Consultative Committee for Amount of Substance

Metrology in Chemistry - CCQM

Robert Kaarls

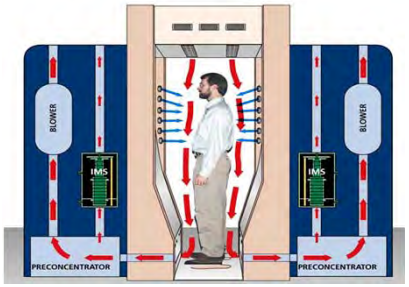
President CCQM

24th meeting of the CGPM, 17 – 21 October 2011, Paris, France

Demanding Metrological Traceability

- Industry, services, fair traders, consumer protection, society
- Legislators, Regulators
- JCTLM (BIPM, IFCC, ILAC, WHO, in-vitro diagnostics industry)
- Codex Alimentarius Commission, HACCP, animal health, plant protection, microbiological measurements
- WMO Global Atmospheric Watch, climate change
- Pharmacopeia (USP, EDQM, JP, a.o; 2008 workshop at BIPM)
- World Anti Doping Agency – WADA
- Forensics authorities and security authorities
- ISO, sector specific standardization bodies
- Conformity Assessment and Accreditation Bodies

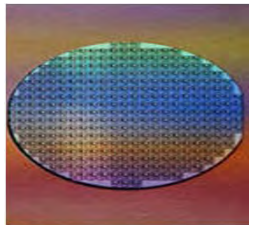
  (ILAC Arrangements, e.g. based on ISO 17025, 15189, 15195, WADA, etc.)



Addressing traceability and measurement uncertainty

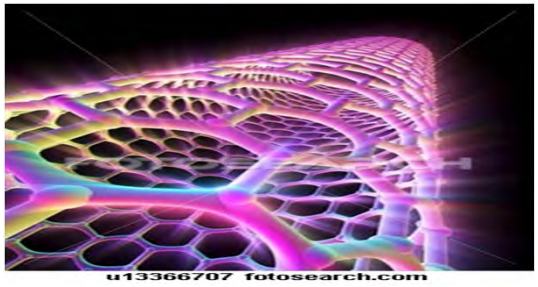
CCQM - Metrology in Chemistry

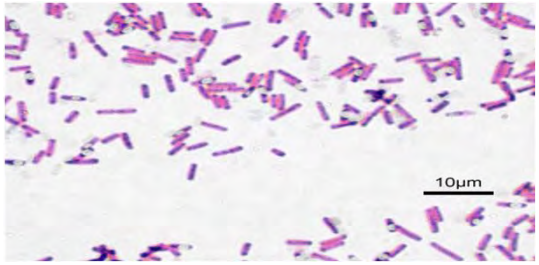
- High purity Chemicals (inorganic and organic compounds, **metals**, isotopics, other)
- Inorganic solutions (elemental, anionic, other)
- Organic solutions (PAHs, PCBs, pesticides, other)
- Gases (high purity, environmental, fuel, forensic, medical, other)
- Water (fresh water, contaminated water, sea water, other)
- pH
- Electrolytic conductivity
- Metals and Metal alloys (ferrous metals, non-ferrous metals, precious metals, other)
- Advanced materials (semiconductors, superconductors, polymers and plastics, ceramics, other)



CCQM - Metrology in Chemistry

- Biological fluids and materials (blood serum, renal fluids, hair, tissues, bone, botanical materials, other)
- Food (nutrional constituents, contaminants, GMOs, other)
- Fuels (coal and coke, petroleum products, bio-mass, other)
- Sediments, Soils, Ores and Particulates (sediments, soils, ores, particulates, other)
- Other Materials (cements, paints, textiles, glasses, thin films, coatings, insulating materials, rubber, adhesives, other)
- Surfaces, films and engineered nanomaterials (inorganic, organic, biomaterials, other)
- Micro-biological pathogens (bacteria, viruses, fungi, yeast, mould)





CCQM – Metrology in Chemistry

CCQM Working Groups (>250 experts)

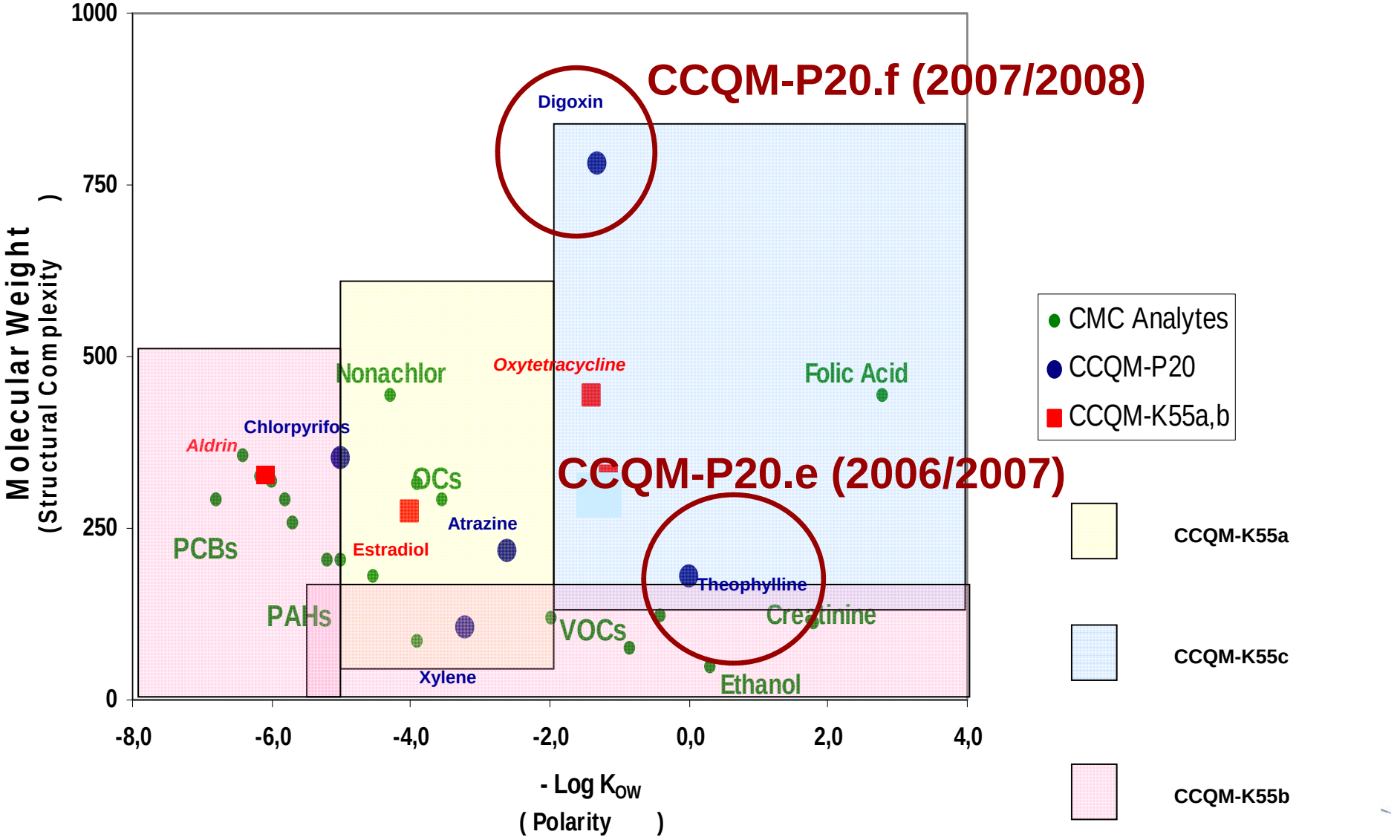
- Key Comparisons and CMC Quality — NMIA, L. Mackay
- Organic Analysis — NIST, W. May
- Inorganic Analysis — LGC, M. Sargent
- Gas Analysis — NPL, M. Milton
- Electro-chemical Analysis — SMU, M. Mariassy
- Surface Analysis — BAM, W. Unger
- Bio-Analysis — LGC, H. Parkes
- 3 ad hoc WGs (EET, KCRV, redefinition SI)
- 1 Advisory Group (BIPM Program of Work)
- 1 ad hoc Steering Group (micro-biology)

CCQM - Metrology in Chemistry (1993)

Aim and tasks

- **worldwide comparability**, through **traceability to SI**, or if not (yet) possible to other internationally agreed references,
- **primary and other methods of higher order**, databases and
- **primary (pure) reference materials** and
- **validation** of traceable methods/procedures/meas. uncertainty
- **Pilot study comparisons** and **Key Comparisons**
  - Key Comparisons testing core competencies
  - Key Comparisons of deliverables, like CRMs
  - Key Comparisons of challenging components and matrices
  - Pilot Study Comparisons (bench marking, research, try out, newcomers, etc.)
- **>90 Key Comparisons and >130 Pilot study comparisons**
- **>4800 chemical CMCs (out of ~24000)**

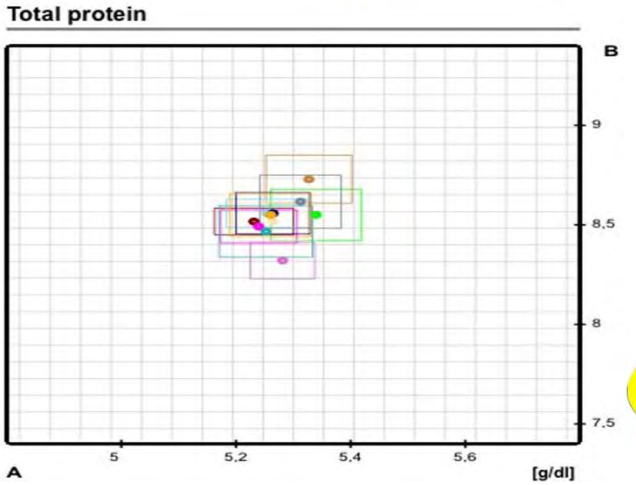
A model for Primary Calibrator Comparisons
How far does the light shine? Testing core competencies



BIPM

Current measurement problems

- Measurand not understood (insufficient knowledge of what the measurand, intended to be measured, should be, and not sure what is really measured)
- Measurand is method/procedure defined
- “reference” methods are not metrologically sound (higher order reference methods, e.g. based on growth of micro-organisms and colony counts)
- Insufficient global harmonization of measurement methods (e.g. moisture in grains and cereals; in coop. with OIML, ISO, Codex A.)
- Measurement uncertainy (based on repeatability and reproducibility, instead of the GUM)
- No calibration chain/hierarchy
- Lack of CRMs
- Commutability problems



RELA-IFCC
DGKL-RFB

EQAS 2010

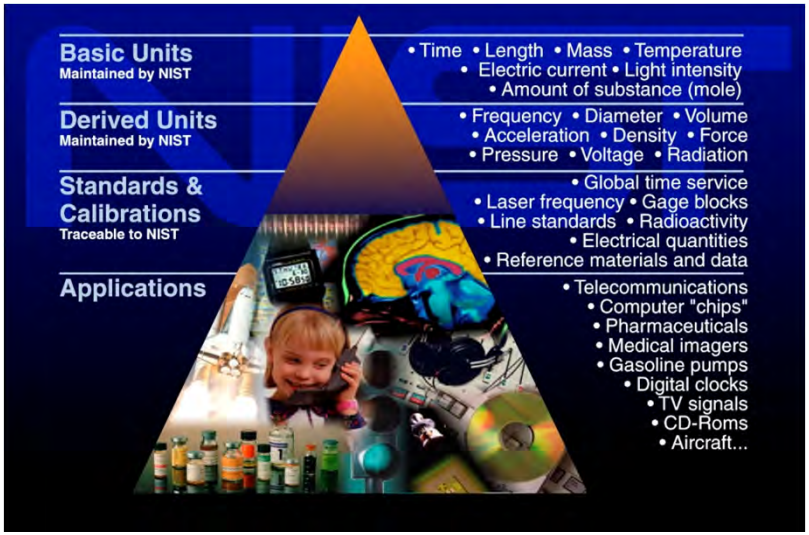
CCQM stakeholder and expert cooperation

- WHO, WMO, ILAC, JCTLM (IFCC and ILAC)
- IAEA, Codex Alimentarius Commission/IAM, IUPAC, WADA, Pharmacopeia, IAFSI/ENFSI, Micro-biology testing, IDF, ISO, a.o.
- CCQM workshops with industry associations, relevant expert laboratories, industries, regulators, EQAS and PT providers, and standardization bodies
- Addressing the “Grand Challenges” in society and economy (EU, APEC, USA, Japan, a.o. with focus areas on food safety, health care, environmental control/climate change, energy, advanced and nano materials)

A Context for the Complexity of Chemical Measurements

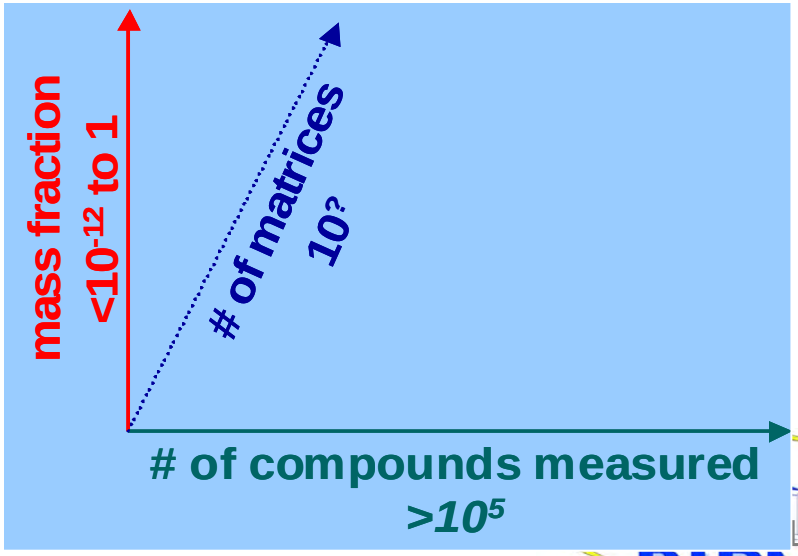
(By courtesy of NIST)

- According to a study released by the Council for Chemical Research, **chemistry is core or important to virtually all industrial sectors and technology areas**
  - ***"Measuring Up: Chemical R&D Counts for Everyone", CCR, 2006***



- **For metrology in chemistry** the task is to determine the quantity of a **specific chemical entity** and not merely "amount of substance"

- Chemical measurements are multidimensional
  - a large number of chemical entities (>10^5)
  - in a broad range of matrices ($10^?$)
  - and mass fractions ranging from <10^{-12} to 1



CCQM-K43.1As, Hg and Me-Hg in marine fish (swordfish), year 2007

Mercurio

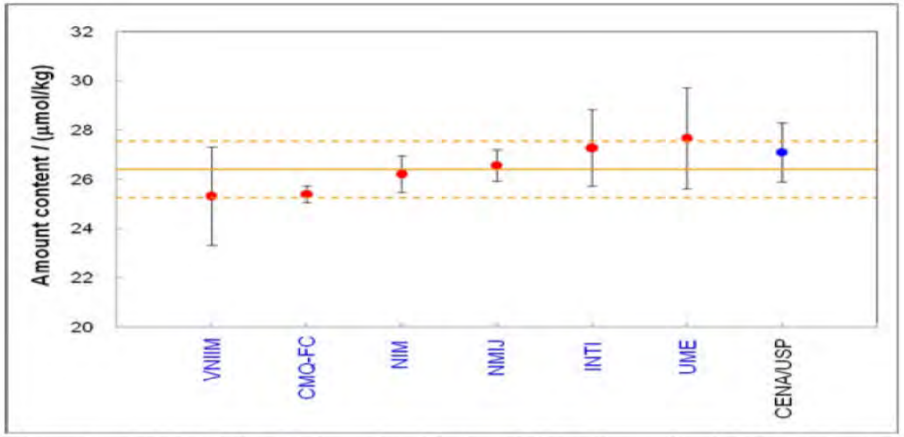


Figure 2 CCQM-K43.1: Hg in marine fish (swordfish), (The results of CMQ-FC: *k=2.18*)

Arsenico

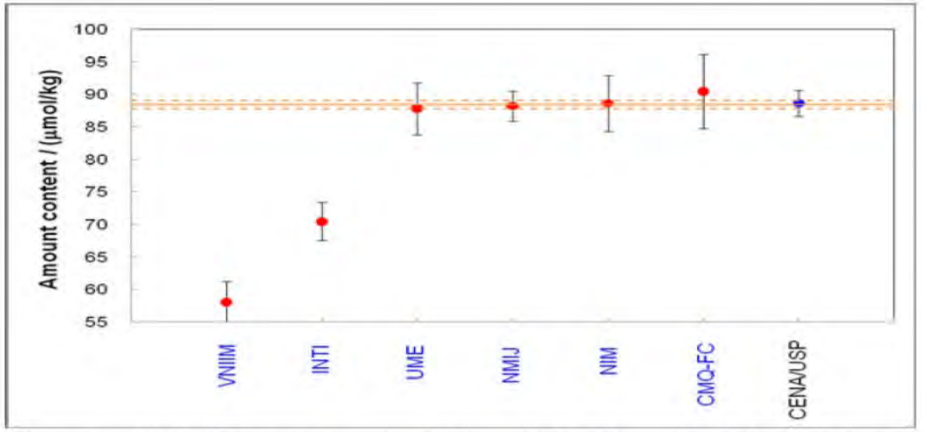


Figure 1 CCQM-K43.1: As in marine fish (swordfish), (The results of CMQ-FC: *k=1.96*)

CCQM-P12.1 Cu, Fe, Pb and Cd in wine, year 2006

Hierro

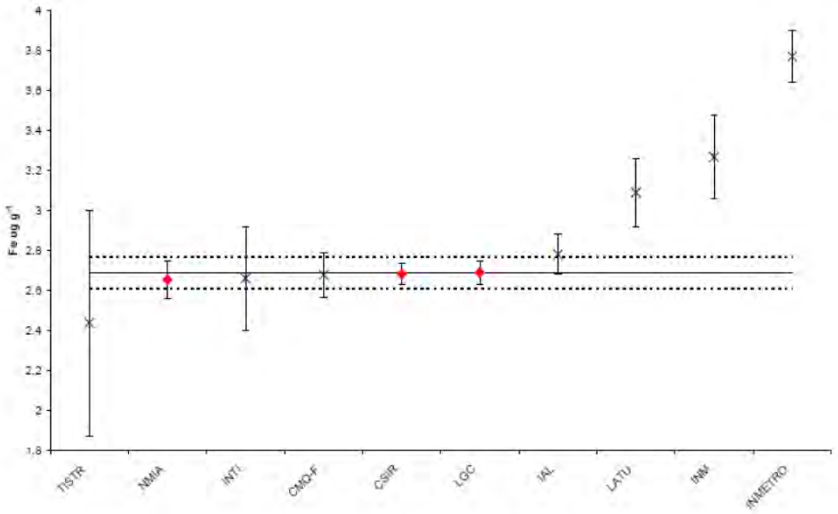


Figure 2: CCQM-P12.1 participants' measurement results for iron

The horizontal lines represent the KCRV and associated uncertainty. Solid, red diamonds represent results obtained using IDMS.

Cobre

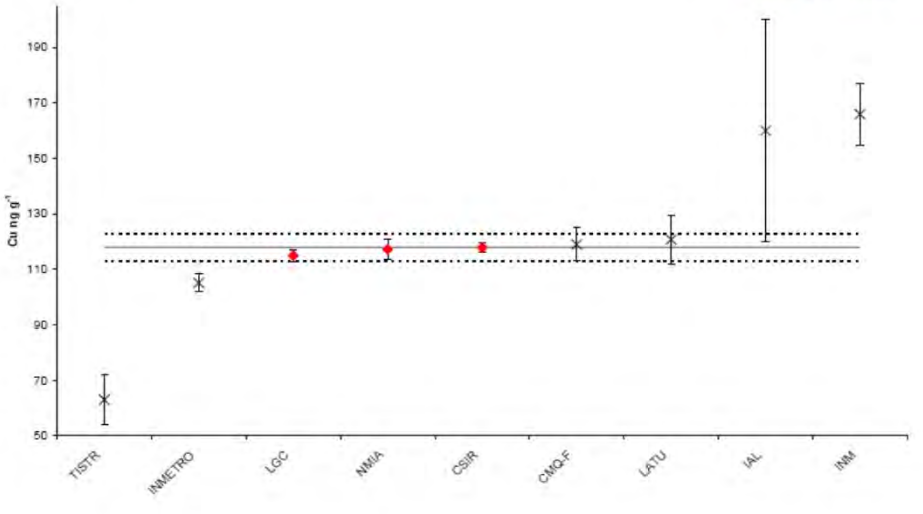


Figure 3: CCQM-P12.1 participants' measurement results for copper

The horizontal lines represent the KCRV and associated uncertainty. Solid, red diamonds represent results obtained using IDMS.

Trade, Health and Food Safety

Recent examples of temporary closure of markets due to the presence of residues

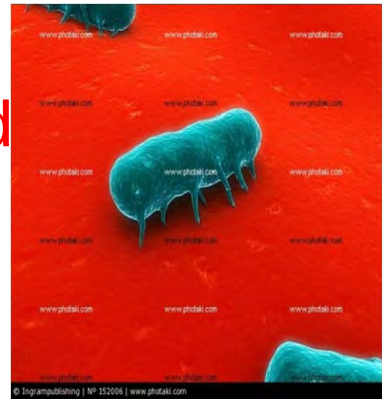
- Antibiotics in pork, Japan
- Antibiotics in meat, Korea
- Antibiotics in salmon, Japan
- Crystal violet in salmon, EU
- Leucomalachite green in salmon, Chinese Taipei
- Amphenicol in salmon, Canada
- Dioxin in pig meat, South Korea
- Melamine in milk
- Carbaryl in wine
- Cd in mussels
- Hg and nitrate in swordfish
- Patulin in apple and azinphos-methyl in pears and grapes
- Etc.

Why need of reliable micro-biological measurements?

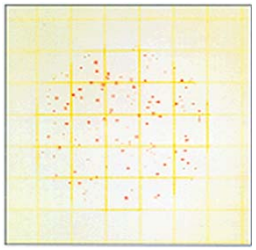
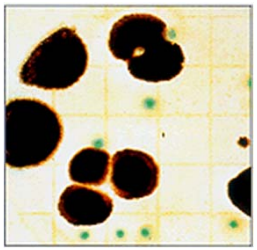
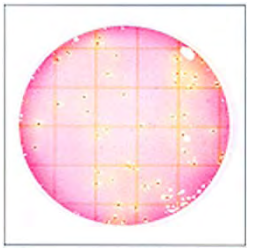
- Already for many years requested by a number of NMIs
- 2008 world export volume of food products > 1100 billion USD
- Estimated that 20% to 30% of total world food production is lost due to microbial spoilage
- USA CDC statistics on food-borne illnesses indicate:
  - 48 million illnesses per year due to food-borne pathogens, of which
  - 128 000 hospitalizations and 3000 deaths
  - It means every year 1 in 6 Americans are affected
- Food poisening in the EU (EFSA 2009 figures)

	EU 2009	USA 2011 estimated
Salmonella	108 614	1 027 561
Campylobacter	198 252	845 024
Listeria	1 645	255 death
VTEC E.coli	3 573	2 100 hospitalized

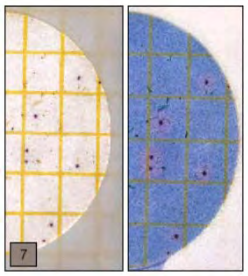
(sources CDC statistics and Campden BRI)

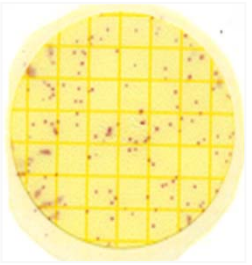


Microbial Stakeholder Steering Group (chair: NIST, L. Locascio)

(By courtesy of 3M)



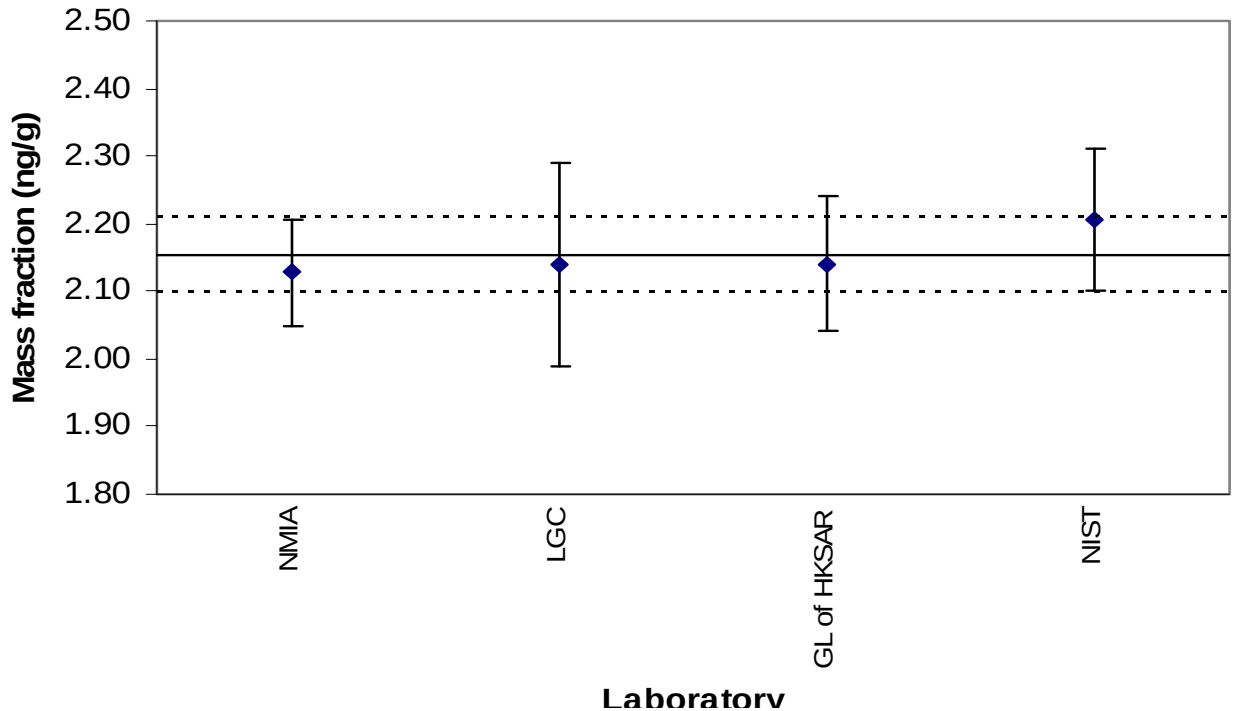


- Sampling
- Cell/organism growth
- Viable colony count
- Viable non-culturable organisms
- Detection
- Isolation
- Identification
- Characterization
- Enumeration/counting and different units, like cfu (colony-forming unit, a measure of viable bacterial or fungal numbers), cfu/g, cfu/ml
- Slow laboratory methods versus rapid methods
- “Reference” methods are based on growth of organisms
- Immunoassay, DNA based tests (e.g. PCR)

CCQM-P68: Anabolic Steroids in Urine

Participants' Methodologies and Results (in collaboration with WADA)

Laboratory	Method Summary	Instrumentation
NMIA	Addition of D_4-NNA, enzyme hydrolysis, solvent extraction, HPLC fractionation, TMS derivatisation	GC/HRMS
GL of HKSAR	Addition of D_4-NNA, enzyme hydrolysis, SPE and liq-liq extraction, TMS derivatisation	GC/HRMS
LGC	Addition of D_4-NNAG, enzyme hydrolysis, solvent extraction, HPLC fractionation, TMS derivatisation	GC/MS
NIST	Addition of D_4-NNA, enzyme hydrolysis, solvent extraction	LC/MS/MS



Mean value:
2.15 ng/g ± 0.06 ng/g

RSD 1.7%

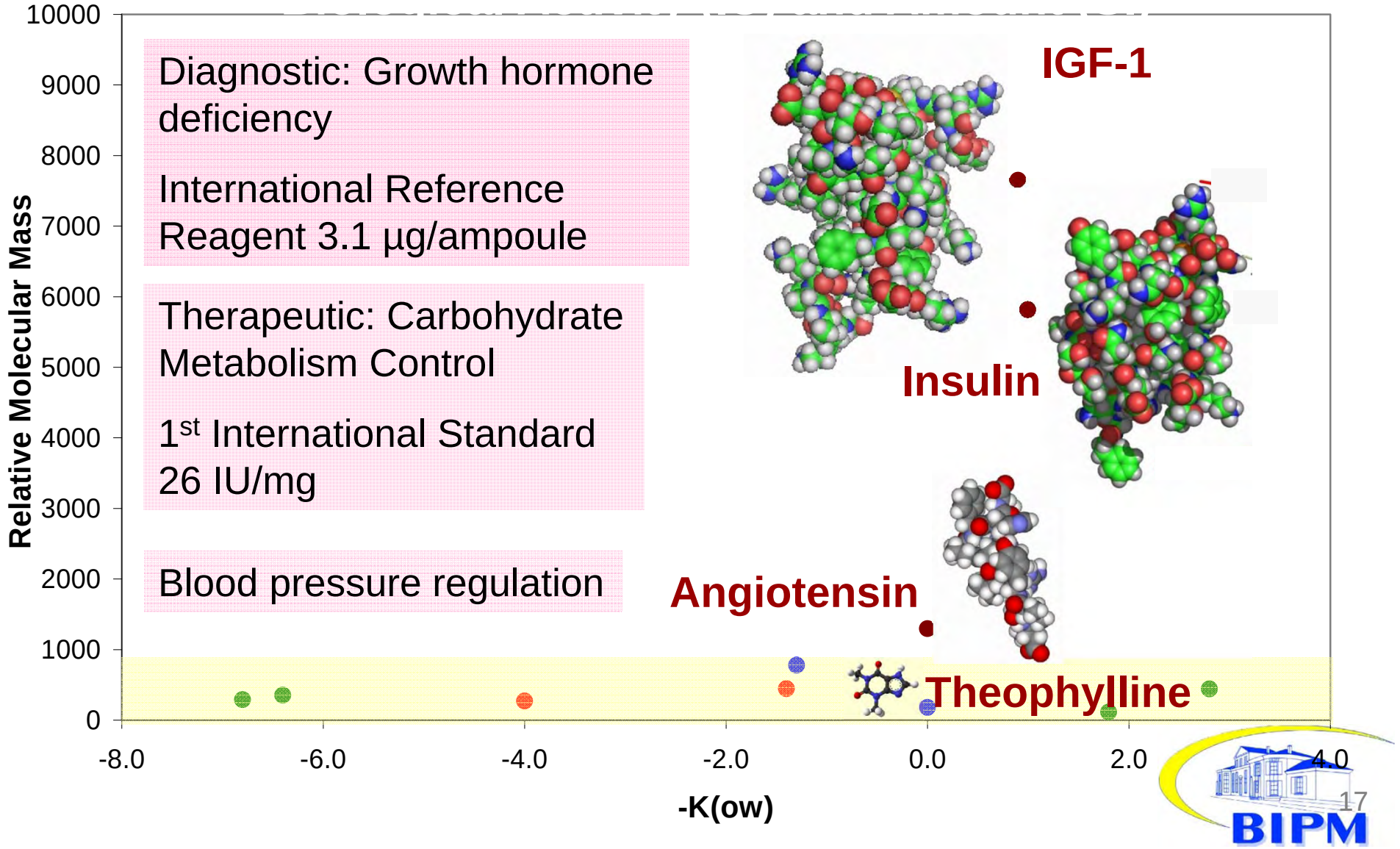
International Units (IU) versus SI

- IU are arbitrary units defined by a batch of biological reference material
- The batch has been defined by the WHO as an International Standard (IS) for a particular biological
- These IS/RMs have a limited life time and need regularly to be replaced by a new IS, defining new IU for the same biological
- The magnitude of the IU defined by successive IS/RMs differ and are not comparable
- The measurand is defined on the basis of what it does in the human body and not on the basis of what it is
- SI traceable insulin would ensure better therapeutic drug characterization, cheaper production and consistent dose of insulin for diabetes patients world wide

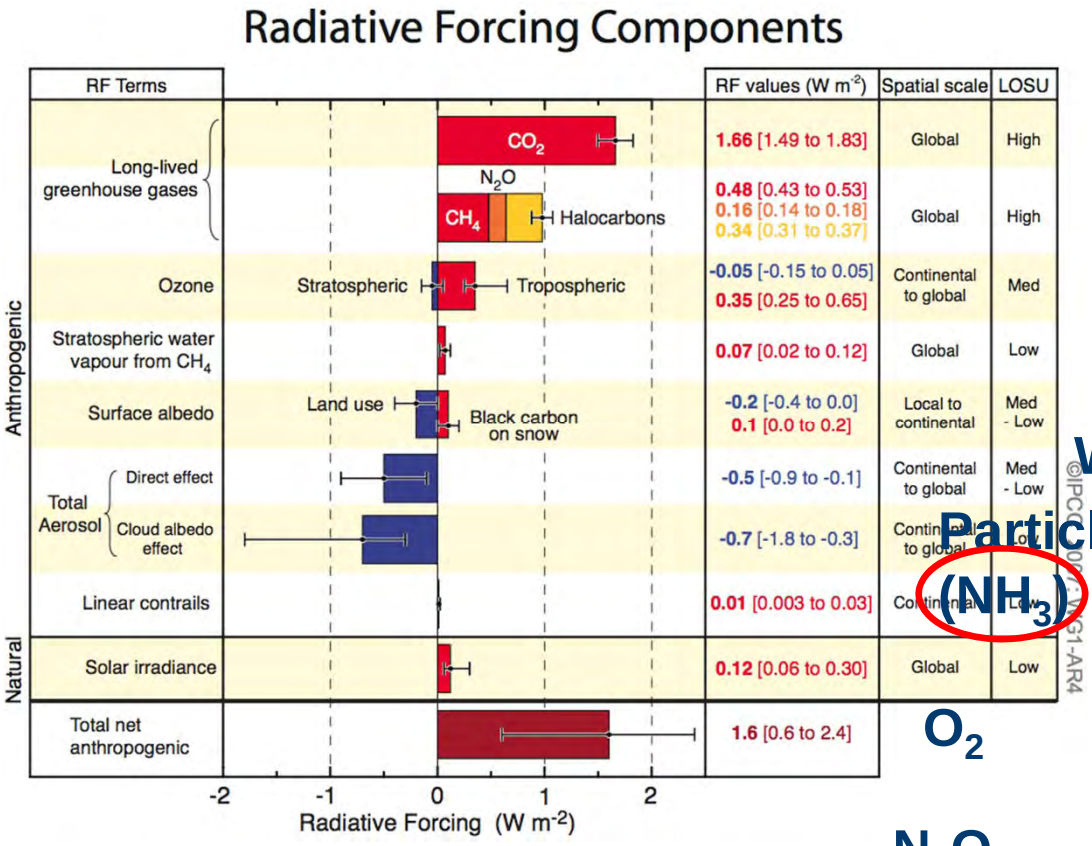
(e.g. in the US ~26 million people suffer diabetes; 4 million taking daily insulin; estimated overall costs in 2007: 174 billion US dollars)

Reference Measurement Systems for Peptides and Proteins

(joint activities by BIPM, NIST, other NMIs, WHO/NIBSC, IFCC, pharmacopoeia, industry)



Driver- Gas Metrology Programme: Climate Change Gases



CO_2 , CH_4 & halocarbons

Water vapour

Carbon trading

Particles

(NH_3)

O_2

N_2O

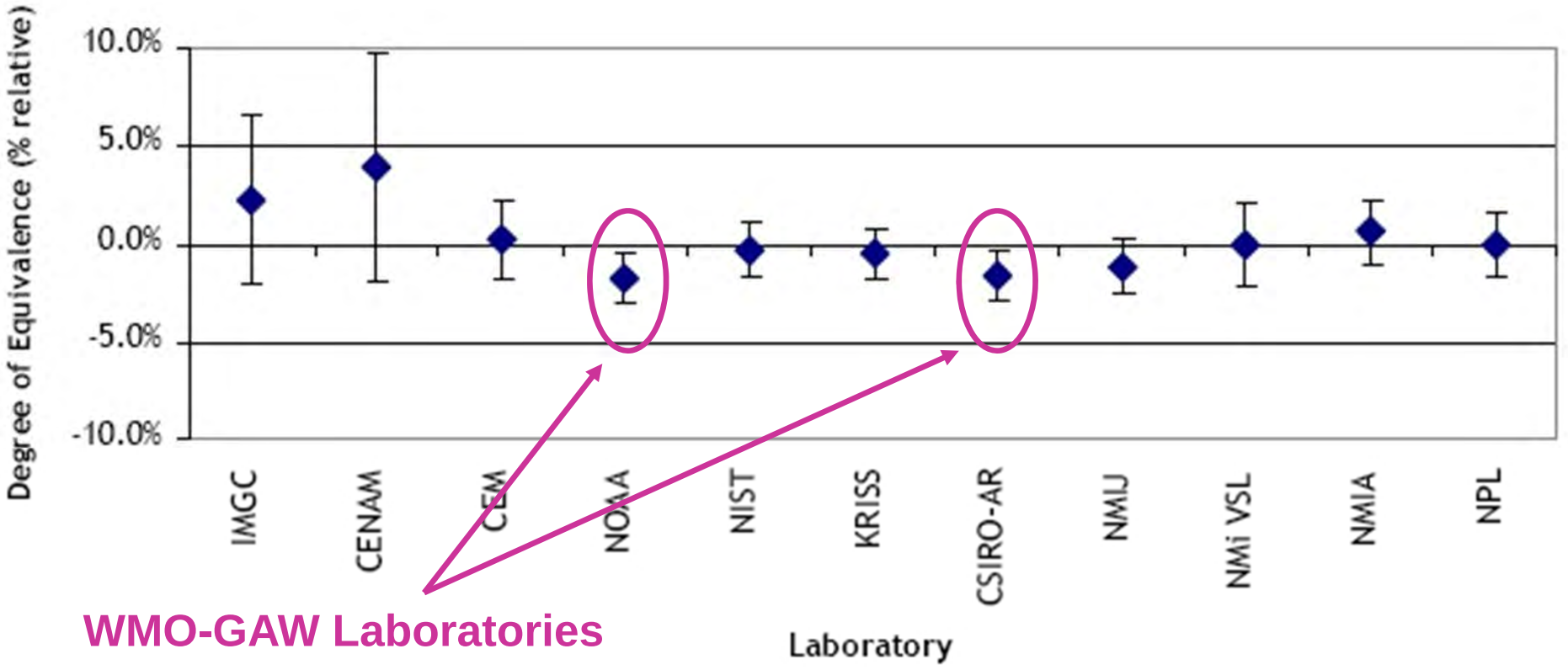
Ozone

VOCs

NF_3

Quantification & Control

CCQM-P41, Methane 1.8 µmol/mol (2003)



WMO-GAW Laboratories

1.7 % difference from gravimetric value

WMO scale is being revised

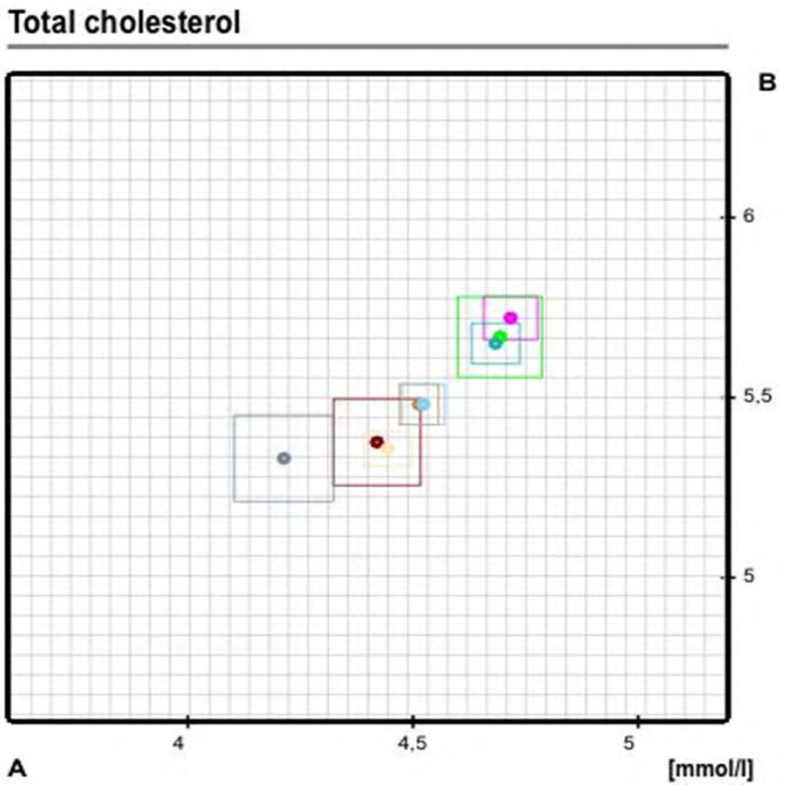
Joint Committee on Traceability in Laboratory Medicine - JCTLM

Principal promotors

- CIPM/BIPM
- IFCC
- ILAC

Supported by

- WHO
- Regulators (FDA, EC, Japan)
- CRM producers (NIST, IRMM, a.o.)
- Reference laboratories (CDC, DGKS, etc.)
- PT and QA organisations (CAP, EQA, etc.)
- Written Standards (NCCLS, JCCLS, ISO)
- IVD industry (ADVAMED, EDMA, JARC)
- Other stakeholders



By courtesy of
RELA-IFCC
DGKL-RFB
EQAS 2010

JCTLM WG 1 Measurand/Analyte-Based Review Teams

Chair: Willie May, NIST and Heinz Schimmel, IRMM

Coagulation Factors	**Elaine Gray, NIBSC,** United Kingdom
Drugs	**Andre Henrion, PTB,** Germany
Electrolytes/Blood Gases	**Brigitte Toussaint, IRMM,** European Union
Enzymes	**Mauro Panteghini, University of Milan**, Italy
Metabolites/Substrates	**Michael Welch, NIST,** United States
Nucleic Acids	**Helen Parkes, LGC,** United Kingdom
Non-Peptide Hormones	**Heinz Schimmel, IRMM,** European Union
Proteins	**David Bunk, NIST,** United States
Blood Groupings	**Susan Thorpe, NIBSC,** United Kingdom
Microbial Serology	**Claude Giroud, Bio-Rad Laboratories,** United States
Vitamins	**Katherine Sharpless, NIST,** United States
Non-electrolyte Metals	**Lee Yu, NIST,** United States
Blood cell counting	**Lili Wang, NIST,** United States
Quality System	**Craig M Jackson**, **HDC,** United States

Review Teams established with worldwide representation from Laboratory Accreditation Organizations, National Metrology Institutes, Professional Societies, and IVD Industry in order to facilitate a fair and transparent review process.

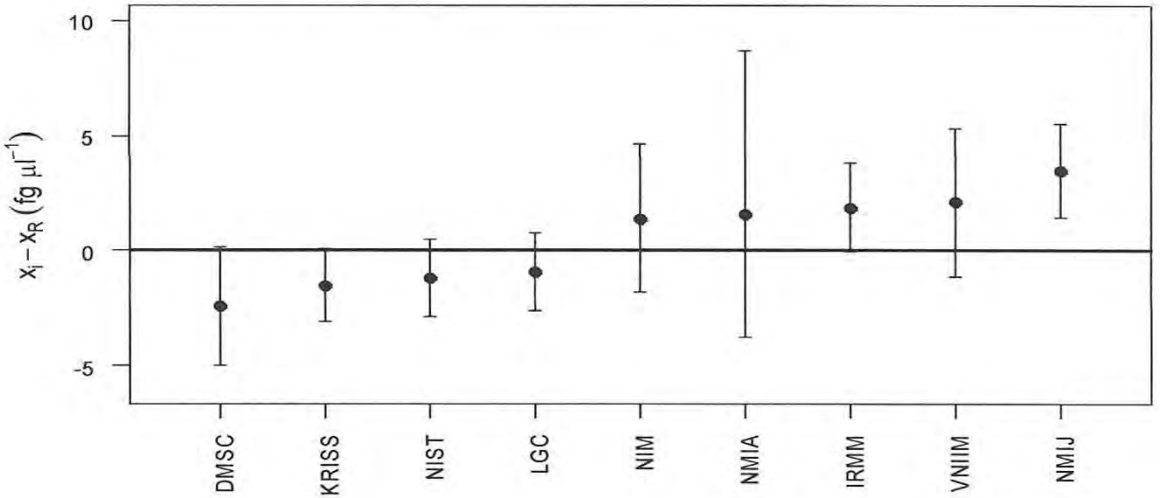
CCQM workshops and other relevant workshops

- "Pharma and Bio Pharma Workshop", December 2008
  (in cooperation with USP, NIBSC, multinational pharmaceutical industry,regulators (EDQM), clinical chemistry/hospitals)
- "Metrology for Forensics", April 2010 (regional networks of Forensics Sciences Institutes, police organizations and accreditors)
- "Metrology and the Need for Reliable Traceable Microbiological Measurements to Ensure Food Quality and Safety", April 2011
  (APEC, IDF, multinational food industries, regulators, CRM producers, PT providers, testing laboratories, standardization bodies, a.o.)
- BIPM "Physiological Quantities and SI Units", Nov. 2009, BIPM
  (WHO International standards and International Units)
- BIPM "Metrology at the nanoscale", February 2010 at the BIPM
  (nanobiotechnology, toxicological testing, personalized medicine, aerosols)
- BIPM-WMO "Measurement Challenges for Global Observation Systems for Climate Change Monitoring: Traceability, Stability and Uncertainty", March-April 2010 at the WMO in Geneva

CCQM-K61

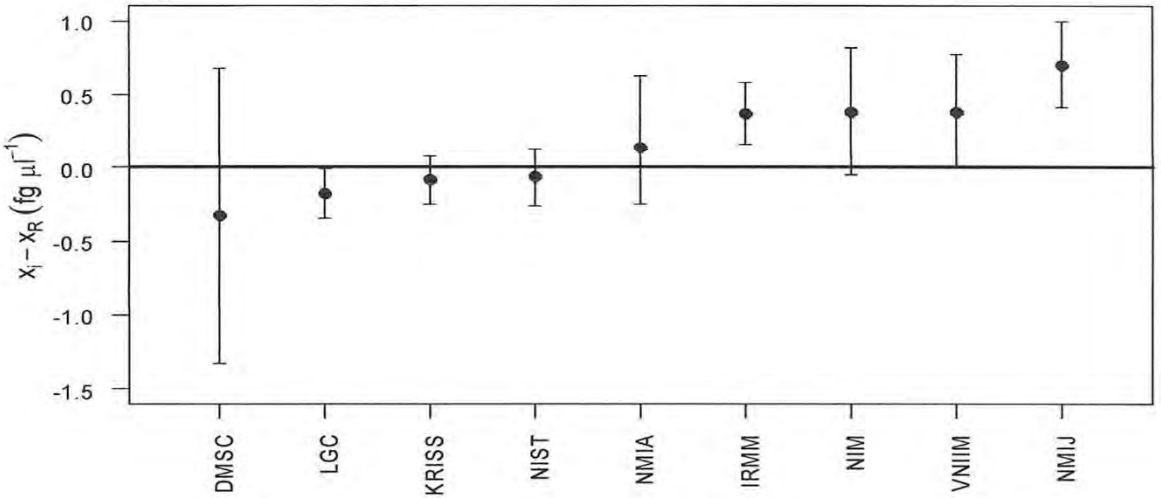
Quantitation of a linearised plasmid DNA

Figure 3: Degrees of equivalence - Unknown 1



The graph shows the degrees of equivalence between participant results and KCRV. Error bars show uncertainties at k=2 or (for NMIA) the same level of confidence assuming a lognormal distribution.

Figure 4: Degrees of equivalence - Unknown 2



The graph shows the degrees of equivalence between participant results and KCRV. Error bars show uncertainties at k=2 or (for NMIA) the same level of confidence assuming a lognormal distribution.

CCQM meetings and other issues of concern

- CCQM Working Group workshops (addressing sector specific issues, technology and method/procedural issues)
- CCQM Working Group Joint meetings (addressing inter-disciplinary issues)
- "Study of Measurement Service and Comparison Needs for an International Measurement Infrastructure for the Biosciences and Biotechnology: Input for the BIPM Work Programme" (Marriott J., O'Connor G., Parkes H., LGC)
- International transportation of chemical samples
- Accreditation of CRM producers; Metrology in Chemistry (inter-)national Infrastructure

CCQM meetings and other issues of concern

- Availability of pure primary reference materials/calibrators, e.g. isotopes, complex organic compounds
- Availability of essential complementary measurement technologies, like reactors for Neutron or photon Activation Analysis, Glow discharge Mass spectrometry, coulometry, etc.
- Measurement Uncertainty, statistics and Degrees of Equivalence
- Isotope ratio measurements of enriched and natural silicon
- “Mise-en-pratique” for the realization of the mole
- Counting/enumeration to be included in the SI brochure

THANK YOU

Acknowledgment

All NMIs, DIs and other international organizations cooperating with the BIPM and the CCQM

www.bipm.org