

## **International Standards**

- Identification and Provision of “Higher Order” Certified Reference Materials and Reference Measurement Procedures Required for U.S. Industry Compliance with the EU IVD Directive
- International Benchmarking of NIST Capabilities for Chemical Measurements
- International Comparisons in Electrochemical Analysis
- Sulfur in Diesel Fuel by Isotope Dilution Mass Spectrometry: Results of the CCQM K35 Key Comparison

**Program:** International Standards

**Title:** Identification and Provision of “Higher Order” Certified Reference Materials and Reference Measurement Procedures Required for U.S. Industry Compliance with the EU IVD Directive

**Authors:** W.E. May and V.L. Vilker

**Abstract:** The goal of obtaining comparability of laboratory diagnostic test results will be possible only when common reference systems can be established for worldwide use. A critical step in reaching this goal is achieving traceability of reference measurement procedures and reference materials to a universally recognized and accepted reference point such as the International System of Units (SI). Recently, traceability requirements for medical devices to be imported into the European Community have been codified. The European Community In Vitro Diagnostic Directive (EC IVDD) states that “The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order.” (98/79/EC, Annex1 (A) (3) 2nd paragraph). The Joint Committee on Traceability in Laboratory Medicine (JCTLM) was created to meet the need for a worldwide platform to promote and give guidance on internationally recognized and accepted equivalence of measurements in Laboratory Medicine and traceability to appropriate measurement standards. At present, neither reference materials nor reference methods are available for the vast majority of the chemical or biochemical species that are measured in medical laboratories using IVDs on a routine basis.

**Purpose:** Excluding home diagnostics, the overall world-wide invitro diagnostic market is approximately \$20 billion. The total IVD market in Europe was about \$5.6 billion in 1998 and has shown growth of about 4% per year over the past five years (data from [www.edma-ivd.be](http://www.edma-ivd.be)). Approximately 60% of the IVD products currently on the European market are imported from the US. The U.S. IVD industry (ADVAMED) has asked NIST to work with our counterparts in Europe and the Asia-Pacific to provide the reference materials and methods of “higher order” that are urgently needed to comply with the requirements of the EU IVD Directive. Without timely completion of these standards, the U S. IVD industry’s access into the European market will be seriously jeopardized.

**Major Accomplishments:** (A) NIST has provided the clinical measurements community with both neat chemical and human body fluid-based Standards Reference Materials for well-defined health status markers such as Electrolytes (sodium, potassium, lithium and magnesium), cholesterol, creatinine, glucose, triglycerides, urea, uric acid, vitamins A, C, E and beta carotene, and several therapeutic and drugs of abuse for more than 20 years.

Over the past few years, NIST has expanded its standards program in clinical diagnostics. A major portion of the expansion of the NIST program has involved the development of new standards for several protein, hormone, peptide, and other large biomolecule-based health status markers. Efforts have been initiated for development of reference methods and SRMs for: Cardiac Troponin I (heart attack occurrence and damage), C-Reactive Protein and Homocysteine (heart attack risk), Cortisol (endocrine function), Folates (neural tube defects), Glycated

Hemoglobin (diabetes status), Prostate Specific Antigen (prostate cancer), and Triiodothyronine and Thyroxine (thyroid function). Many of these new markers show great promise from the clinical diagnostic perspective, but offer new and more difficult challenges for standardization. They are present in the blood at very low concentrations and many are thermally labile, very polar, and heterogeneous -- both in conformation and in what is attached to them. Because of the vast market for tests for these new markers, many different measurement approaches have been developed that often provide quite different results. These discrepancies can lead to erroneous diagnoses and/or the need for retesting -- both very costly.

During the past year, work was completed on three new SRMs and three high-priority SRM renewals. A calibration standard for Cardiac Troponin-I (SRM 2921) was completed along with materials for Toxic Metals in Urine (SRM) and Homocysteine and Folate in Human Serum serum (SRM 1955). Renewals were completed for 956b – Electrolytes in Human Serum, SRM 965a - Glucose 1851b - Lipids in Human Serum.

(B) During the past year, NIST led the efforts of the Joint Committee on Traceability in Laboratory Medicine (JCTLM) Working Group on Reference Materials and Reference Laboratory Procedures in establishing a process for identifying, reviewing against agreed upon criteria, and publishing a List of “higher order” Certified Reference Materials and Reference Measurement Procedures required for IVD industry compliance with the EC IVD Directive regarding in vitro diagnostic medical devices. In order to facilitate a fair and transparent review process, eight analyte categories were identified and Review Teams established for each. To the extent possible, each Review Team has representation from IVD manufacturers, National Metrology Institutes, accreditation organizations, and professional societies from the US, Europe, and the Asia Pacific Region.

On April 1, 2004, the JCTLM published its first List of Higher Order Reference Materials and Reference Measurement Procedures. This initial List (List I) comprises Certified Reference Materials and Reference Measurement Procedures for well-defined chemical entities or internationally recognized reference method-defined measurands. Reference Materials and Measurement Procedures included in List I are those that provide values that are traceable to the SI units; e.g., electrolytes, enzymes, drugs, metabolites and substrates, non-peptide hormones and some proteins. List II, to be published during the last quarter of 2004, will comprise International Conventional Reference Materials, i.e., those for which the measurand(s) is/are not SI-traceable and/or no internationally recognized reference measurement procedure is available; e.g., WHO reference materials for coagulation factors, nucleic acids, and some proteins.

The current List contains approximately 100 Reference Measurement Procedure entries for 58 different health status markers. Thirty of these “higher order” reference measurement procedures are from NIST. For Reference Materials, the List contains approximately 150 entries for 96 measurands; NIST SRMs provide traceability for 72 of these. A laboratory-based quality assurance audit program has been initiated to provide measurement results regarding the comparability of multiple “higher order” Reference Materials for the same measurand on the list as well as to verify the veracity of the review process. Nominations are currently being accepted for high purity substance reference materials and for human hair and body fluid-based reference

materials and reference measurement procedures in the eight original plus five new analyte categories.

In a related activity, a NIST Traceable Reference Laboratory Network is being developed to provide higher order reference measurements to IVD industry. We are working with Mayo Clinic (a potential member of the reference laboratory network) and Dade Behring (an IVD manufacturer with a need for higher order reference measurements) to establish the guidelines and operating conditions. An exercise was completed this year to evaluate the comparability of reference measurements of calcium in serum, plasma, and urine made at Mayo Clinic with measurements made at NIST has been completed. This will serve as a model for establishment of the Network.

Reference Measurement Procedure					
Procedure Name and/or ID #	Analyte Name	Applicable Matrices	Measurement Principle	Reference Procedure Citation(s) or Document(s)	Reference Procedure Comparability Assessment Studies
NIST definitive method for serum cholesterol	cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Anal Chem 61, 1718-1723 (1989)	CCQM-K6; <a href="http://kcdb.bipm.org/appendixB/appbresults/ccqm-k6/ccqm-k6_final_report.pdf">http://kcdb.bipm.org/appendixB/appbresults/ccqm-k6/ccqm-k6_final_report.pdf</a> ; Clin Chem 36, 370-375 (1990)
U. Of Ghent reference method for cholesterol	cholesterol	lyophilized, fresh, or frozen serum	ID/GC/MS	Clin Chem 39, 1001-5 (1993) [part II of Clin Chem 39, 993-1000 (1993)]; Eur J Clin Chem Clin Biochem 34, 853-60 (1996); Clin Chem 42, 531-5 (1996)	EUROMET 563
DGKC definitive Method for Serum Cholesterol	cholesterol	lyophilized, fresh, or frozen human serum or plasma	ID/GC/MS	Siekman et al., Z. anal. Chem. 279, 145-146 (1976)	PTB - National Key Comparison for Accreditation
CDCAbell-Kendall method for cholesterol	cholesterol	lyophilized, fresh or frozen human serum	Spectrophotometry	Cooper, GR, et al, Clin Chem 32: 921-929, 1986	Clin Chem 36, 370-375 (1990)

Reference Materials							
Information about Material				Contact Information	References		Comments
Analyte	Matrix	Material Name and/or ID #	Estimated * Availability (months, as of Jan 2004)	- Producer - Country - Website - Email Address - Phone Number - Fax Number	Commutability Study Information and/or Citations	Other Relevant Publications	Hyperlink to Comparability Assessment Studies
cholesterol	cholesterol	GBW09203b	60	NRCCRM China Tel: 06-10-64221811 Fax: 06-10-64213149 Email: ccmiservice@nrccrm.com.cn	Primary calibrator for higher order reference methods		
cholesterol	cholesterol	SRM 911b	21	NIST USA <a href="http://ts.nist.gov/ts/hdocs/230/232/232.htm">http://ts.nist.gov/ts/hdocs/230/232/232.htm</a> Email: smm6@nist.gov Tel: (301)975-6776 Fax: (301)948-3730	Primary calibrator for higher order reference methods		
cholesterol	human serum	JCCRM 211		HECTEF Japan: <a href="http://www.inb.co.jp/hectef/staite.htm">http://www.inb.co.jp/hectef/staite.htm</a> Tel: 81-44-813-0055 Fax: 81-44-813-0024			NIST study presented at JCLM Meeting, June 20, 2003, BPM, Seves, France
cholesterol	human serum (frozen)	SRM 1951b	60	NIST USA <a href="http://ts.nist.gov/ts/hdocs/230/232/232.htm">http://ts.nist.gov/ts/hdocs/230/232/232.htm</a> Email: smm6@nist.gov Tel: (301)975-6776 Fax: (301)948-3730	Material prepared following NCCLS Document C3P-A "Preparation and Validation of Commutable Frozen Human Serum Pools as Secondary Reference Materials for"	Previous lot (1951a) was measured in NIST study presented at JCLM Meeting, June 20, 2003, BPM, Seves, France	
cholesterol	human serum (lyophilized)	SRM 1952a	60	NIST USA <a href="http://ts.nist.gov/ts/hdocs/230/232/232.htm">http://ts.nist.gov/ts/hdocs/230/232/232.htm</a> Email: smm6@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Method used for certification: Anal Chem 61, 1718-1723 (1989)	NIST study presented at JCLM Meeting, June 20, 2003, BPM, Seves, France
cholesterol	human serum (lyophilized)	SRM 968c	38	NIST USA <a href="http://ts.nist.gov/ts/hdocs/230/232/232.htm">http://ts.nist.gov/ts/hdocs/230/232/232.htm</a> Email: smm6@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Method used for certification: Anal Chem 61, 1718-1723 (1989)	NIST study presented at JCLM Meeting, June 20, 2003, BPM, Seves, France
cholesterol	human serum (lyophilized)	SRM009b	60	NIST USA <a href="http://ts.nist.gov/ts/hdocs/230/232/232.htm">http://ts.nist.gov/ts/hdocs/230/232/232.htm</a> Email: smm6@nist.gov Tel: (301)975-6776 Fax: (301)948-3730		Certification process described: Fresmann J Anal. Chem. 361:2 71-80 (1989). Method used for certification: Anal Chem 61, 1718-1723 (1989)	NIST study presented at JCLM Meeting, June 20, 2003, BPM, Seves, France

**Impact:** Clinical measurement results that are reliable and comparable over both space and time are essential for optimal patient care, most efficient use of available healthcare funds, and full utilization of the potential of new information technology tools. Incorrect interpretation of measurement results by the physician can lead to incorrect diagnosis and treatment, additional unnecessary tests and medical procedures, and increased pain and suffering for the patient. Measurements are responsible for 10%-15% of the \$1.7 T annual costs of healthcare in the United States. A significant portion (25% - 30%) of health-related measurements is performed for non-diagnostic reasons (re-tests, error prevention and detection). The “German Health Report of 1998” states explicitly that “the costs of repeat measurements amount to 1.5 billion US \$ per year in Germany.” If normalized to the U.S. GDP for that year, these costs would be \$7.4 B. Even modest improvements in measurement accuracy and quality assurance will result in multi-billion dollar savings in health-care costs. In addition to measurements reliability and related cost issues, timely completion of these standards will also assure U S. IVD industry’s continued access to the European market.

**Future Plans:** Work will continue on the high priority list presented above. Work will begin on standards for gene expression including RNA standards and a fluorescence standard for microarray scanning devices. The JCTLM List of “higher order standards” will be updated and expanded to include Reference Materials and Reference Laboratory Procedures for Blood Gases, Blood Groupings, Microbial Serology, Non-Electrolyte Metals and Vitamins.

**Program:** International Standards

**Title:** International Benchmarking of NIST Capabilities for Chemical Measurements

**Authors:** W.E. May, G.C. Turk, S.A. Wise, F.R. Guenther, G.W. Kramer, R.R. Greenberg, and R.M. Parris

**Abstract:** Traceability to stated references and global confidence in this realization are the basis for mutual recognition and confidence in data used to facilitate and underpin international trade and decisions regarding health, safety, commerce, and scientific studies. In October 1999, the Directors of National Metrology Institutes (NMIs) for the thirty-eight member states of the Meter Convention, and representatives of two international organizations signed a Mutual Recognition Arrangement on national measurement standards and calibration and measurement certificates issued by national metrology institutes (MRA). The NIST Analytical Chemistry Division has ongoing major activities to meet the MRA requirements for NMIs:

1. Declaring and documenting calibration and measurement capabilities
2. Evidence of successful participation in formal, relevant international comparisons
3. Demonstration of system for assuring quality of each NMI's measurement services

**Purpose:** Traceability to stated references and global confidence in this realization are the basis for mutual recognition and confidence in data used to facilitate and underpin international trade and decisions regarding health, safety, commerce, and scientific studies. In October 1999, the Directors of National Metrology Institutes for the thirty-eight member states of the Meter Convention, and representatives of two international organizations signed a Mutual Recognition Arrangement on national measurement standards and calibration and measurement certificates issued by national metrology institutes (MRA). This MRA provides an open, transparent, and comprehensive framework for obtaining reliable quantitative information on the comparability of metrological services needed for mutual recognition of national measurement standards and measurement certificates issued by national metrology institutes around the World. This Arrangement also provides governments and other parties with a secure technical foundation for wider agreements related to international trade, commerce, and regulatory affairs.

**Major Accomplishments:** For implementation of this MRA, the signatory NMIs agreed to:

1. declare and document their calibration and measurement capabilities (CMCs)[Appendix C]
  - CSTL's Analytical Chemistry Division has over 1000 CMCs for Chemical Measurements included in ~3000 CMCs for Chemical Measurements published in the CIPM MRA Appendix C (<http://kcdb.bipm.org/AppendixC/default.asp>)
2. participate in relevant international comparisons to support their CMCs [Appendix B] (<http://kcdb.bipm.fr/BIPM/KCDB/>, <http://icdb.nist.gov>)
  - CSTL's Analytical Chemistry Division has participated in >80 international comparisons to meet requirements of the CIPM MRA. Results of selected recent comparisons are shown below.

3. implement and document the existence of a system for assuring the quality of the measurement services provided.
  - CSTL's Analytical Chemistry Division's Quality Manual that summarizes and formalizes policies and approaches for addressing quality-related issues concerning the services that it provides has been updated to assure appropriate compliance with ISO/EC 17025 and ISO Guide 34.

The implementation of the CIPM MRA is carried out by a Joint Committee of Regional Metrology Organizations (RMOs) and the BIPM (JCRB). The JCRB is made up of representatives from each RMO and the BIPM, and provides oversight for results included in the Key Comparisons Database (Appendix B of the MRA), as well as the determination of the degree(s) of equivalence of results from individual NMIs. RMOs have the responsibility for carrying out supplementary comparisons and other actions within their regions to support mutual confidence in the validity of calibration and measurement certificates through the Joint Committee of the RMOs and the BIPM (JCRB). They are also responsible for approval of calibration and measurement capabilities (CMCs) of their member NMIs.

Systema Interamericano de Metrologia (SIM) is the metrological regional organization (RMO) for the Americas. CSTL provides the Chair for the Chemical Metrology Working Group and SIM representative to the JCRB. In order to assure the effective, fair and metrologically sound implementation of the MRA. CSTL staff have led the critical review of both SIM and international chemistry CMC data for Appendix C of the BIPM.

CSTL staff also play a leadership role the International Committee of Weights and Measures-Consultative Committee on the Quantity of Material (CCQM). The CCQM has formed seven working groups: (1) Gas Analysis, (2) Organic Analysis, (3) Inorganic Analysis, (4) Electrochemistry (5) Biometrology, (6) Surface Analysis and (7) Key Comparisons and CMC Quality. These working groups are responsible for selecting and overseeing the operation of key comparisons that address chemical measurement-related issues important for international trade, environmental, health, and safety-related decision making. CSTL staff are active in all seven and has provided formal leadership for the Organic Analysis, Biometrology, and Key Comparisons Working Groups.

**Impact:** NIST and other National Metrology Institutes around the world have the responsibility for establishing, maintaining, and disseminating the highest level of metrological references for a given country or economy. The calibration and measurement services that these NMIs provide must be of high quality and delivered to our customers in a consistent and transparent manner.

**Future Plans:**

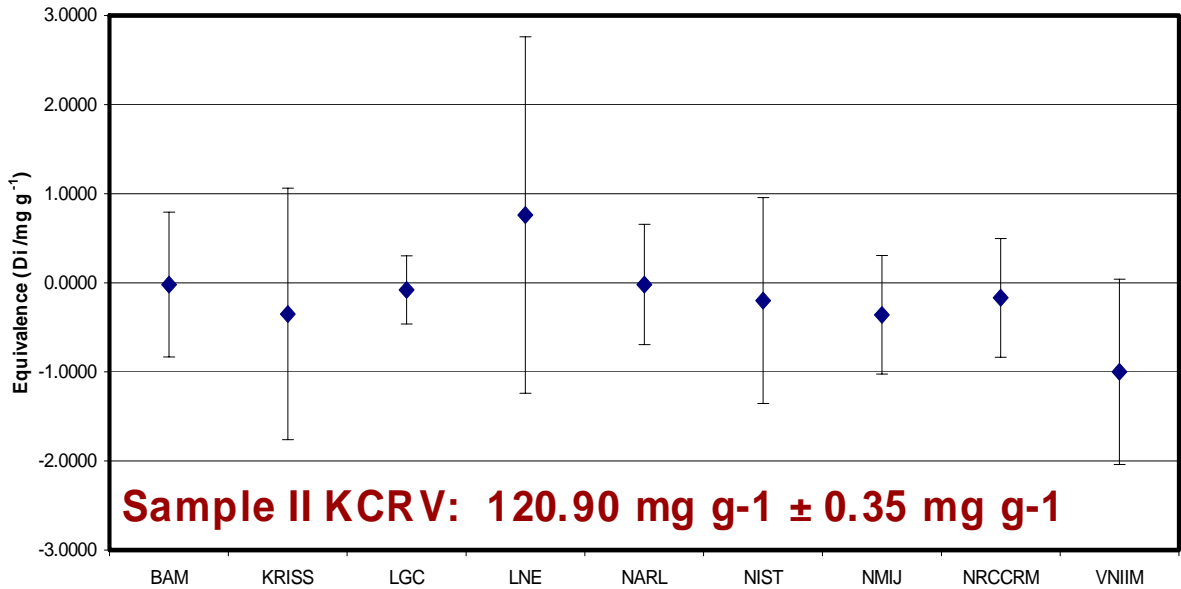
Over 25 additional CCQM studies are planned to be conducted over the next two years and the Analytical Chemistry Division has already committed to coordinate at least 7 of these. In addition, the Division's Quality System for its measurement services will be presented to and assessed by the SIM Quality System Task Force. The results of this review will be reported to the CIPM JCRB the complete the requirements for maintaining our CMCs in the CIPM Database.

## Examples of NIST participation in recently completed international comparisons

### CCQM-K27: Determination of Ethanol in Aqueous Matrices Study Period: 2002

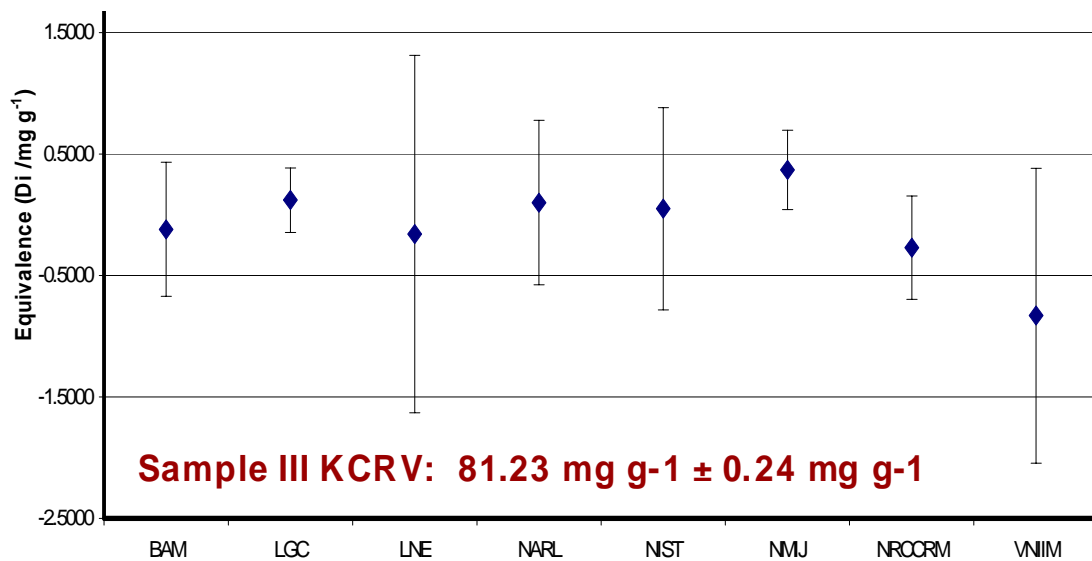
CCQM-K27a Forensic level

Samples II (aqueous solution spiked gravimetrically with ethanol)



CCQM-K27b Commodity level

Sample III (commercial red wine stabilized by irradiation)





## Determination of Ethanol in Aqueous Matrix

**Study Period: 2003**

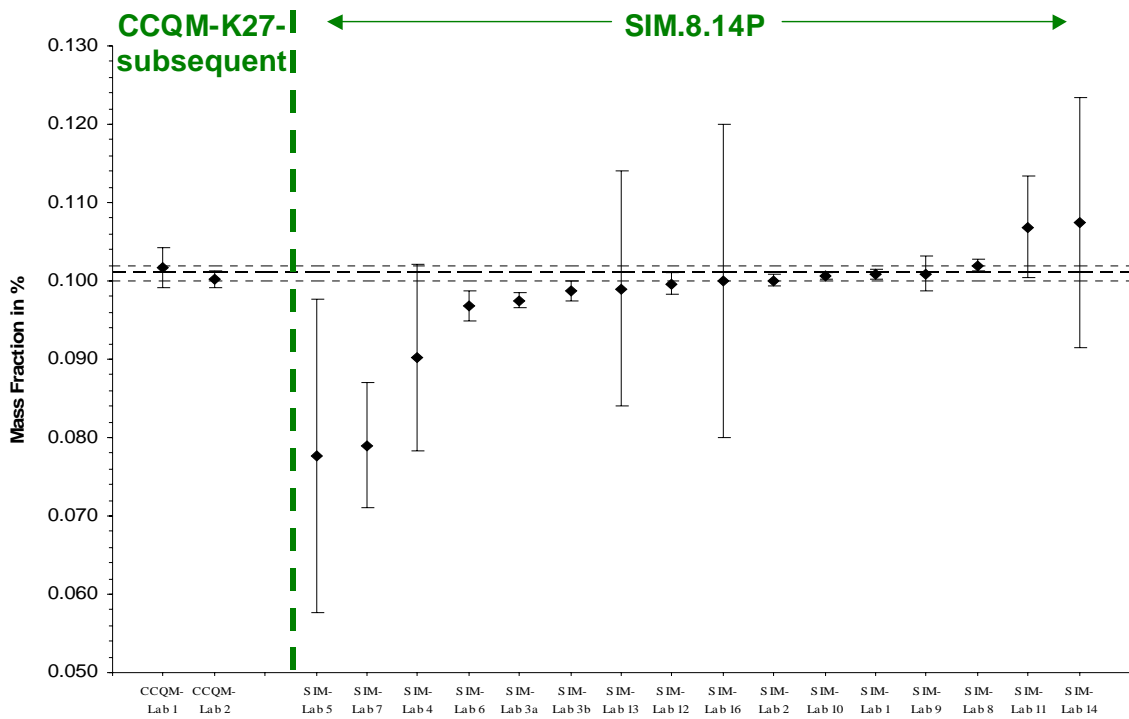
As SIM Pilot Comparison: SIM.8.14P (16 participants)

As Key Comparison: CCQM-K27-subsequent (4 participants)

### Ethanol in Aqueous Matrix

**Sample SII: nominal concentration 0.1% ethanol in water**

(showing gravimetric value and upper and lower limits of the 95% CI of the gravimetric value based on the CCQM-K27a study)

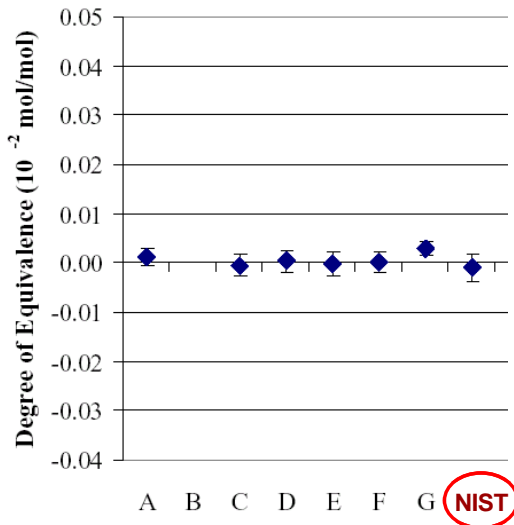


## Determination of Components of Natural Gas

### CCQM-K16a: Natural Gas

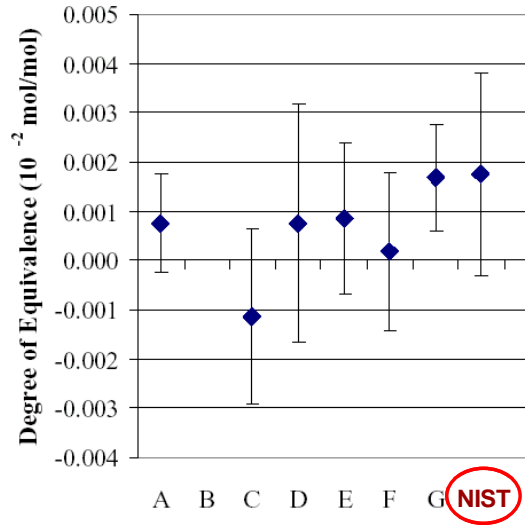
Propane

Nominal composition: Propane 0.30 %, mol/mol

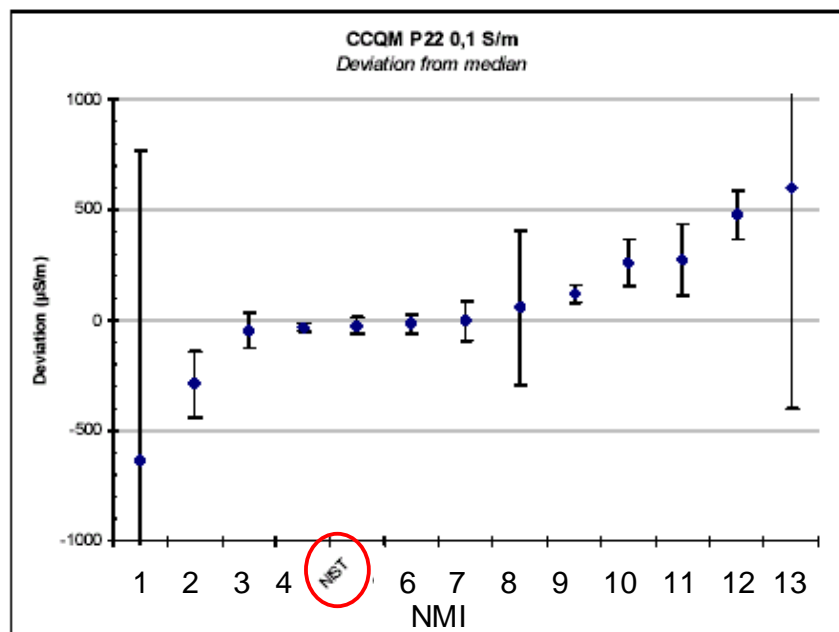


iso-butane

Nominal composition: iso-Butane 0.20 %, mol/mol



## CCQM-P22: Electrolytic Conductivity (primary and secondary measurements)



Nominal 0.1 S/m (1000 µS/cm)

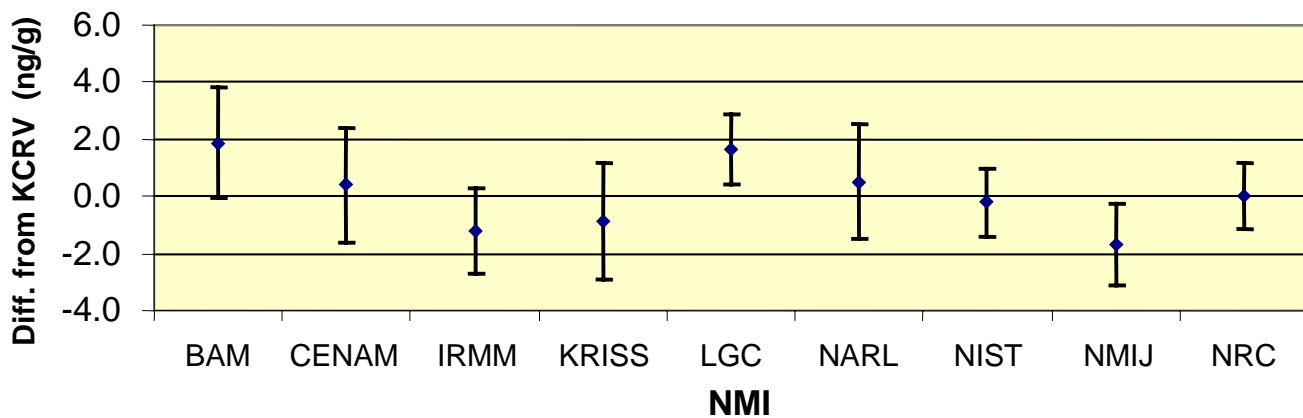
## CCQM-K25: PCB Congeners in Sediment

The five PCB congeners measured in CCQM-K25 were selected to be representative of the approximately 150 congeners found in environmental samples. These five congeners also provided the typical analytical measurement challenges encountered including problematic GC separations and a wide volatility range and concentration range for the individual congeners. The results for PCT 153 are shown below.

- PCB 28 - volatile and potential coelution with PCB 31
- PCB 101 - potential coelution with minor congener, PCB 90
- PCB 105\* - lower concentration and potential elution order changes with PCB 153 and/or PCB 132
- PCB 153 - potential coelution with PCB 132
- PCB 170 - lower concentration and potential coelution with PCB 190

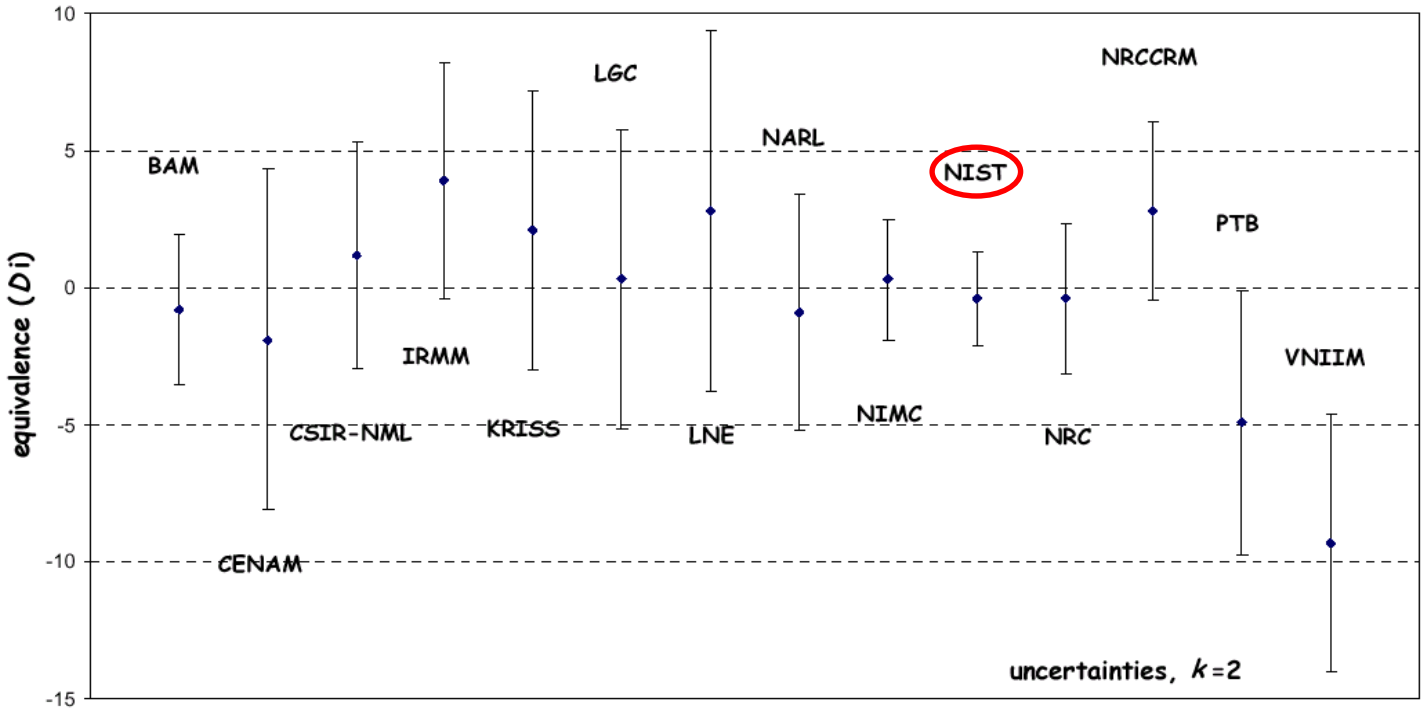
### CCQM-K25 PCB 153 Equivalence

**KCRV: 31.9 ng/g (dry basis)  $\pm$  1.1 ng/g (dry basis)**



Determination of Cadmium and Lead in Sediment

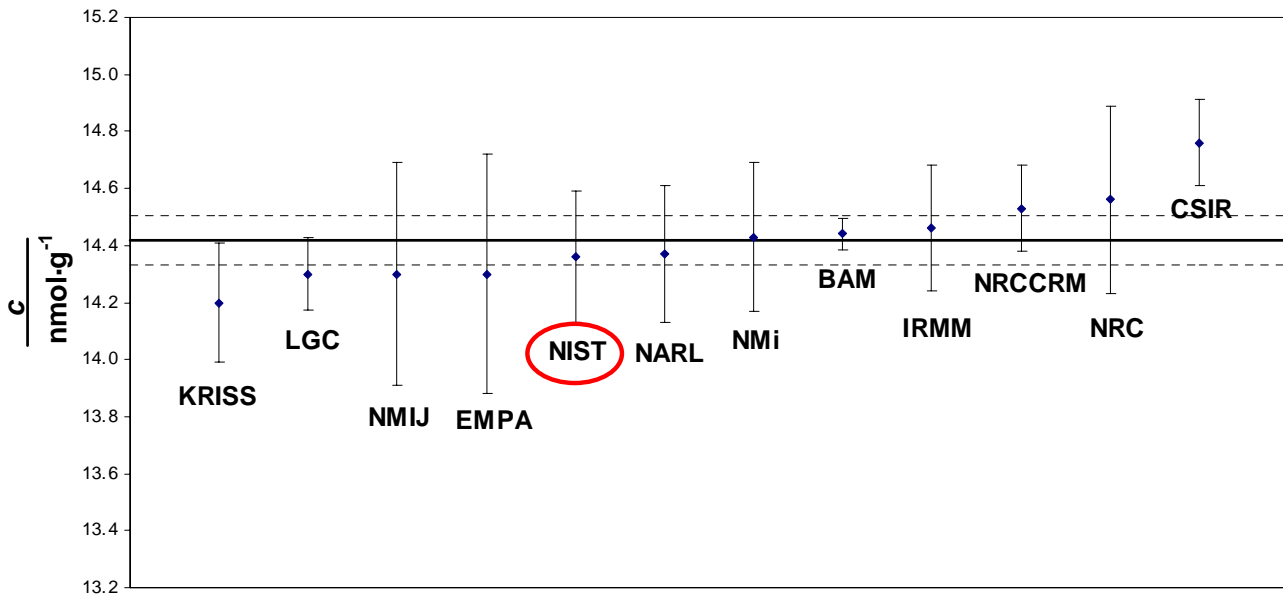
*CCQM-K13 key comparison Pb in sediment*



Determination of Cadmium in Rice

**CCQM-K24: Cd in rice**

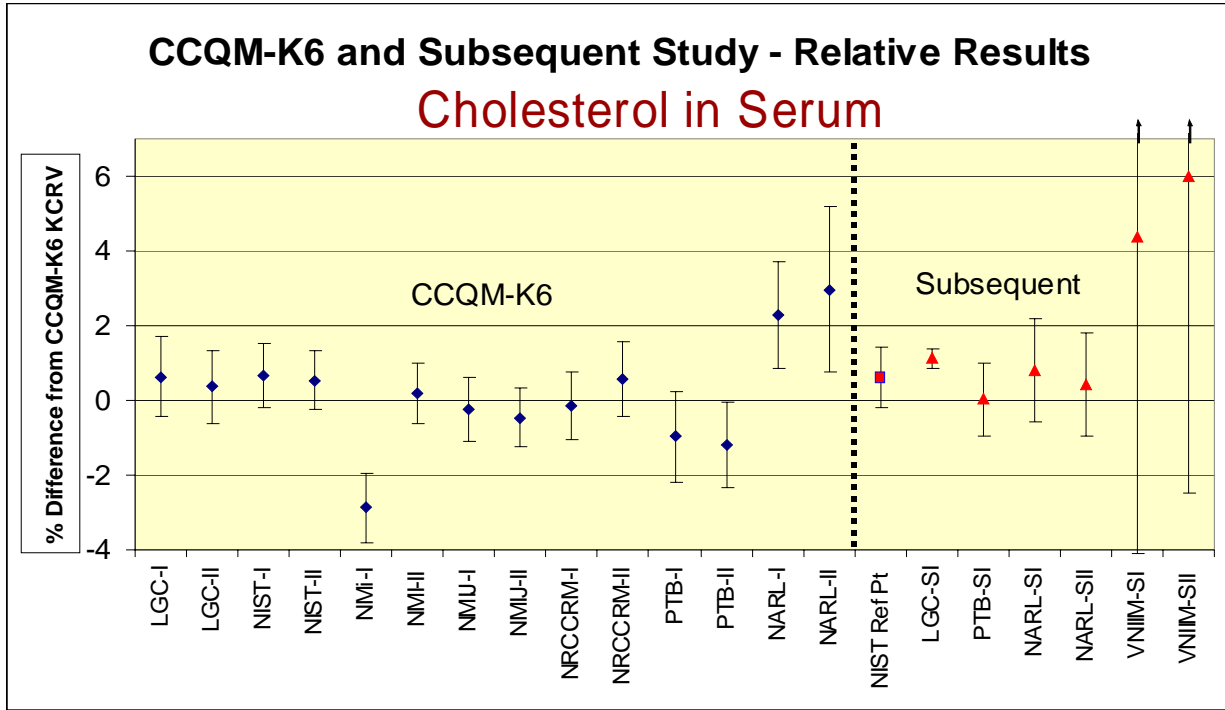
KCRV:  $14.418 \pm 0.087 \text{ nmol}\cdot\text{g}^{-1}$ ;  $U=ku_c, k=2$



Expanded uncertainties with coverage factor of k=2

*Uncertainty of prescribed drying protocol was major component of NIST expanded uncertainty.*

## Determination of Cholesterol in Serum



**K6 results are plotted as % differences from KCRVs**

**Subsequent results are plotted relative to NIST results in K6S and are offset by average (NIST-KCRV) result from K6 (NIST Ref Pt)**

**Program:** International Standards

**Title:** International Comparisons in Electrochemical Analysis

**Authors:** K.W. Pratt

In FY 2004, NIST participated in three international comparisons in the area of electrochemical analysis: SIM.8.11P in pH measurement, CCQM-K34 in assay of potassium hydrogen phthalate (KHP), and CCQM-P47 in electrolytic conductivity.

SIM Pilot Study SIM.8.11P, piloted by CENAM, was a follow-up to the previous SIM.8.P4, which had been piloted by NIST in 2000. Five participants, including NIST, performed Harned cell pH methods (primary method). The NIST results were in excellent agreement (within  $\pm 0.0017$  pH) with other experienced NMIs (those that had participated in previous CCQM pH Key Comparisons CCQM-K9 or CCQM-K17). The NIST uncertainties, which included all known Type A and Type B sources, were equal to or smaller than those of the other participating NMIs in the primary measurement. The reduction in the NIST combined uncertainty resulted from a threefold reduction in the Type A uncertainty of the extrapolation of the acidity function to obtain  $pa^\circ$ , the acidity function in buffer without added chloride (from which the pH in directly obtained). This reduction was directly attributable to the implementation of pre-equilibration of the Ag|AgCl electrodes used in the Harned cells. The results of this Pilot Study correspond directly to the procedure for the certification of the phosphate pH SRM 186g and support the validity of its certification.

CCQM Key Comparison CCQM-K34 was designed to evaluate the agreement obtainable for the assay of potassium hydrogen phthalate (KHP) using high-accuracy assays. The seven participants each used coulometry. The NIST result and its estimate of uncertainty agreed well with those of the other “experienced” NMIs (who had participated in the corresponding pilot study, CCQM-P36). In addition, the NIST estimate of uncertainty was more complete than those submitted by all but one of the other participants (one included the same set of sources), in that more possible sources of uncertainty were included in the estimate.

CCQM Pilot Study CCQM-P47 evaluated the performance of NMIs in the measurement of electrolytic conductivity of two KCl solutions of nominal conductivity equal to 50 mS/m (500  $\mu$ S/cm) and 5 mS/m (50  $\mu$ S/cm). For the 5 mS/m solution, the pilot laboratory (NMI, Netherlands) discovered a time-instability in the solution as stored in the bottles used for distribution of the solution. Following discussion of the original results among the participants in April 2004, the pilot laboratory, NMI (Netherlands), decided to institute a time-dependent correction of the reference value. For the 50 mS/m solution, the NIST result was initially higher than the reference value. Following discussion at the CCQM Electrochemical Analysis Working Group, April, 2004, the cell calibration procedure used at NIST was modified to eliminate the non-IUPAC primary calibrants that previously had been used. With this modification, the NIST result for the 50 mS/m solution was in excellent agreement with the reference value.

In addition to the above three comparisons, NIST also completed and submitted to the CCQM the Final Report of Pilot Studies CCQM-P19/P19.1, Assay of 0.01 mol kg<sup>-1</sup> Hydrochloric Acid,

in which NIST was the pilot laboratory. The analyses for the two phases of this Pilot Study had been completed in preceding years, with 14 participants from NMIs worldwide. The submission of the Final Report formally completes this study and constitutes the official record of its results.

**Program:** International Standards

**Title:** Sulfur in Diesel Fuel by Isotope Dilution Mass Spectrometry: Results of the CCQM K35 Key Comparison

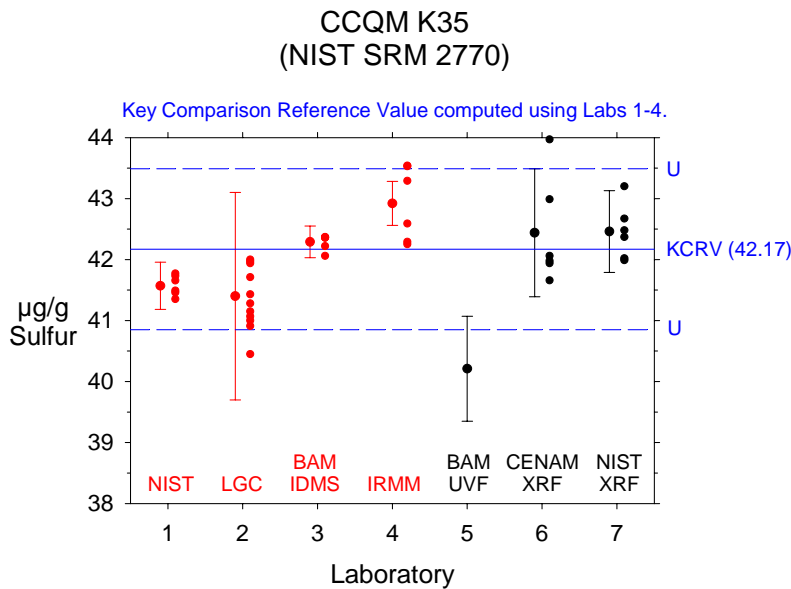
**Authors:** W.R. Kelly, R.D. Vocke, J.L. Mann, and G.C. Turk

**Abstract:** NIST planned and conducted a CCQM Key Comparison (K35) and a concurrent pilot study (P26.1) on sulfur in diesel fuel and kerosene. Participants in the studies measured sulfur concentrations in three candidate SRMs covering a wide range of sulfur concentrations. There was generally good agreement among the NMIs for both the Key Comparison nominal 40  $\mu\text{g/g}$  diesel fuel and the nominal 8  $\mu\text{g/g}$  kerosene used in the Pilot Study. Participants also measured a nominal 4000  $\mu\text{g/g}$  check sample included in the studies to distinguish measurement issues associated with sulfur blanks at the lower concentrations from other potential measurement problems.

**Purpose:** There is a regulatory requirement in North America and Europe that the petroleum industry and regulatory environmental agencies be able to measure accurately sulfur in diesel fuel between 5 and 50  $\mu\text{g/g}$  with a total combined uncertainty of less than 1  $\mu\text{g/g}$ . Both Europe and the United States will be moving to 50  $\mu\text{g/g}$  and below fuels in the next year. Lower sulfur in fuels will make possible extremely efficient and long-lived after-treatment technologies based on noble metal catalyst. This Key Comparison and associated Pilot Study was undertaken to assess and document the capability of National Metrology Institutes (NMIs) to perform accurate determinations of sulfur in diesel fuel at and below future regulatory limits.



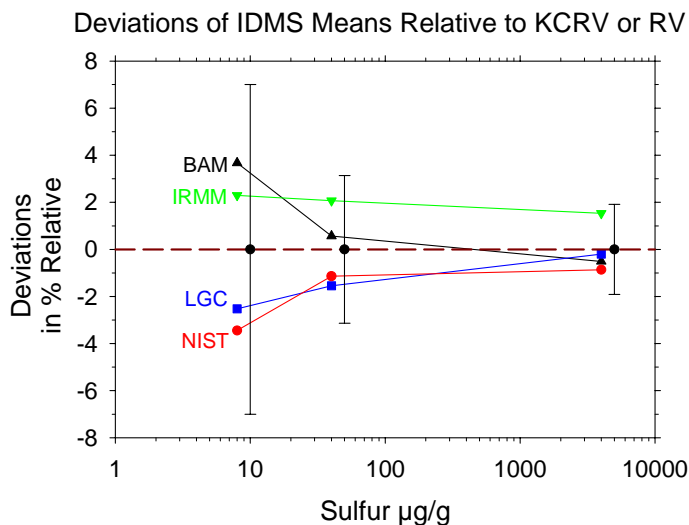
**Major Accomplishments:** Results of CCQM K35 and P26.1 were reported to the Inorganic Working Group of the CCQM at their meeting in April 2004. The Key Comparison data are shown graphically in figure below.



The four laboratories shown in red were registered Key Comparison participants using isotope dilution mass spectrometry either with thermal ionization instruments (NIST and BAM) or ICP-MS (LGC and IRMM). The other values were submitted as Pilot Study results. Shown in the figure are the means and total expanded uncertainties expressed as 95 % confidence intervals and the individual determinations (solid circles to the right of the estimates) submitted by the NMIs. The Key Comparison

Reference Value (KCRV) was computed using the Mixture Model Median method developed by D. Duewer of NIST. The agreement among the four NMIs is considered good since the computed standard deviation is less than 1 µg/g.

The results on all three samples are shown in the next figure as deviations from the reference values in relative percent. The reference values and total uncertainty are indicated by the points and error bars that are centered on the zero reference line. The reference values have been arbitrarily shifted to higher values for clarity of presentation. The greater spread in the data at the lower concentrations is a consequence of the greater influence of the blank.



**Impact:** The International Council on Clean Transportation states the following:

Worldwide, many jurisdictions have recognized the public health and environmental costs of allowing motor vehicle fuels to contain High levels of sulfur. The European Union, United States, and Japan have led the way in sulfur reduction, and will reach near-zero sulfur levels later in this decade.

CCQM K35 Key Comparison has demonstrated the capability of 4 NMIs to perform sulfur measurements in diesel fuel at a nominal 40  $\mu\text{g/g}$  concentration. Today the regulated upper sulfur limit in US on-road diesel fuel is 500  $\mu\text{g/g}$ , but this limit will drop to 15  $\mu\text{g/g}$  in year 2006 and perhaps to near-zero ( $< 5 \mu\text{g/g}$ ) in the next decade. Japan and Europe will adopt a 50  $\mu\text{g/g}$  limit in years 2004 and 2005. Europe will phase in a 10  $\mu\text{g/g}$  limit between 2005 and 2009 and Japan will adopt the same limit in year 2007. The incremental measurement challenges increase non-linearly as sulfur concentrations decrease from 500 to near zero levels. The regulatory agencies and the petroleum industry look to the national metrology laboratories to produce calibration standards with certified concentrations and uncertainties that will ensure a smooth and cost effective transition to low sulfur diesel fuel. CCQM K35 and P26.1 address present and near future measurement needs at the NMI level.

**Future Plans:** At the present time there are no plans to conduct a Key Comparison at the lower level, but this may change as sub-10  $\mu\text{g/g}$  capabilities will be needed by Europe and Japan starting in 2005 and that must be phased in completely by 2009.