a private, non-profit organisation, which has been approved as a technological service institute (GTS institute)
EC	European Commission
EEC	European Economic Community
ELISA	Enzyme linked immunosorbent assay
EN	European Norm
EPA	Environmental Protection Agency
EQAS	External quality assurance organizer
EULAR	European League against Rheumatism
EUROMET	Cooperation between 22 national metrology institutes in Europe, Turkey, and the European Commission
FAO	Food and Agriculture Organization of the United Nations
FAPAS	The Food Analysis Performance Assessment Scheme
FID	Flame Ionisation Detector
FTIR	Fourrier Transformation Infrared Spectrometry
GC	Gas Chromotography
GC-PID	Gas Chromotograph Photo Ionization Detector
GTS	GTS – Advanced Technology Group is a grouping of independent Danish research and technology organizations
HPLC	High-Pressure Liquid Chromotography
ICES	International Council for the Exploration of the Sea
ICH	The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively Coupled Plasma - Mass Spectrometry
ICP-OES	Inductively Coupled Plasma - Optical Emission Spectrometry
IEC	International Electrotechnical Commission
IEF	Iso-Electric Focusing
IEN	Istituto Elettrotecnico Nazionale
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
Ig	Immunoglobulin
ILAC	International Laboratory Accreditation Cooperation
ILC	InterLaboratory Comparison
IMEP	International Measurement Evaluation Programme
INR	International Normalized Ratio

Abbreviation	Name
IR	Infra Red
IRMM	Institute for reference materials and measurements, part of European Commission – Directorate-General - Joint Research Centre
ISO	International Organisation for Standardisation
IUIS	International Union of Immunological Society
IUPAC	International Union of Pure and Applied Chemistry
IUPAP	International Union of Pure and Applied Physics
IVD directive	Directive for in vitro diagnostic devices within the European Union, IVDD 98/79/EEC- Annex I
JCTLM	Joint Committee on Traceability in Laboratory Medicine, a cooperation between CIPM, IFCC and ILAC
JP	Japanese Pharmacopoeia
kDKK	Thousand Danish Crowns
LC	Liquid Cromatography
LNE	Laboratoire National d'Essais
MDKK	Million Danish Crowns
MRA	Mutual Recognition Arrangement
MS	Mass Spectrometry or Mass Selective (detector)
NDIR	Non-Dispersive Infra Red Detection
NERI	National Environmental Research Institute
NFKK	Nordisk Forening for Klinisk Kemi
NIR	Near Infra Red
NIST	National Institute of Standards and Technology
NMI	National Metrology Institute
NMKL	Nordic Committee on Food Analysis
NPL	National Physical Laboratory. The National Metrology Institute of Great Britain
NRL	National Reference Laboratories in individual member countries
OIE	Office International des Epizooties
OIML	Organisation Internationale de Métrologie Légale, International Organization of Legal Metrology
OMH	Office of Metrology, Hungary
PAH	Polycyclic aromatic hydrocarbons
PCB	Polychlorinated biphenyls
PCR	Polymerase chain reaction
Ph. Eur.	European Pharmacopoeia

Abbreviation	Name
Pro-BNP	Pro-Brain Natriuretic Peptide
PTB	Physikalisch-Technische Bundesanstalt, the National Metrology Institute of Germany
QUASIMEME	Quality Assurance in Marine Environmental Measurements
RIA	Radio-Immuno Assay
RT	Refractometry
SI	The International System of Units (Le Système International d'Unités), including the formal definition of all SI base units, approved by the General Conference on Weights and Measures
SMU	Slovensky Metrologicky Ustav, the National Metrology Institute of the Slovak Republic
SP	Sveriges Provnings- och Forskningsinstitut, the National Metrology Institute of Sweden
SSI	Statens Serum Institut
TLC	Thin Layer Chromatography
USEPA	United States Environmental Protection Agency
USP	United States Pharmacopeia
UV	Ultra Violet
VDI	Verein Deutsche Ingenieuren
VIM	International Vocabulary of Basic and General Terms in Metrology
VIRM	The European Virtual Institute for Reference Materials
VIS	Visible
WGEA	Working Group on Electroanalysis
WHO	World Health Organization, part of the United Nations