Chemical Metrology and Its Impact on Trade, Innovation and Quality of Life

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Chemical Science and Technology Laboratory
National Institute of Standards and Technology

- **Needs for Metrology; Historical Perspective**
- **Increasing Need for Chemical Measurements of Known Quality**
- **Drivers and Scope of Activities within the NIST Chemical Science and Technology Laboratory**
- **A few Program Details/Examples**
  showing need and impact
  - *Food Safety and Nutrition*
  - *Health Care*
  - *Forensics*
  - *The Environment*
- **Resource and Infrastructure Requirements**

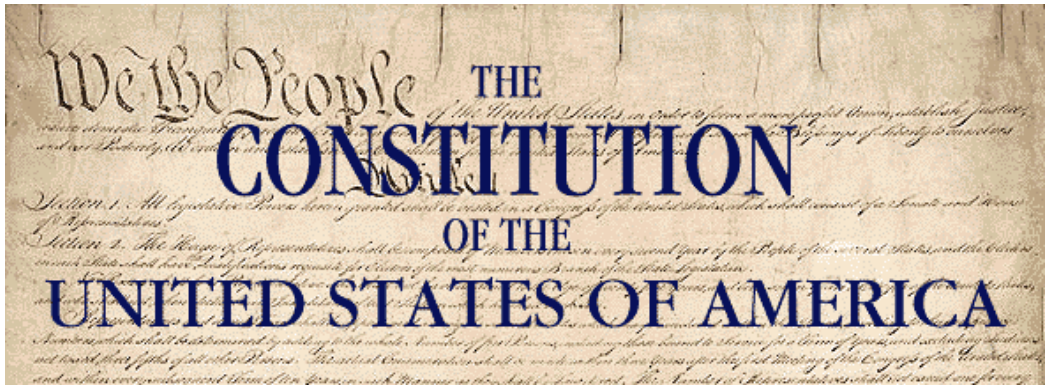
Metrology in Ancient Times

- **Standard unit of length** - the length of Pharaoh's forearm plus the width of his palm
  - **The Cubit**
- The "Royal Cubit Master"
  - **Primary standard** in granite
- Realization of the Cubit: A stick of wood
  - **Working Standard** / Comparability
- Re-calibration of cubit stick on each full moon
  - **Calibration / Traceability**
  - Severe penalty for non-compliance

- **Uniformity of length measurement in Egypt was achieved to a relative accuracy of 0.05 % over a distance of 230 meters**

U.S. Federal Role in Metrology

The Constitution of the United States



Article 1, Section 8: The Congress shall have the power … *to coin money, regulate the value thereof, and of foreign coin … and fix the standard of weights and measures … (1788)*

"Foreign traders had begun to voice concern that goods might not be assigned a proper quantitative value at American custom-houses and that, as a result, assessed duties might be unfair and uneven from port to port."

John Quincy Adams (1817)

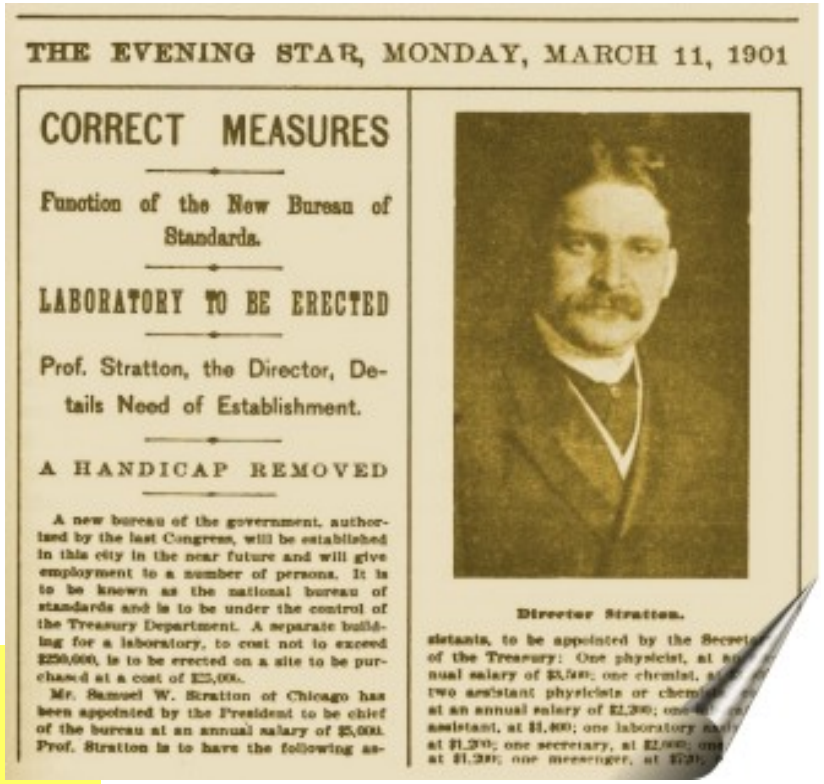
NIST (NBS) established in 1901

"It is therefore the unanimous opinion of your committee that no more essential aid could be given to

- **manufacturing**
- **commerce**
- **the makers of scientific apparatus**
- **the scientific work of Government**
- **schools, colleges, and universities**

than by the establishment of the institution proposed in this bill."

House Committee on Coinage, Weights and Measures ...
May 3, 1900
on the establishment of the National Bureau of Standards (now NIST)



THE EVENING STAR, MONDAY, MARCH 11, 1901

CORRECT MEASURES

Function of the New Bureau of Standards.

LABORATORY TO BE ERECTED

Prof. Stratton, the Director, Details Need of Establishment.

A HANDICAP REMOVED

A new bureau of the government, authorized by the last Congress, will be established in this city in the near future and will give employment to a number of persons. It is to be known as the national bureau of standards and is to be under the control of the Treasury Department. A separate building for a laboratory, to cost not to exceed $250,000, is to be erected on a site to be purchased at a cost of $25,000.

Mr. Samuel W. Stratton of Chicago has been appointed by the President to be chief of the bureau at an annual salary of $5,000. Prof. Stratton is to have the following as-

Director Stratton.

sistants, to be appointed by the Secretary of the Treasury: One physicist, at an annual salary of $3,500; one chemist, at [illegible] two assistant physicists or chemists at an annual salary of $1,200; one [illegible] assistant, at $1,000; one laboratory [illegible] at $1,200; one secretary, at $2,000; one [illegible] at $1,200; one messenger, at $720;

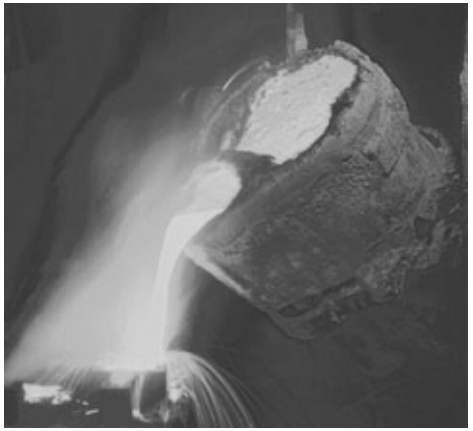
Early Drivers for Standards and Measurements

1904

Out-of-town fire companies arriving at a Baltimore fire cannot couple their hoses to the hydrants. 1526 buildings razed. In 1905 NFPA adopted NBS-developed national hose coupling standard

1905

Standard samples program begins with "standardized irons" in collaboration with the American Foundrymans Association



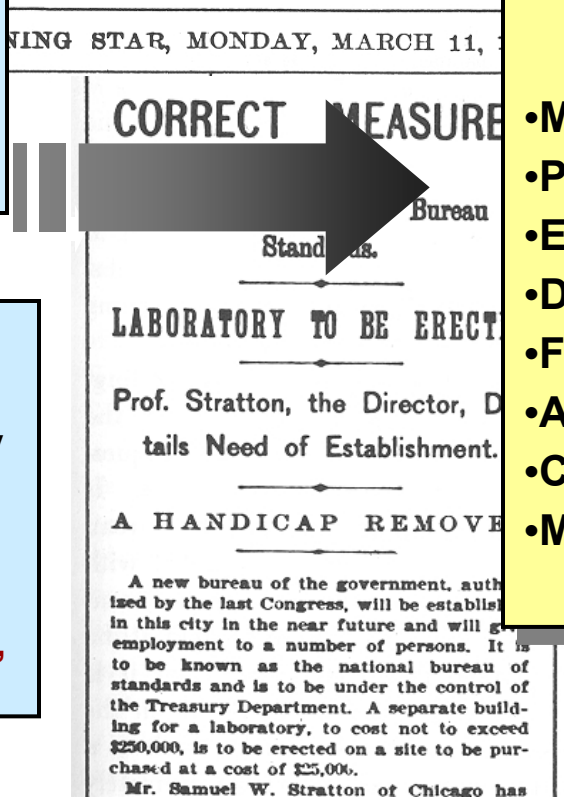
1912

41,578 train derailments in the previous decade led to NBS measurement and test program

Chemistry at NIST – Past and Present

Division I
Heat and Thermometry
"As primary standards, this section had acquired a number of specially constructed … thermometers in Europe and was prepared to certify almost any precision thermometers used in scientific work, industrial and commercial thermometers."

Division III
Chemistry
"This section was increasingly involved in its investigation of properties for the Government testing program and produced standard samples of alloys, steels, iron ores, copper slags, cements, and lubricating oil."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Bureau

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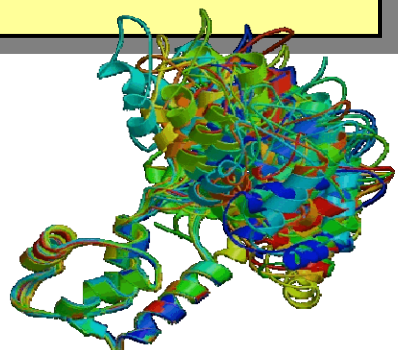
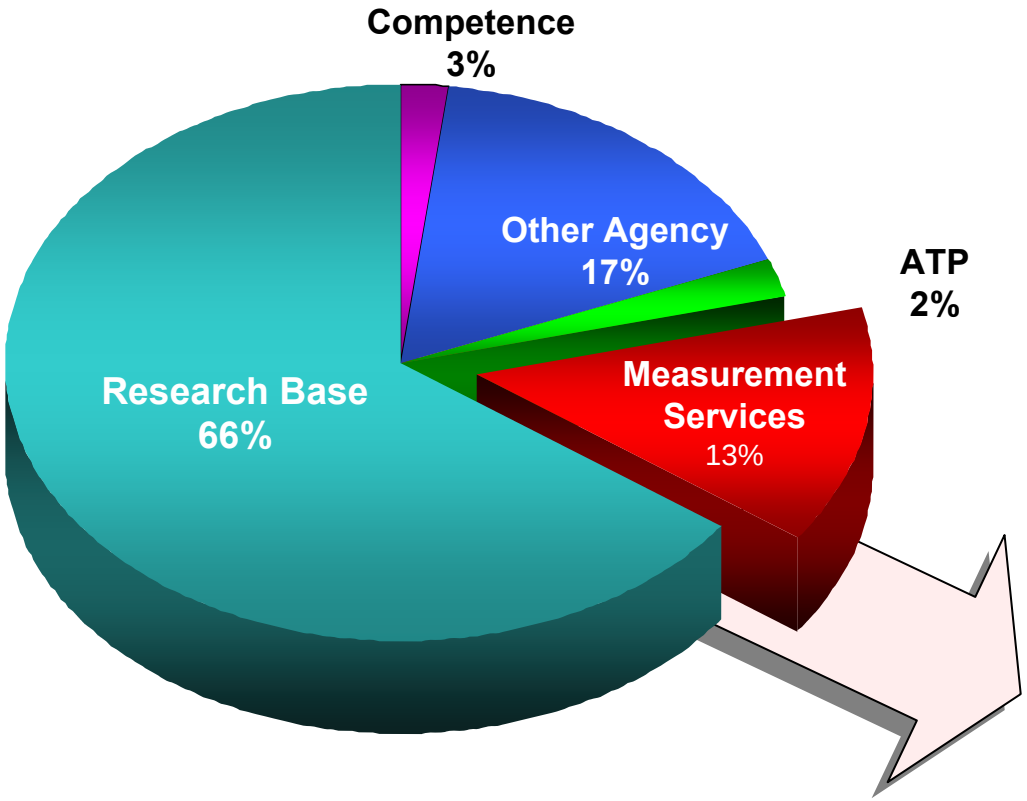
Mr. Samuel W. Stratton of Chicago has

New Industries and New Technologies

- **Medical Diagnostic Markers**
- **Point-of-Care Testing**
- **Environmental Measurements**
- **DNA Technologies**
- **Food and Nutraceuticals**
- **Advanced Materials**
- **Commodities**
- **Microfluidic Technologies**

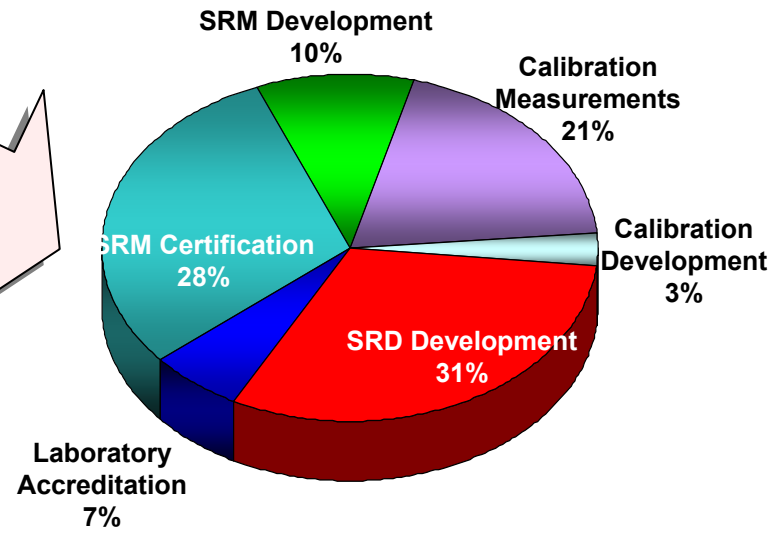


CSTL Funding, FY2005 est.

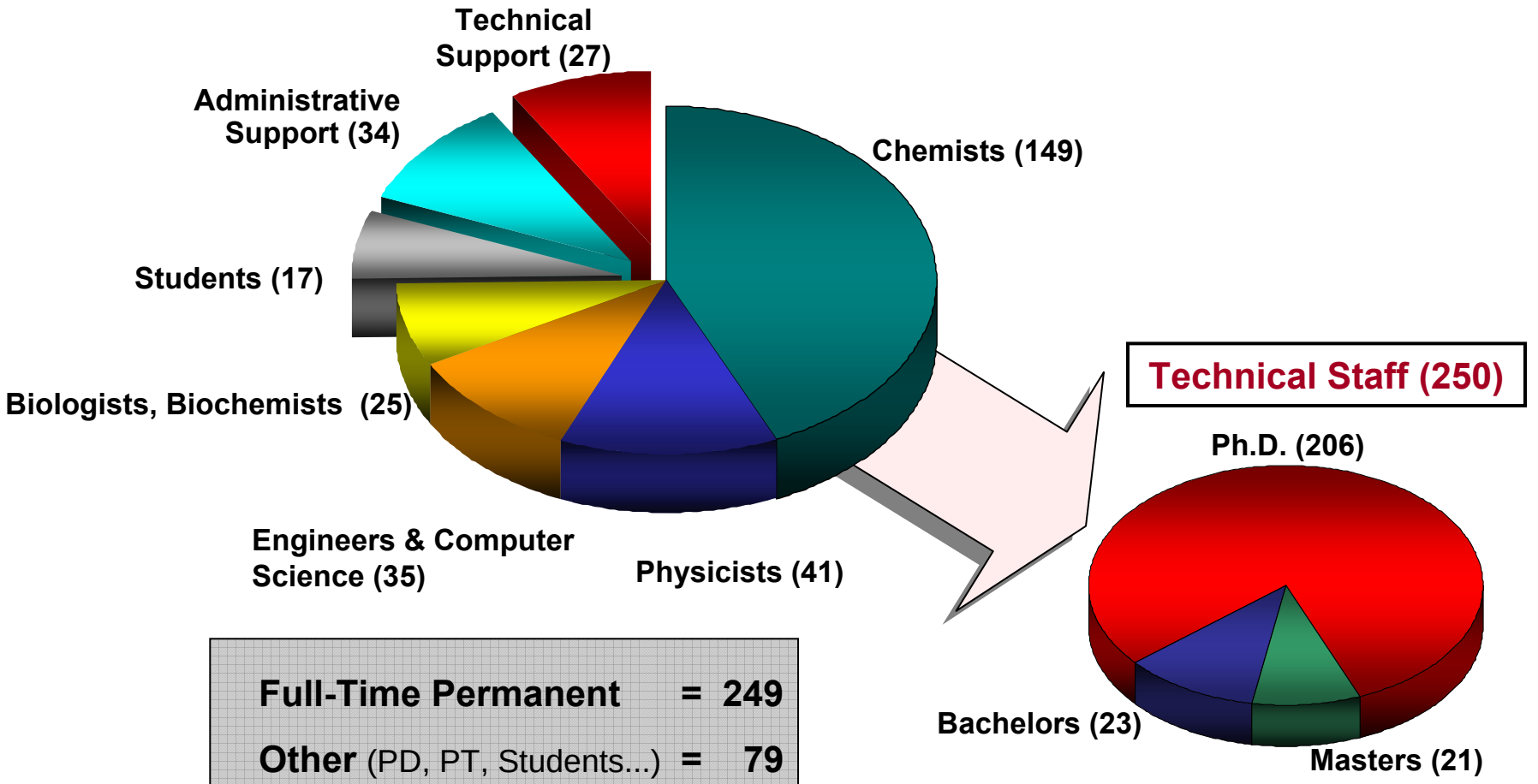


Funding Sources
Total = $70M

Measurement Services
Total = $9.8M



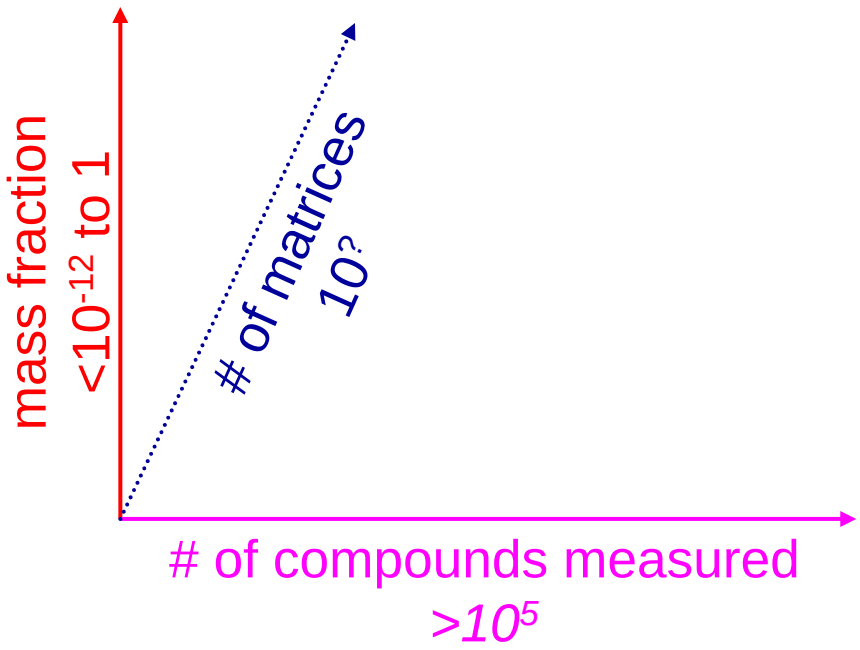
CSTL Staff



Full-Time Permanent	=	**249**
Other (PD, PT, Students...)	=	**79**
Guest Researchers	=	**237**

… and Executed by an Exceptional and Diverse Staff.

Chemical Measurement Universe



diverse customers - diverse needs

advanced materials

process chemistry

environmental

aerospace

food

healthcare

polymers

analytical instrumentation

pharmaceuticals

agricultural

forensics/defense/security

energy/fuel

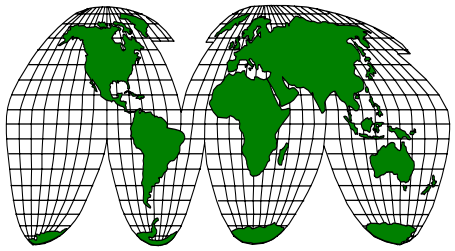
semiconductor

metal alloys

automotive

Increasing Importance and International Interest in Chemical Measurements of known quality

- National and International Trade Issues
- Environmental Decision-Making
- Assessing Food Quality
- Healthcare Decision-Making
- National Security
- Innovation and Industrial Competitiveness



National and International Trade

- Food Importing/Exporting
- Pricing of Commodities
- Source of Origin
- GMO

".... the traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or reference materials of a higher order ..."

EC-IVD Directive Annex 1 (3)

Approximately 60 % of the in vitro diagnostic medical devices (IVD MD) currently on the ~ $6 B/yr European market are imported from the US. (Worldwide, the in vitro diagnostic device market is ~$20B)

International Regulations on the Restriction of Hazardous Substances

European Union member nations are about to restrict the use of hazardous substances in electrical and electronic products and components.

China recently announced similar restrictions as part of their drive to reduce the problem of electronic waste in their country.

In **Japan**, electronics manufacturers recently set specifications to restrict the use of 24 substances by their suppliers and their own manufacturing facilities.

Many States in the US either have or are considering RoHS-like statutes

These regulations and specifications are aimed at products going to market.

EU Directive 2002/95/EC, Restriction of Hazardous Substances (RoHS)

- **Restricts *Cd, Pb, Hg, Cr6+, Flame retardants*** *(PBBs, PBDEs)*
- **Requires *manufacturers to implement testing procedures* for raw materials and finished products to ensure compliance with these mandates**

Legislation in the EU and US for Food Labeling

- Labeling of nutrient concentrations
- Limits on contaminants and additives
- Disclosure of possible allergen cross-contamination
- Disclosure of GMO content
- Health claims
- Authenticity/adulteration

Current prominent food issues:

- Allergens
- Carbohydrate/Fiber
- Trans Fats (Natural vs. Incurred)
- Genetically-Engineered Foods (GMOs)
- Mycotoxins and Phycotoxins
- Hormones and Drug Residues
- Methylmercury, PAHs, PCBs, Pesticides, PBDEs, Perfluorinated Compounds
- “Functional” Foods
- Food Safety/Security

Mercury in the Environment

- **On February 24, 1998 EPA issued a report to Congress on air toxics emissions from the utility industry. *"…on balance, mercury from coal-fired utilities is the hazardous air pollutant of greatest public health concern."***

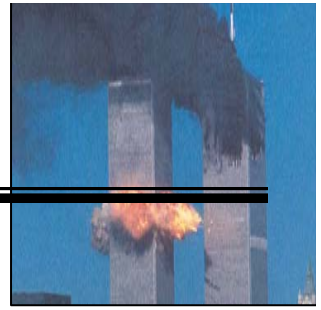
  - **EPA is to regulate Hg air emissions from coal-fired power plants, which contribute a third (50 tons) of the anthropogenic Hg released to the environment each year**
  - **Hg bio-accumulates as the highly toxic species methylmercury in the aquatic environment, the primary source of risk to human health being consumption of fish (freshwater and marine). The NRC estimated that *"… ~60,000 US children may be born each year with neurological defects resulting from in utero exposure to Hg in seafood."***

    - **FDA report states: *"Commercial fish sold through interstate commerce that are found to have levels of methylmercury above an "action level" of 1 ppm cannot be sold to the public."***

Environmental Decision-Making:

- Emissions Trading
- Waste Disposal Issues
- Air and Water Quality

Public Safety and Security



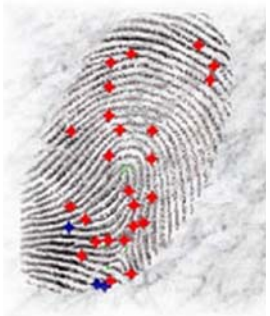
Measurements and standards infrastructure that ensures the accuracy, reliability, and security of systems critical to public safety and homeland security

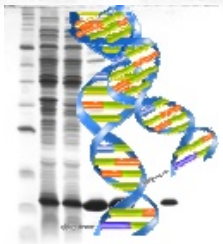
Develop, compare, and test new technologies.
Enable safe and effective response to incidents.

mail irradiation

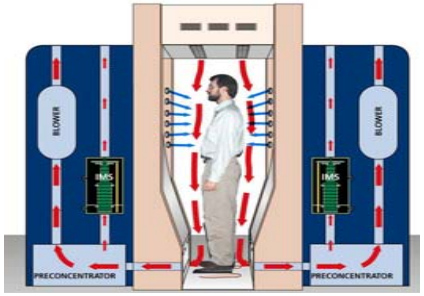
gas mask performance standards

biometrics



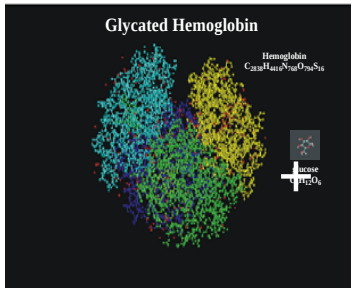


Trace explosives detection technology assessment



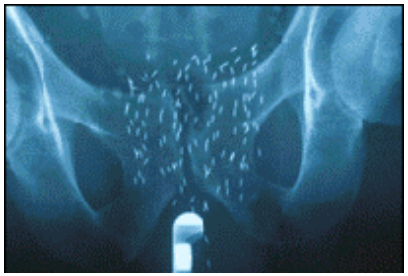
and strengthens the innovation infrastructure to…

… improve quality of life

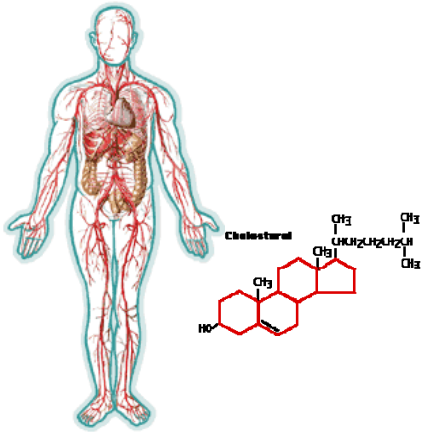


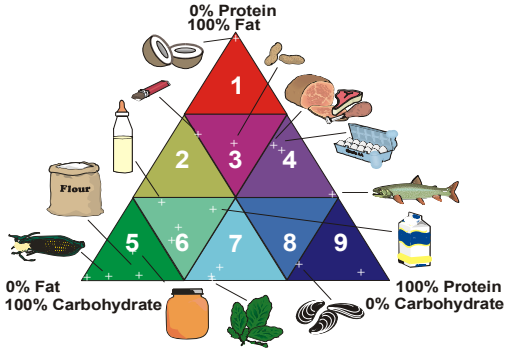
Improved clinical diagnostic measurements

Drinking water quality

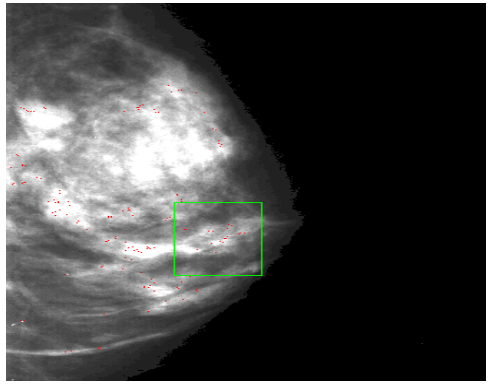


Dosimetry standards for Prostate Cancer treatment





Standards for nutritional labeling



Standards for Mammography

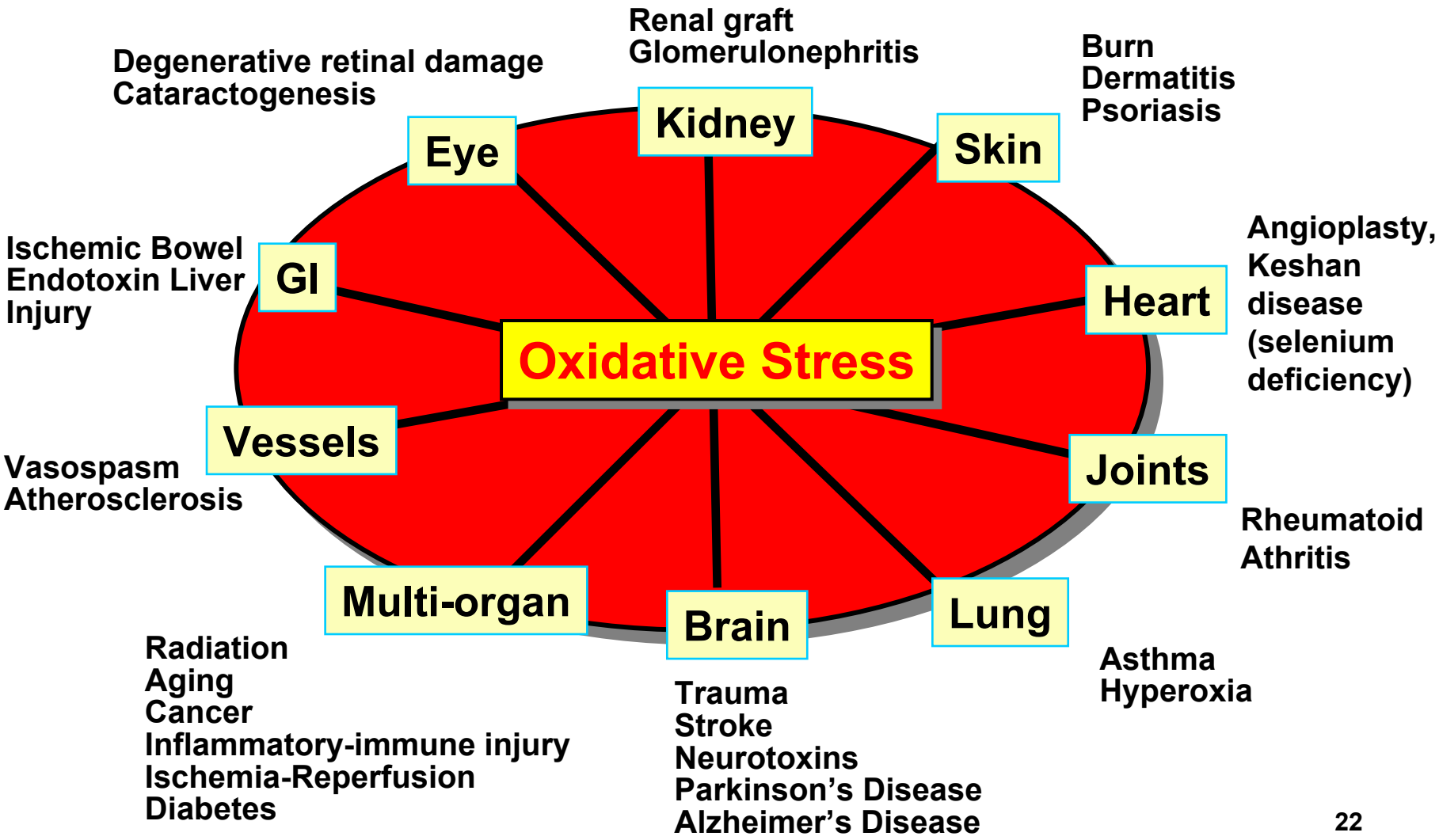
PROSTATE SPECIFIC ANTIGEN (PSA)

- **>37,000 deaths annually in U.S. from prostate cancer**
- **Blood tests for PSA are used to screen for the likelihood of prostate cancer**
- **PSA is a heterogeneous protein that occurs both free and complexed**
- **Immunoassays are the approach favored for routine measurement of PSA**
- **Wide variability among the results from immunoassays (see below)**
- **High incidence of false positives and false negatives**

# of Labs	- Low -	- Med.-	-High-	-Mean-	- S.D. -	%RSD	95% Confidence Range
2672	10.8	19.4	34.5	19.67	2.14	10.9	15.39-23.95
2653	7.2	9.8	18	9.92	1.11	11.2	7.70-12.14
2689	5.3	7.3	12.8	7.36	0.79	10.7	5.78-8.94
2509	2.1	3	4.7	3.03	0.33	10.8	2.37-3.69
2504	0.6	0.7	1.5	0.73	0.11	14.5	0.51-0.95
2591	0.1	0.2	0.8	0.24	0.1	40.2	0.04-0.44

From: http://www.cooleyville.com/cancer/capsava.htm

Oxidative stress-associated clinical conditions



Monitoring Changes to Tissue-Engineered Medical Products

Making TE Skin*

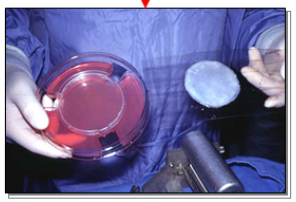
- 4 step process
  - 30 days to manufacture

STORAGE

-20 °C
-70 °C
liq. N_2
Freeze thawing

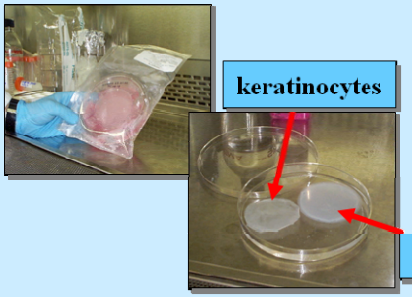
SHIPPING

Rm. Temp.
Freezer pack
Dry ice
Temp. change



"Large-Scale Biology"

*Organogenesis

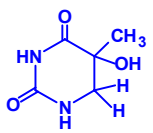


Tools to assess:

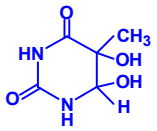
- Base Modifications
  - –oxidative DNA damage
- Permanent Mutations
  - –point mutations
- Chromosomal Changes
  - –chromosomal loss

Rodriguez, H., O'Connell, C., Barker, P.E., Atha, D.H., Jaruga, P., Birincioglu, M., Marino, M., McAndrew, P. and Dizdaroglu, M. (2004) *Tissue Engineering* 10:1332-1345.

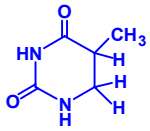
Products of oxidative damage to DNA bases



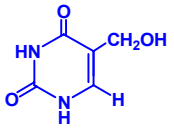
5-hydroxy-6-hydro-thymine



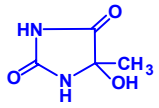
thymine glycol



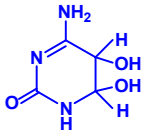
5,6-dihydrothymine



5-hydroxymethyl-uracil

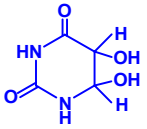


5-hydroxy-5-methyl-hydantoin

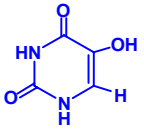


cytosine glycol

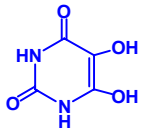
5-hydroxycytosine



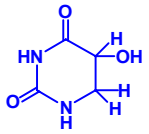
uracil glycol



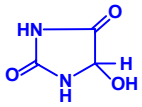
5-hydroxyuracil



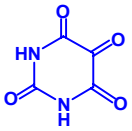
5,6-dihydroxyuracil



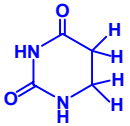
5-hydroxy-6-hydro-uracil



5-hydroxyhydantoin



alloxan



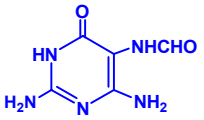
5,6-dihydrouracil

8-hydroxyadenine

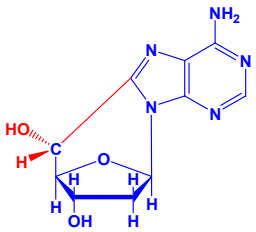
4,6-diamino-5-form-amidopyrimidine

2-hydroxyadenine

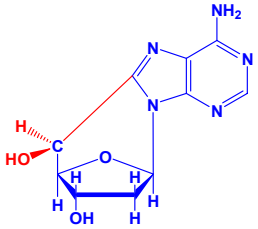
8-hydroxyguanine



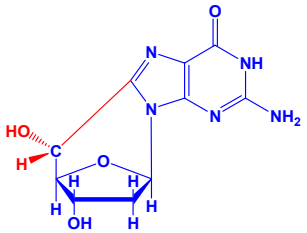
2,6-diamino-4-hydroxy-5-formamidopyrimidine



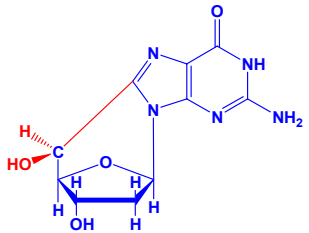
(5'R)-8,5'-cyclo-2'-deoxyadenosine



(5'S)-8,5'-cyclo-2'-deoxyadenosine

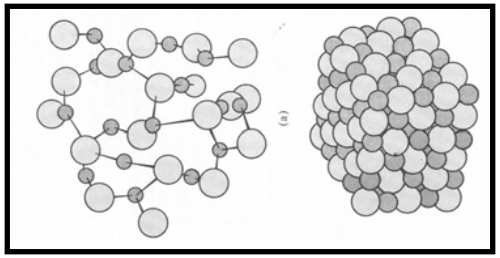


(5'R)-8,5'-cyclo-2'-deoxyguanosine



(5'S)-8,5'-cyclo-2'-deoxyguanosine

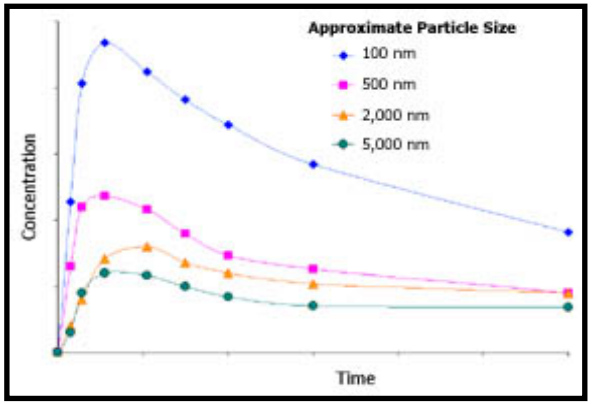
Rigidity vs Bioavailability

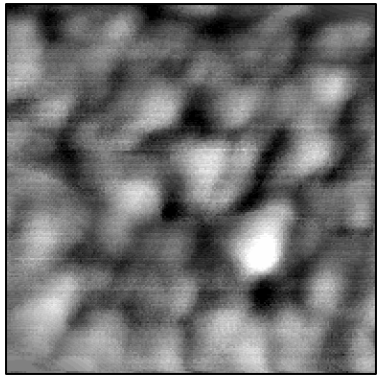


CRADA: CN-1819

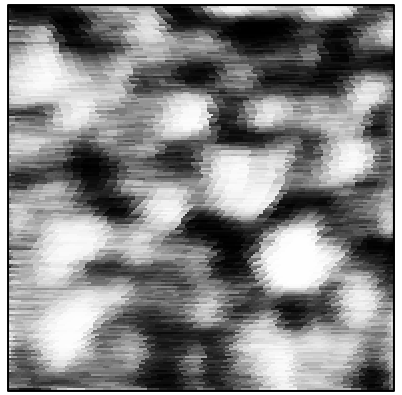
"Dielectric Measurement of Particles" (nano size and larger)

- This collaborative effort will utilize.. ..Evanescent Probe dielectric measurements of solid pharmaceutical compounds as a potential predictive measure of molecular entity rigidity and oral bioavailability.



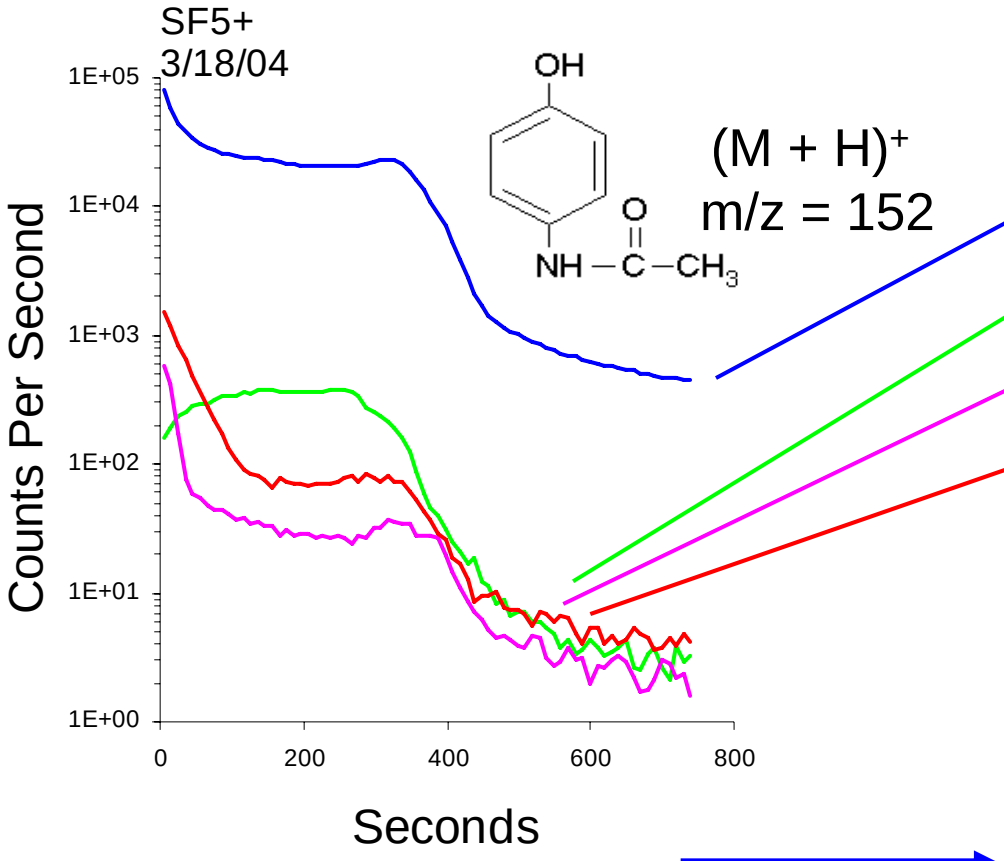


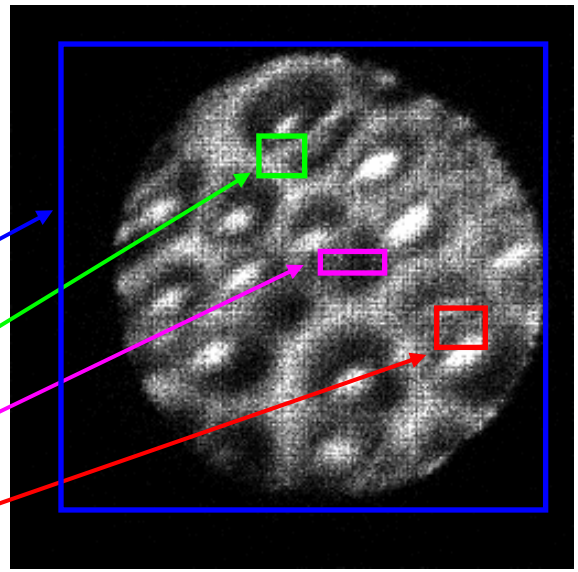
5 μm x 5 μm images of lead zirconate titanate nanoscale particles show the topography (left), with the simultaneously recorded dielectric response of these particles (right). The bright features in the dielectric map indicate regions of higher dielectric response relative to the silicon substrate; the frequency shift shown as the white-to-black scale is proportional to the dielectric constant, ε'.



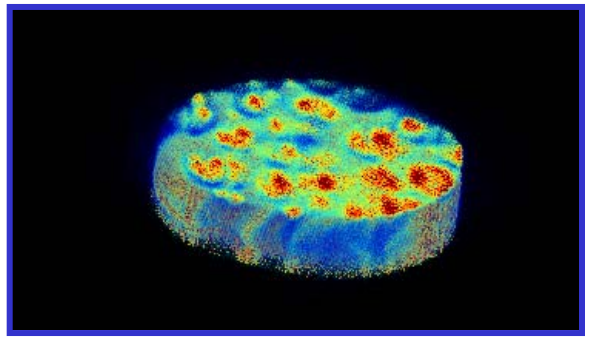
20% Acetominophen in PLA- Selected Area Molecular Image Depth Profiles

Selected area molecular depth profiling

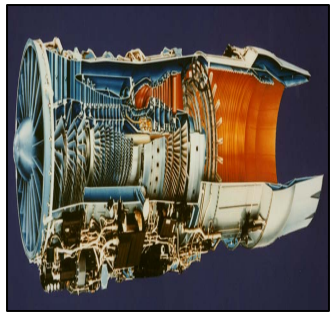




3D Volumetric image of $(M+H)^+$, m/z 152



NIST Provides Chemical Measurement Services to High Technology Industries ...

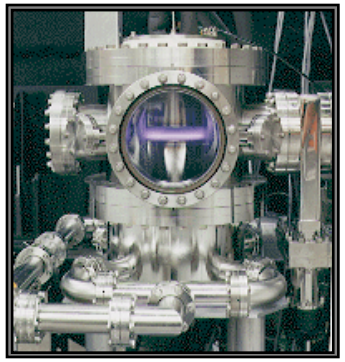


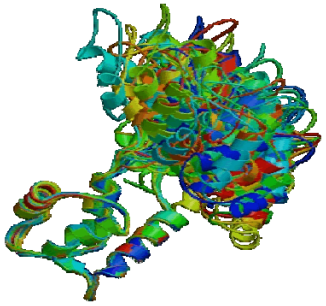
Aerospace and Transportation

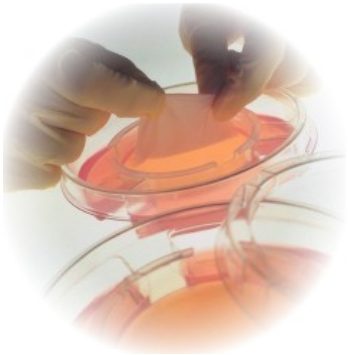
- Standards for low NO emissions from vehicles
- Standards for Hydrogen in Titanium

Semiconductors

- SRMs for measuring P, As, and B in Si
- Thermometry and plasma process monitoring in semiconductor fabrication



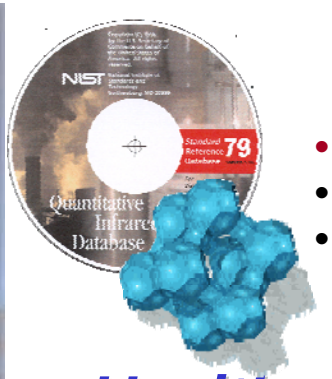




Biotechnology

- Advanced Bioprocessing Technologies
- Technology and Standards for DNA diagnostics
- Tissue engineering

… and Mature Industries



Chemical Processing

- Chemistry WebBook, MS Database, IR Database
- Molecular property data for chlorinated hydrocarbons
- Zeolite reference materials

Health and Food

- Reference methods and SRMs for clinical markers
- Methods and SRMs for dietary supplement safety
- Nutritional composition SRMs
- Environmental contamination SRMs

Energy

- SRMs for Hg and low-sulfur fuels
- Natural gas composition standards
- Stds. For Global Warming Gases

Constantly Balancing the "Old" with the "New"

SRM 1d - Argillaceous Limestone

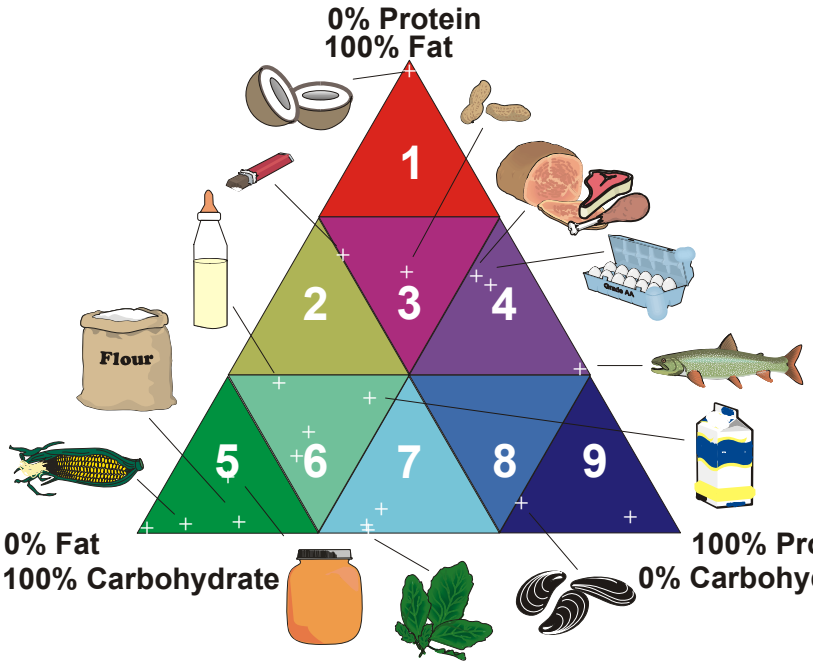
Versions of SRM 1 have been provided by NBS/NIST since 1910. It is a critical natural resource as is building material, it is also used to manufacture lime for agricultural and chemical processes, cement and concrete, and iron and steel.

SRM 2399, Fragile X Human DNA Triplet Repeat Standard

And we support emerging industries and genetic testing laboratories in accurately counting fragile-X repeat sequences, NIST has developed a new reference material that can be used as a check on test procedures and for quality control. SRM 2399 consists of nine samples of DNA measured and certified by NIST for triplet repeats ranging from 20 to 118. **The triplet repeat standard joins more than 50 reference materials produced by NIST for quality control in clinical testing.**

Methods and Standards for Food Safety and Nutrition

- Nutrients [as defined by Nutritional Labeling Law]
- Contaminants and Adulterants
- Biotech Foods
- Dietary Supplements



Supplement Facts
Serving Size 1 Tablet

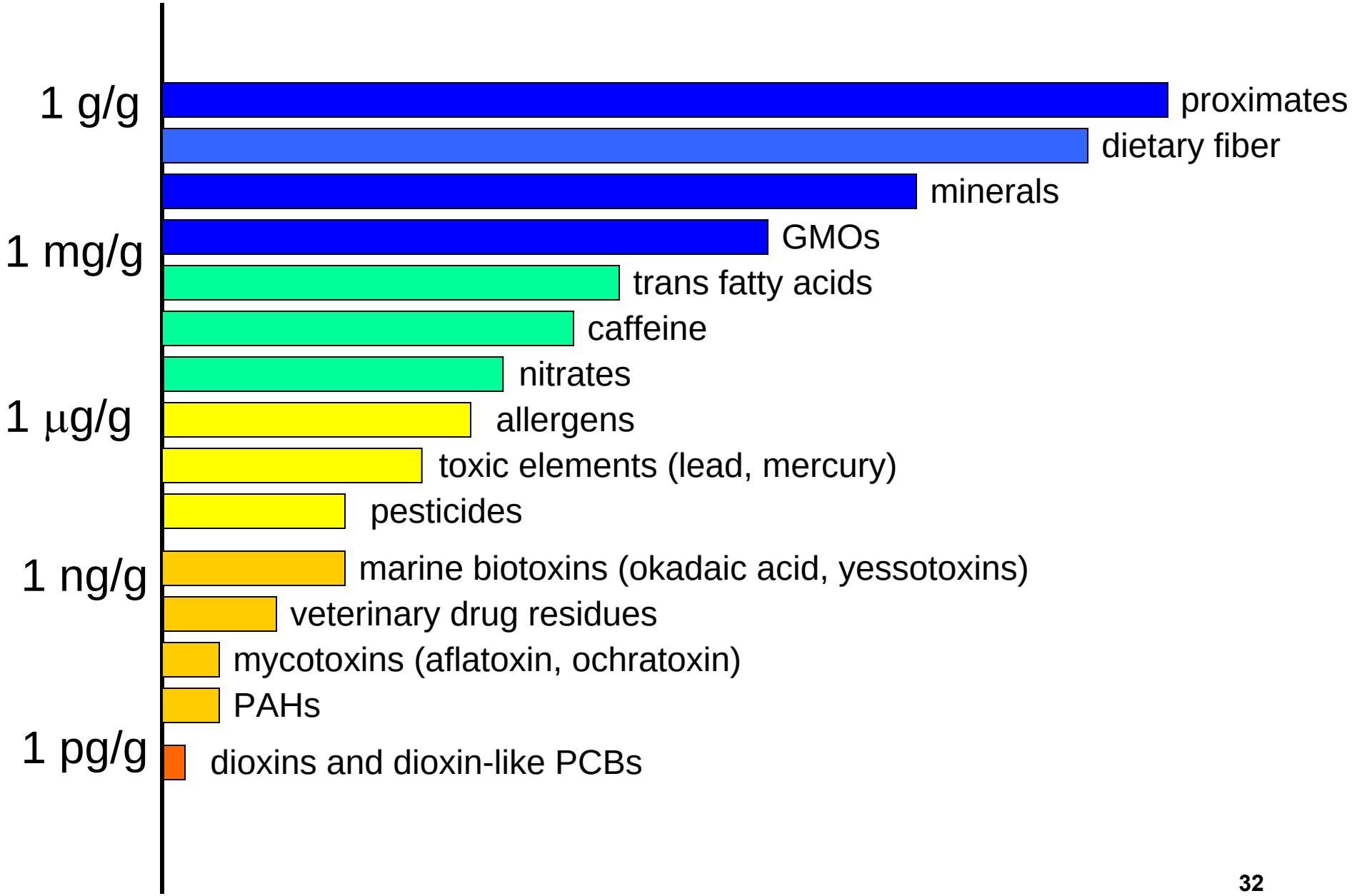
Each Tablet Contains	%DV
Vitamin A 3500 IU (29% as Beta Carotene)	70%
Vitamin C 60 mg	100%
Vitamin D 400 IU	100%
Vitamin E 30 IU	100%
Vitamin K 25 mcg	31%
Thiamin 1.5 mg	100%
Riboflavin 1.7 mg	100%
Niacin 20 mg	100%
Vitamin B_6 2 mg	100%
Folic Acid 400 mcg	100%
Vitamin B_{12} 6 mcg	100%
Biotin 30 mcg	10%
Pantothenic Acid 10 mg	100%
Calcium 162 mg	16%
Iron 18 mg	100%
Phosphorus 109 mg	11%
Iodine 150 mcg	100%
Magnesium 100 mg	25%
Zinc 15 mg	100%
Selenium 20 mcg	29%
Copper 2 mg	100%
Manganese 2 mg	100%
Chromium 120 mcg	100%
Molybdenum 75 mcg	100%
Chloride 72 mg	2%
Potassium 80 mg	2%
Boron 150 mcg	*
Nickel 5 mcg	*
Silicon 2 mg	*
Tin 10 mcg	*
Vanadium 10 mcg	*
Lutein 250 mcg	*
Lycopene 300 mcg	*

*Daily Value (%DV) not established.

Regulation-Driven Measurements in Foods

- **Nutrients (proximates, vitamins, elements)**
- **Phytochemicals**
- **Allergens**
- **Additives and Contaminants**
  - **Colors**
  - **Flavors**
  - **Growth Hormones**
  - **Drug Residues**
  - **Mycotoxins**
  - **Preservatives**
  - **GMOs**
  - **Pesticides**
  - **Other pollutants (i.e., MeHg)**

Nominal Mass Fractions of Measurands in Foods

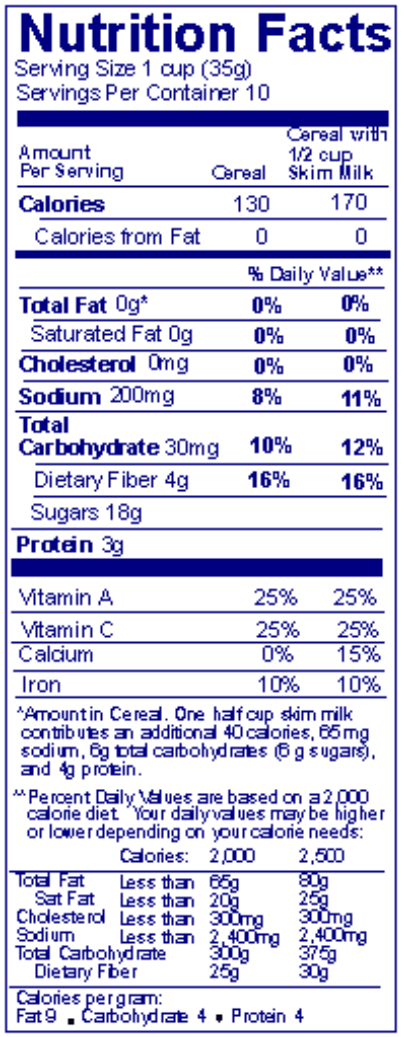


Nutrition Labeling and Education Act of 1990

(Public Law 101-535)

Label on processed foods must specify:

- serving size in common household units
- number of servings per container
- total number of calories derived from all sources and derived from fat in each serving
- amount of total fat, saturated fat, cholesterol, sodium, total carbohydrate, dietary fiber, sugars, total protein, vitamin A, vitamin C, calcium, and iron contained in each serving
- any other vitamin or mineral or other nutrient required to assist the consumer in maintaining a healthy diet



Nutrition Facts

Serving Size 1 cup (35g)
Servings Per Container 10

Amount Per Serving	Cereal	Cereal with 1/2 cup Skim Milk
Calories	130	170
Calories from Fat	0	0
		% Daily Value**
Total Fat 0g*	**0%**	**0%**
Saturated Fat 0g	**0%**	**0%**
Cholesterol 0mg	**0%**	**0%**
Sodium 200mg	**8%**	**11%**
Total Carbohydrate 30mg	**10%**	**12%**
Dietary Fiber 4g	**16%**	**16%**
Sugars 18g		
Protein 3g		
Vitamin A	25%	25%
Vitamin C	25%	25%
Calcium	0%	15%
Iron	10%	10%

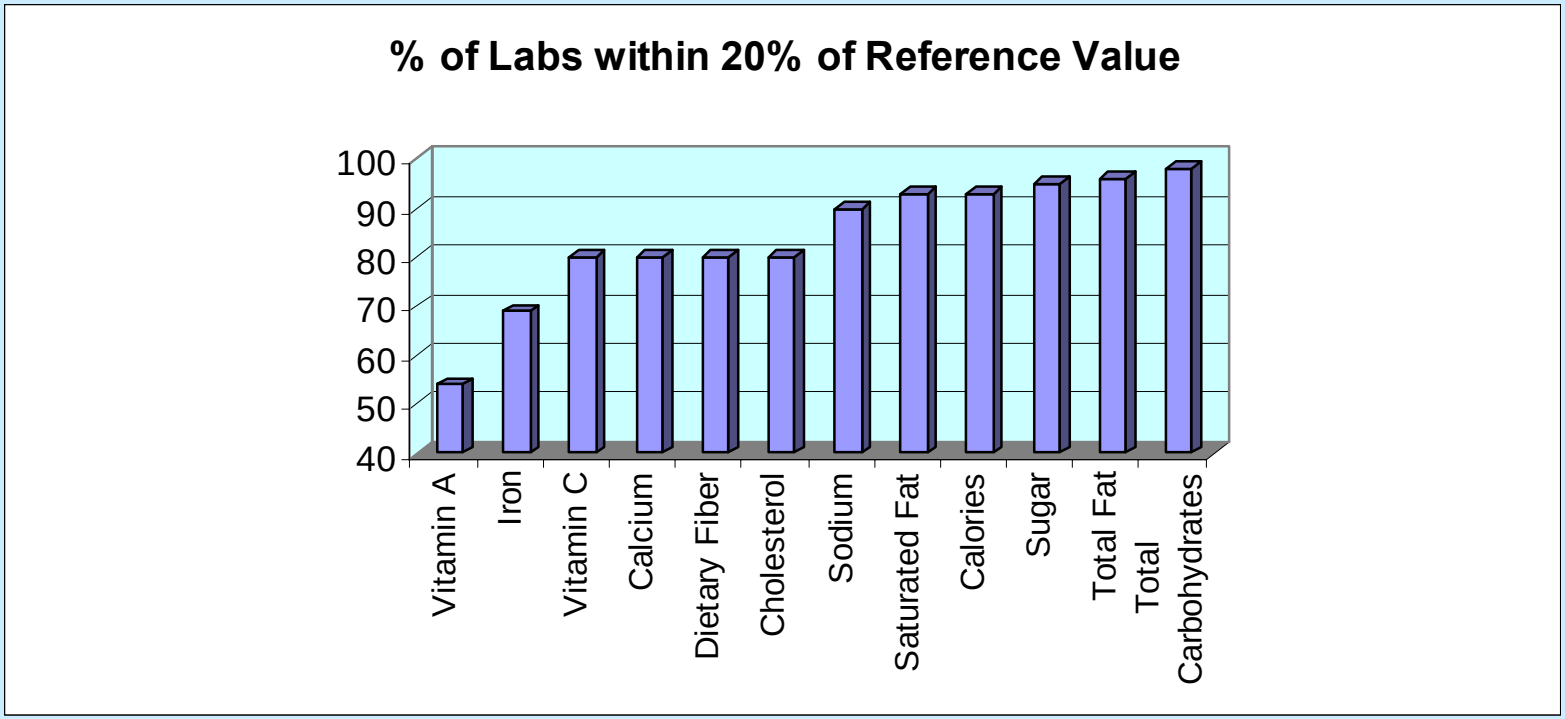
*Amount in Cereal. One half cup skim milk contributes an additional 40 calories, 65mg sodium, 6g total carbohydrates (6 g sugars), and 4g protein.

** Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

		Calories:	2,000	2,500
Total Fat	Less than		65g	80g
Sat Fat	Less than		20g	25g
Cholesterol	Less than		300mg	300mg
Sodium	Less than		2,400mg	2,400mg
Total Carbohydrate			300g	375g
Dietary Fiber			25g	30g

Calories per gram:
Fat 9 • Carbohydrate 4 • Protein 4

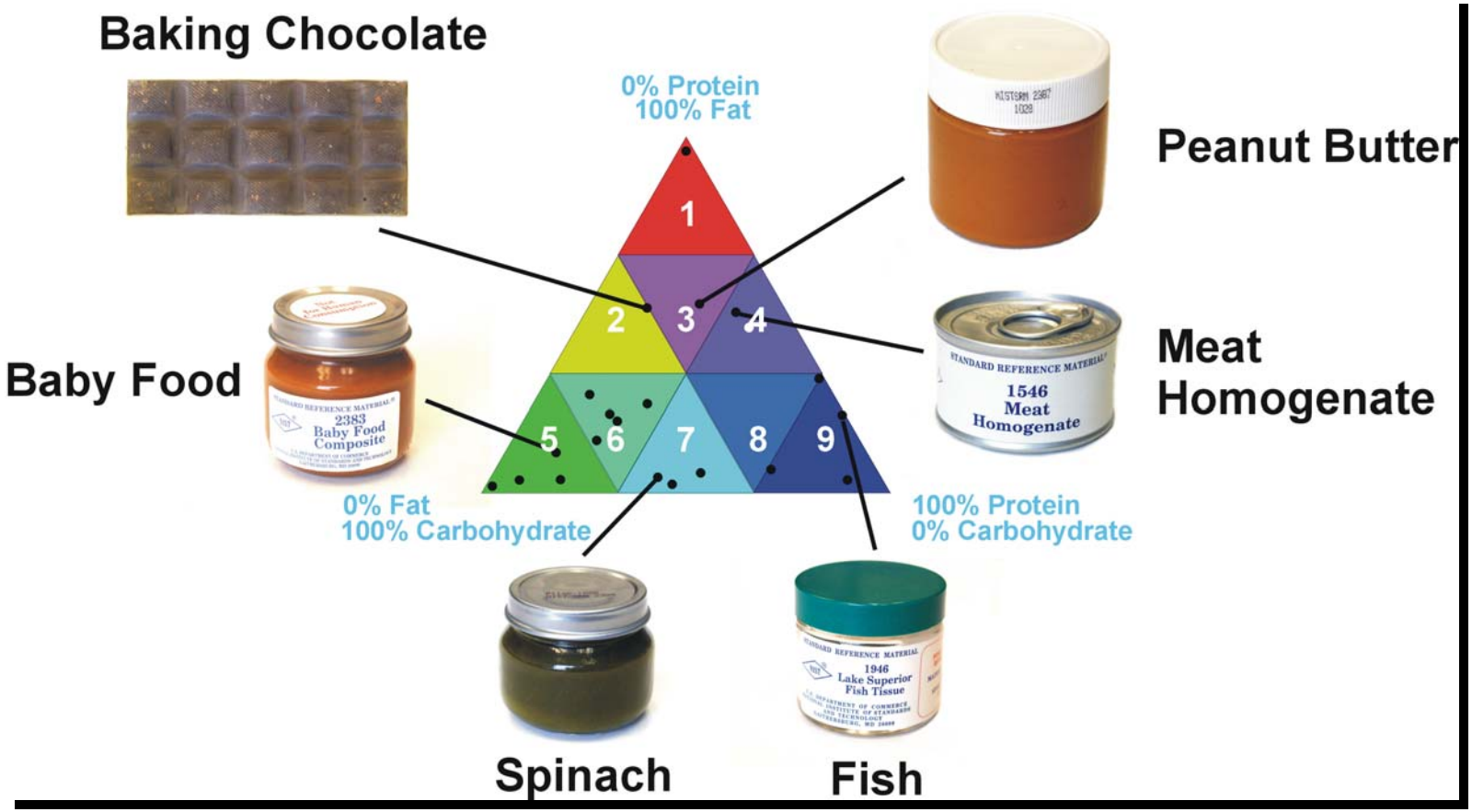
FDA STUDY ON NUTRITION LABEL ACCURACY



FDA sent 300 foods to commercial reference laboratory to test accuracy Of nutritional information on the food packages (1996)

SRMs for Nutrients and Contaminants in Food

Examples of Food-matrix Standard Reference Materials by Sector



Most food analysis labs provide analyses for a similar set of analytes, but matrix Differences and concentration differences are the primary measurement challenges. By providing SRMs across the major sections of the food triangle, NIST will have covered most of the field for the measurement of common food analytes.

Food Supplements (E.U.)/ Dietary Supplements (U.S.)

- **European Directive 2002/46/EC. (Food Supplements Directive).** Provides rules for labeling food supplements, rules on vitamins and minerals in food supplements, lists of vitamins and minerals that may be sold or used as ingredients in the EU. (2001/83/EC, a Pharmaceutical Directive, would cover supplements not included in the Food Supplements Directive.)

- **U.S. Dietary Supplement Health and Education Act of 1994 (DSHEA).** Defines a dietary supplement as "any product that is intended to supplement the diet and that contains one or more of the following: vitamins, minerals, herbs or botanicals, amino acids, metabolites or extracts". Regulates products as foods and puts the burden of proof for safety on the Food and Drug Administration.

Dietary Supplements: Legislation

- Formal definition given by the Dietary Supplement Health and Education Act (DSHEA) of 1994
  - Established the Office of Dietary Supplements (ODS) within NIH

- Dietary Supplement: Any product that is intended to supplement the diet and that contains one or more of the following:
  - Vitamins
  - Minerals
  - Herbs or botanicals
  - Amino acids
  - Metabolites or extracts

SUGGESTED USE: Take one mid-morning, and one mid-afternoon as desired.

Supplement Facts

Serving Size 1 Tablet
Servings Per Container 120

Amount Per Serving		% Daily Value
Vitamin B_6 (as pyridoxine hydrochloride)	10 mg	500%
Vitamin B_{12} (as cyanocobalamin)	3 mcg	50%
Pantothenic Acid (as d-calcium pantothenate)	15mg	150%
DynaChrome® Chromium (as arginate/chelidamate)	100 mcg	83%
Potassium (as potassium chloride)	50 mg	1%
Proprietary Blend	652 mg	
Ephedra (standardized plant body extract yielding 18 mg ephedrine)		*
Guarana (standardized seed extract yielding 48 mg caffeine)		*
Siberian Ginseng (root)		*
Green Tea (standardized leaf extract yielding 2 mg caffeine)		*
Dandelion (leaf)		*
Ginger (root)		*
Passion Flower (aerial portion)		*
Kelp (leaf)		*
Gymnema Sylvestre (leaf extract)		*
Pullulan		*
Choline (as choline bitartrate)	50 mg	*
Inositol	50 mg	*
Bromelain	50 mg	*

* Daily Value not established

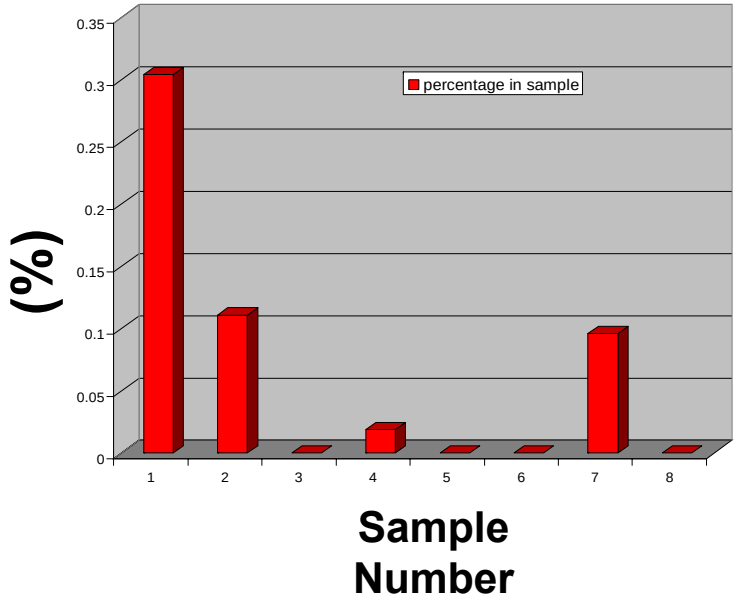
Other ingredients: Microcrystalline cellulose, cellulose gum, silicon dioxide, stearic acid, magnesium stearate.

Dietary Supplements and Functional Foods

Currently $70 billion Industry in North America alone and projected to be $500 billion by 2010

Measurement Traceability increasingly required to:

- support label claims - truth in advertising
- **facilitate regulatory control and/or compliance**
- support public health and safety
- assess conformance with import/export requirements



I. Khan, University of Mississippi

Eight commercial products sold as **Valerian Supplements** were analyzed in one Laboratory for valerenic acid content as shown below:

Standards for Dietary Supplements

US Senate Language FY2002

"NIH-ODS to allocate sufficient funds to speed up an ongoing collaborative effort to develop and disseminate validated analytical methods and reference materials for the most commonly used botanicals and other dietary supplements."

Matrix	*Targeted Physiological Agents*
• Ephedra	Alkaloids
• St. John's Wort	Hypericins, Hyperforin
• Saw Palmetto	Fatty Acids, Sterols
• Ginkgo Biloba	Flavonol glycosides, ginkgoterpenoids
• Green Tea	Catechins, Gallic Acid
• Multivitamin/mineral tablets	Vitamins and minerals

Priorities determined in consultation with NIH, FDA, USDA and AOAC

Measurements and Standards Impact Healthcare Costs and Quality of Life

Problem Magnitude and Scope:

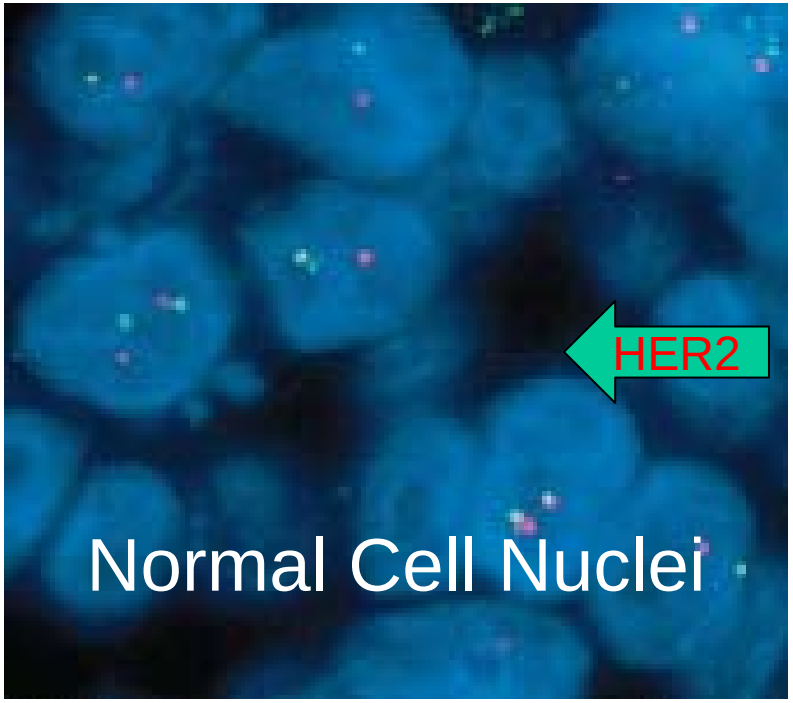
U.S. Spends ~ $1.8 trillion on Health Care

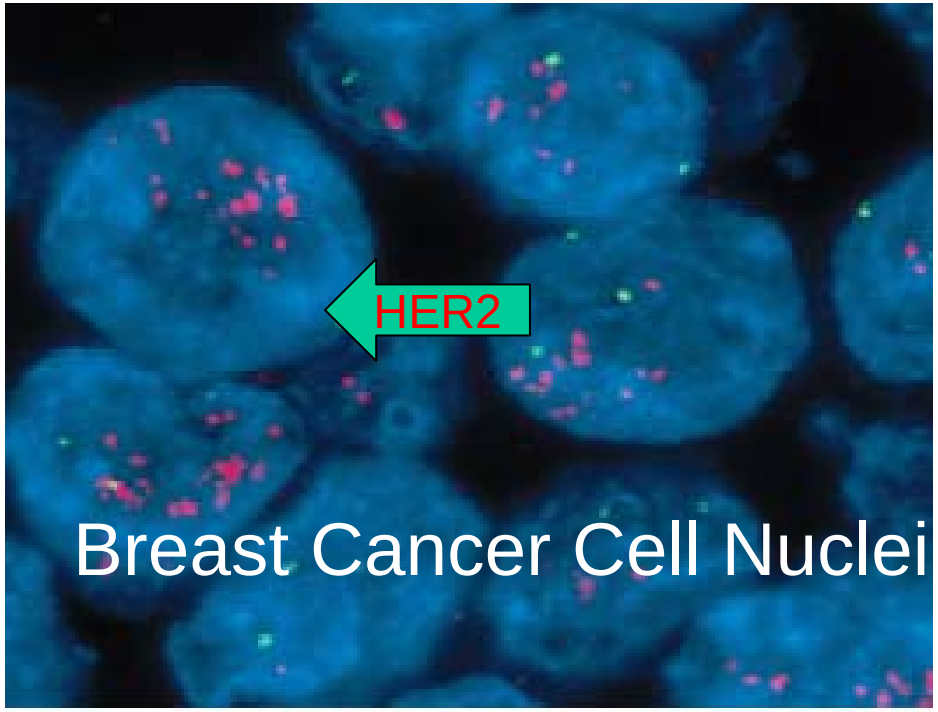
- ~10-15% of this amount is associated with measurement **(>$180B**)
- Non-diagnostic measurements cost **> $40B**

Costs of repeat measurements in Germany amounts is ~ 1.5 B US$ per year – from German Health report 1998 (www.gbe-bund.de)

Measurement Bias Affects Quality of Life and leads to inefficiency in the application of new HC technologies

- Incorrect diagnosis and treatment
- Impairment of patient well-being
- Excessive costs





FISH DNA Test Detects Extra Copies of HER2 Gene in Breast Cancer Patients

Measurement Problem:

-Technologies and assay variants for HER2 DNA, mRNA and protein (receptor) have no universally accepted standard calibrant and therefore results concerning HER2 levels vary significantly.

Solution:

-NIST is developing a common standard fixed cell line SRM to benchmark all types of HER2 gene, mRNA and protein assay

".... the traceability of values assigned to calibrators and control materials must be assured through available reference measurement procedures and/or reference materials of a higher order ..."

EC-IVD Directive Annex 1 (3)

Approximately 60 % of the in vitro diagnostic medical devices (IVD MD) currently on the ~ $6 B/yr European market are imported from the US. (Worldwide, the in vitro diagnostic device market is ~$20B)

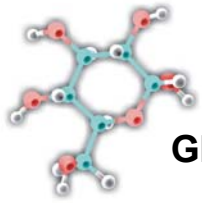
NIST has Maintained Standards for 12 Health Status Markers for 20-years

Reference Systems are Currently in Place for Many Well-Defined Markers that are:

- **Relatively small well-defined molecular or elemental species**
- **Typically, can be determined using well-established ID/MS –based methodology**
- **Such as the following:**

Marker	*Disease State*
Calcium	Cancer, Blood Clotting
Chloride	Kidney Function
Cholesterol	Heart Disease
Creatinine	Kidney Function
Glucose	Diabetes
Lithium	Antipsychotic Treatment
Magnesium	Heart Disease
Potassium	Electrolyte Balance
Sodium	Electrolyte Balance
Triglycerides	Heart Disease
Urea	Kidney Function
Uric Acid	Gout
Vitamins	Nutrition Status

Demand for these SRMs have increased dramatically since the EU IVD Directive was implemented in December of 2003.

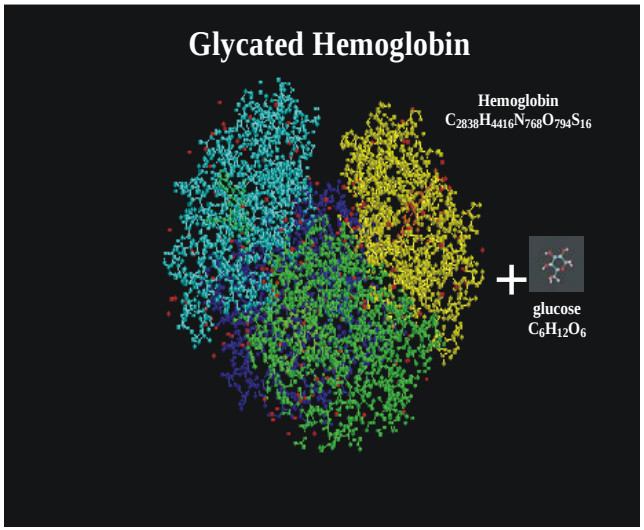


Glucose

NIST has Expanded its Standards Program to Support New IVD Industry Needs

Reference Systems Being Developed for New Markers that typically exhibit:

- High molecular mass (>20,000 daltons)
- Heterogeneity of analyte
- Low concentration
- Instability of analyte form
- Cannot all be determined using ID/MS or other definitive methodologies
- Such as the following:



Marker	***Disease State***
Troponin-I	Myocardial Infarction
C-Reactive Protein	Risk of Heart Attack
Homocysteine	Risk of Heart Disease
Glycated Hemoglobin	Diabetes Status
T3, T4 and TSH	Thyroid Function
Speciated Iron	Hemochromatosis
PSA	Prostate Cancer
Cadmium & Mercury	Toxic Metal Poisoning
Folates	Neural Tube Defects
HER2	Breast Cancer
Fragile X	Mental Retardation

Drivers for NIST Activities:

- Standardization necessary before full medical diagnostic benefit can be realized
- EU IVD Directive
- Well-articulated US "Other-Agency" Needs (FDA, NCI, CDC etc)

Joint Committee on Traceability in Laboratory Medicine (JCTLM)

WG-I of this International body is charged with:

Establishing a process for identifying, and reviewing against agreed upon criteria "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.

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.

Published 1 April 2004, the Current List contains:

- approximately 100 Reference Measurement Procedure entries for **58** different health status markers **NIST has Reference Methods for 30**
- approximately 150 Reference Material entries for **96** measurands **NIST has Reference Materials for 72**

http://www.bipm.org/en/committees/jc/jctlm/jctlm-db/

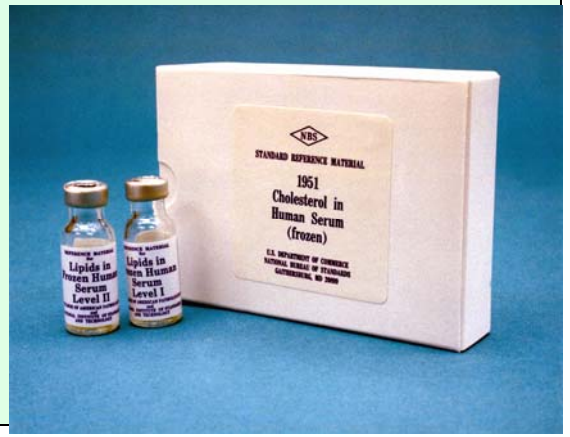
EXAMPLES OF HEALTH-RELATED SRMs

EXISTING SRMs

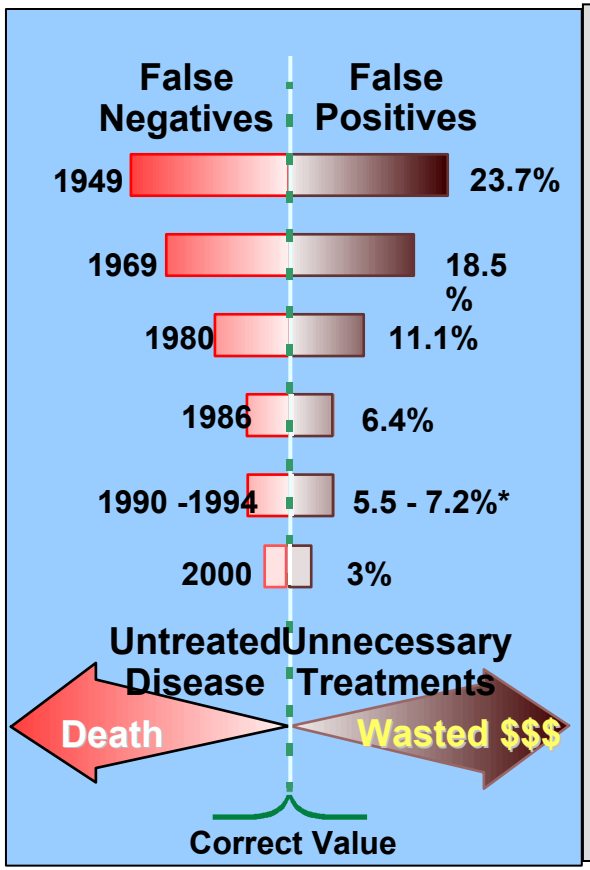
	Certified for
SRM 1951a Lipids in Fresh-Frozen Human Serum	**Cholesterol, triglycerides (reference values for HDL-C and LDL-C)**
SRM 956 Electrolytes in Frozen Human Serum	**Ca, Li, Mg, K, Na**
SRM 965 Glucose in Frozen Human Serum	**Glucose**
Toxic Metals in Bovine Blood	**Pb, Cd, and Hg (methyl-Hg and total)**

NEW!!!!!

Troponin I Calibration Solution
Homocysteine and Folates in Human Serum
T4, T3 and Cortisol in Human Serum



Improved Cholesterol Measurement Accuracy Saves Health Care Dollars



NIST Contributions to National Reference System for Cholesterol

1967 – Pure Cholesterol SRM *(SRM 911)*

1980 – Cholesterol in Serum Definitive Method

1981 – First Cholesterol in Human Serum SRM *(SRM 909)*

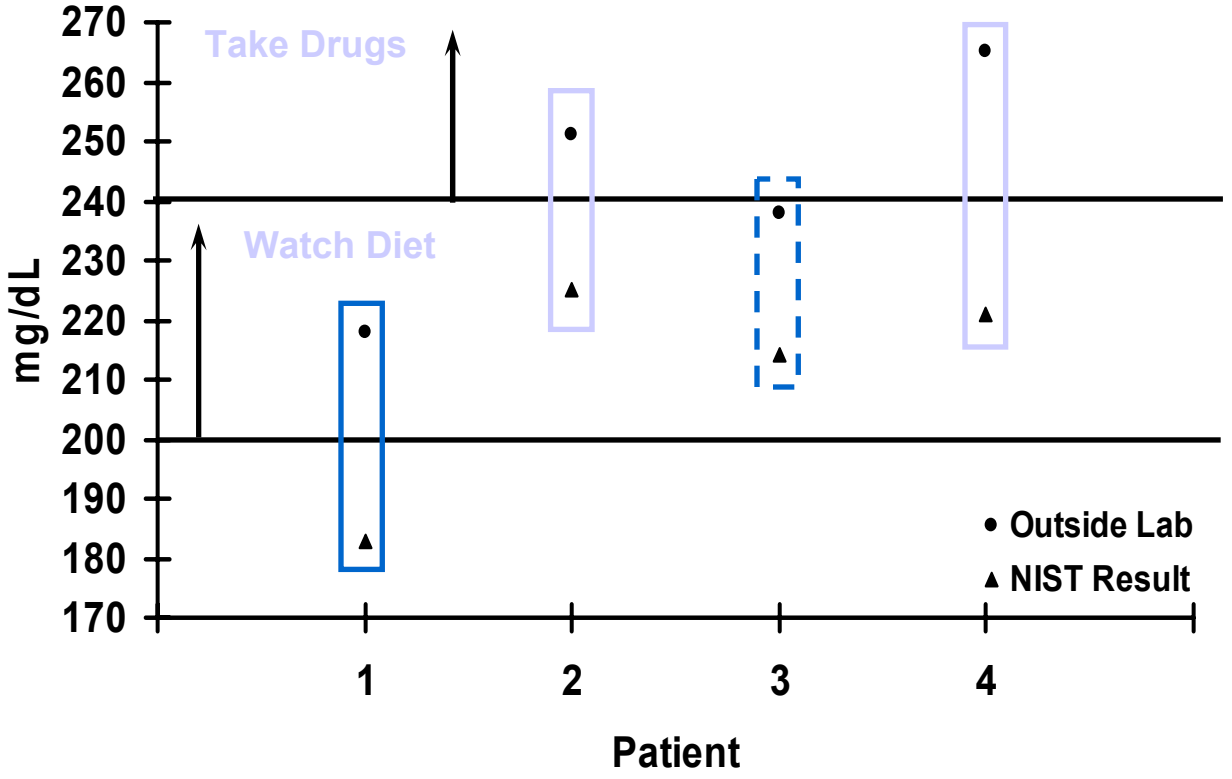
1988 – New Suite of Cholesterol in Serum SRMs at Medical Decision Points

1997 – New Suite of Fresh-Frozen Serum SRMs designed to address clinical analyzer commutability issues; Total-, HDL-, and LDL-Cholesterol and Triglyceride Values

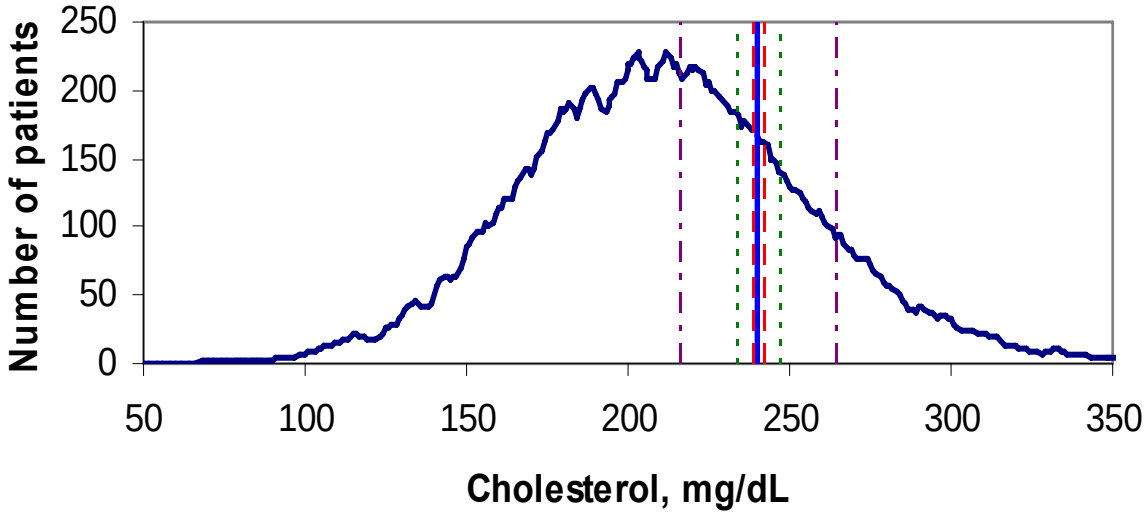
Improvement in precision since 1968 has been estimated to save $100M/yr in treatment costs

*Data from GAO and CAP

NIST Cholesterol in Blood Experiment - Impact of Inaccurate Measurements

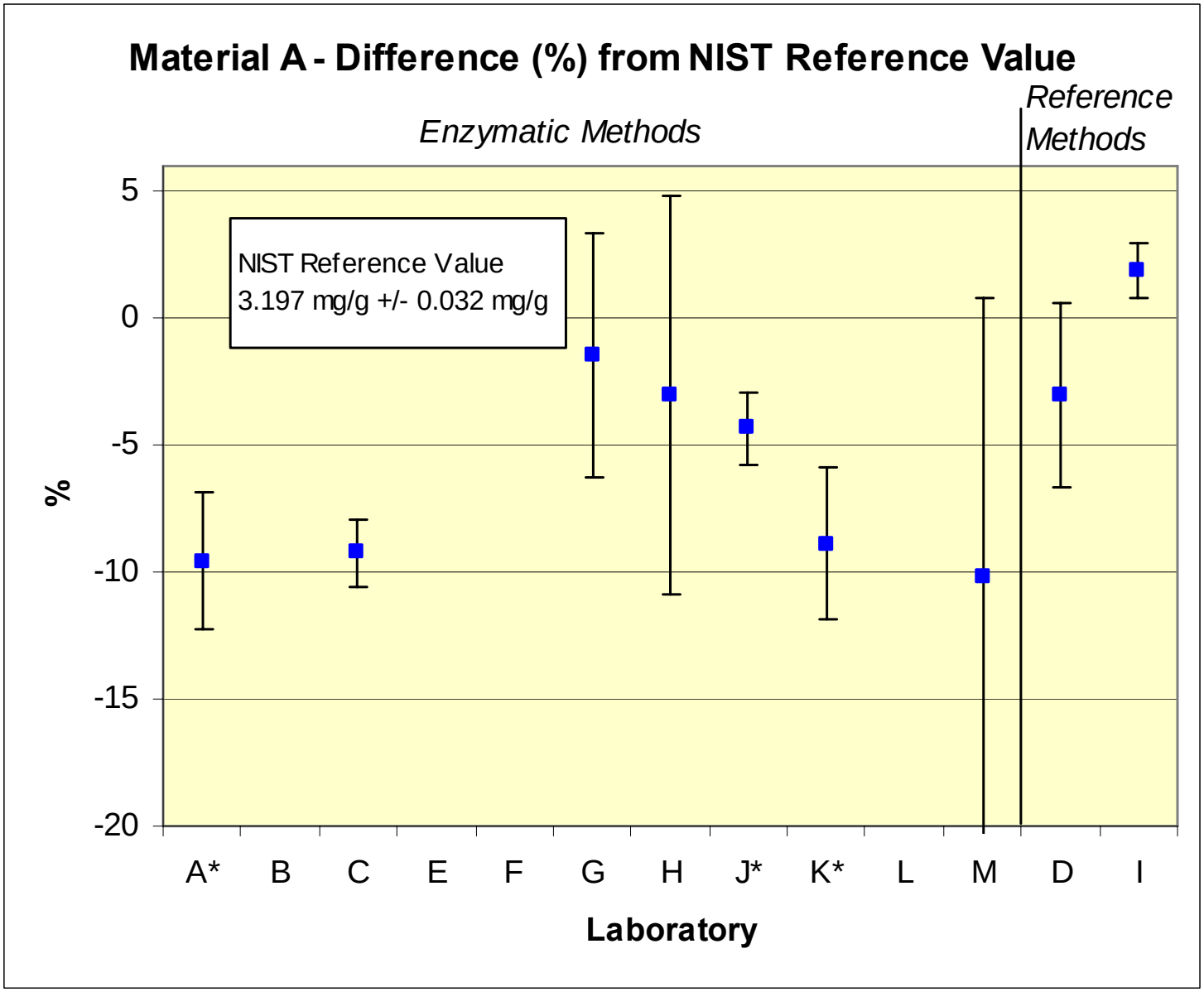


Bias in Cholesterol Measurement Effects Medical Decision-Making



Cholesterol Frequency Distribution of >20,000 Mayo Clinic Patients
(with +1%, +3% and +10% limits around 240 mg/dL criteria point)

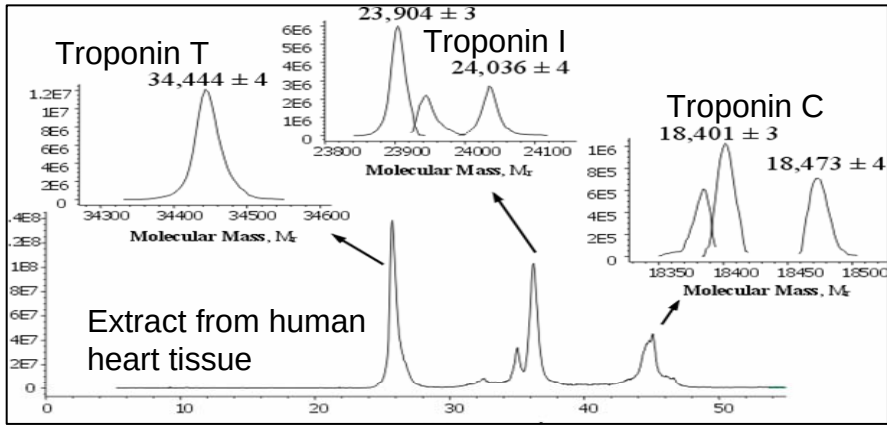
If measurement bias were:	Positives (>240 mg/dL) per 1000	Predicted Change in "Positives/1000"
-10% bias	120	-129
-3% bias	203	-46
-1% bias	234	-15
0% bias	249	
+1% bias	263	+14
+3% bias	300	+51
+10% bias	446	+197


Material A - Difference (%) from NIST Reference Value
Enzymatic Methods
Reference Methods
NIST Reference Value
3.197 mg/g +/- 0.032 mg/g
%
5
0
-5
-10
-15
-20
A*
B
C
E
F
G
H
J*
K*
L
M
D
I
Laboratory

Troponin I is a marker for the occurrence and damage from heart attack

Assay	Conc.	# Labs
Manufacturer	ng/mL	
A	19.9	115
B	6.7	489
C	0.85	27

From G. S. Bodor, Denver Health and Hospitals -- personal communication 1997



PROBLEM:

Troponin I is a complex, heterogeneous protein that may be free or may be complexed with Troponin C and/or Troponin T. Different assay antibodies do not recognize the same form.

NIST Response:

Developed SRM 2921, a Troponin - I, C, T - complex from human heart tissue. Concentrations of Troponin I and Troponin-T value assigned by NIST. Proper use of this SRM by the industry has been shown to reduce data variability by a factor of 10.

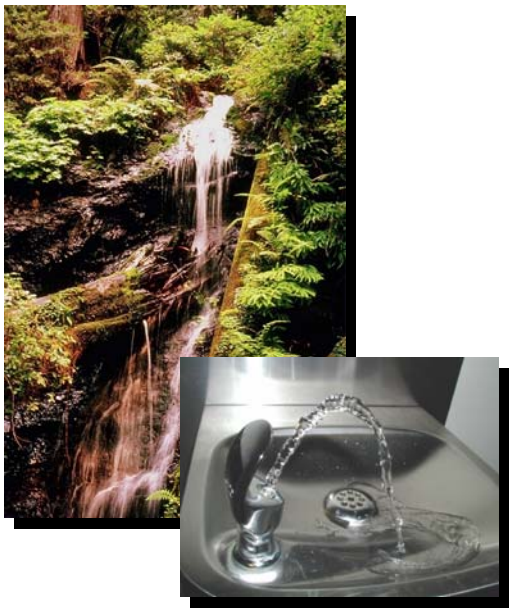
Forensics & Homeland Security Overview

- Forensics
  - Crime Scene Investigations
  - Drugs of Abuse
  - Human Identification Technology
- Homeland Security
  - Biological Threat Detection
  - Chemical Threat Detection
  - Nuclear Threat Detection

Environmental Measurements

Marine Environment

Drinking and Waste Water

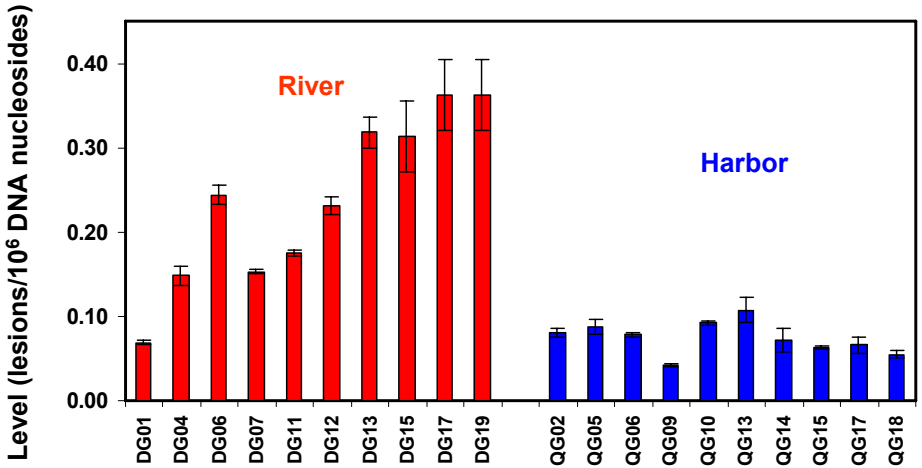


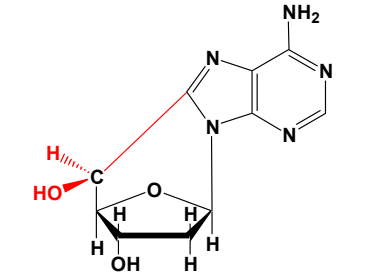
Stationary and Mobile Source Emissions

National Reference System for Environmental Measurements

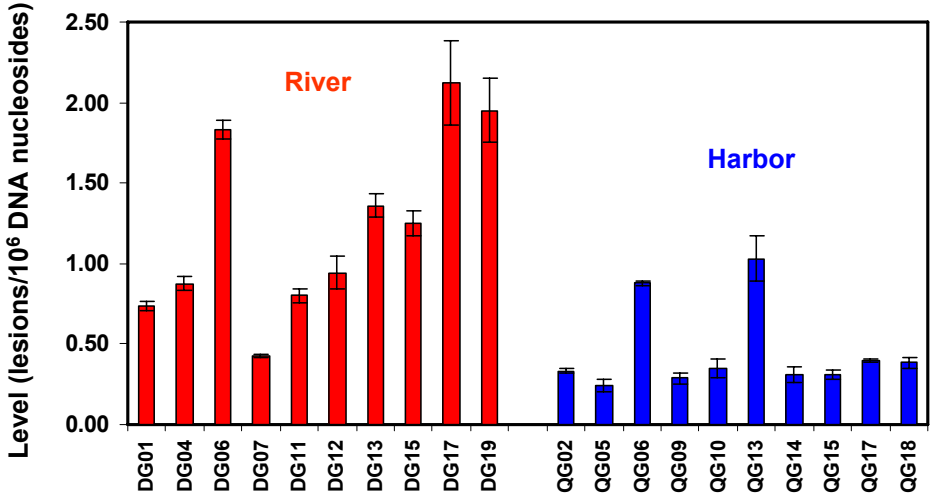
- **Measurement Research**
- **Standards Development**
- **Quality Assurance Activities**
- **International Activities**

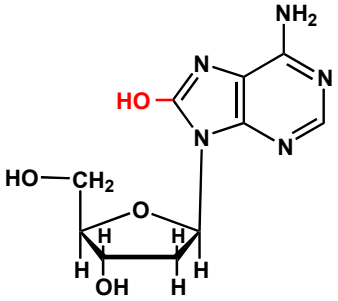
Effect of pollution on fish DNA





(5'S)-8,5'-cyclo-2'-deoxyadenosine

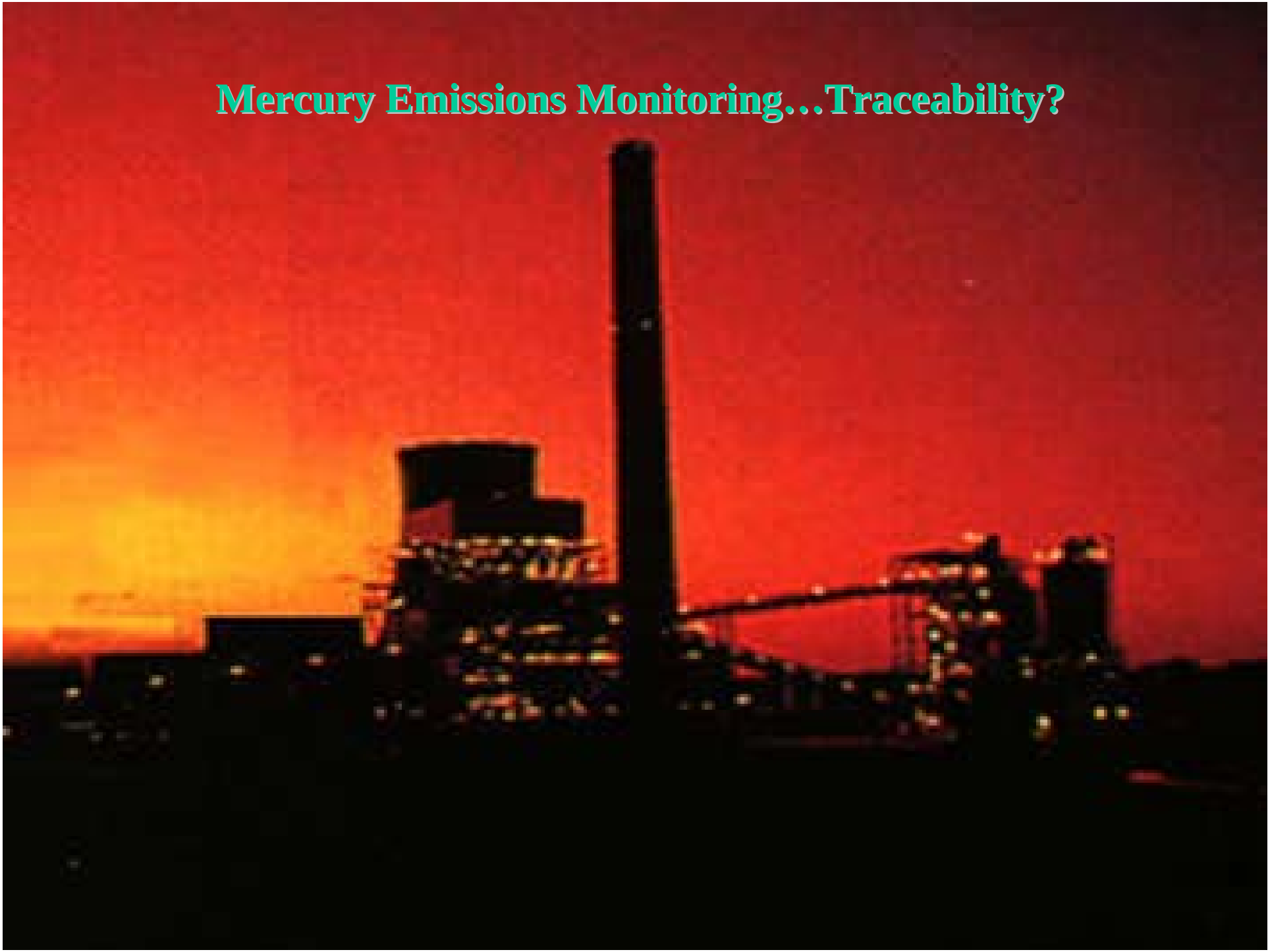




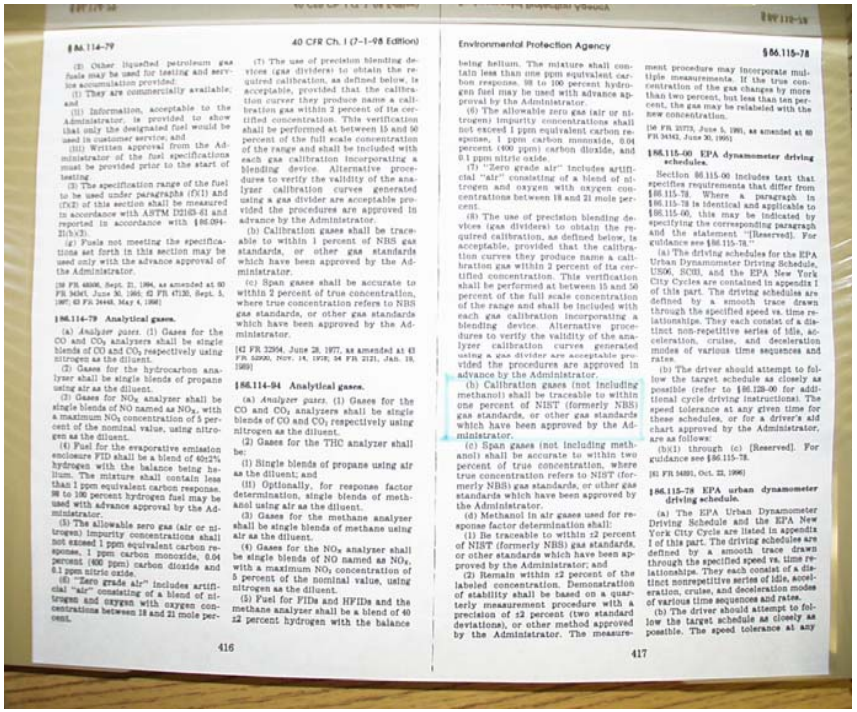
8-hydroxy-2'-deoxyadenosine

Malins, D.C., Jaruga, P., Stegeman, J.C., Green, V. M., Gilman, N.K., Anderson, K.M. and Dizdaroglu, M. (submitted)

Mercury Emissions Monitoring…Traceability?



40 CFR Part 86.114(b)



§ 86.114-79

40 CFR Ch. I (7–1–98 Edition)

(3) Other liquefied petroleum gas fuels may be used for testing and service accumulation provided:

(i) They are commercially available; and

(ii) Information, acceptable to the Administrator, is provided to show that only the designated fuel would be used in customer service; and

(iii) Written approval from the Administrator of the fuel specifications must be provided prior to the start of testing.

(3) The specification range of the fuel to be used under paragraphs (f)(1) and (f)(2) of this section shall be measured in accordance with ASTM D2163-81 and reported in accordance with § 86.094-21(b)(3).

(g) Fuels not meeting the specifications set forth in this section may be used only with the advance approval of the Administrator.

[50 FR 48806, Sept. 27, 1985, as amended at 60 FR 34367, June 30, 1995; 62 FR 47120, Sept. 5, 1997; 63 FR 26460, May 4, 1998]

§ 86.114-79 Analytical gases.

(a) *Analyzer gases.* (1) Gases for the CO and CO_2 analyzers shall be single blends of CO and CO_2 respectively using nitrogen as the diluent.

(2) Gases for the hydrocarbon analyzer shall be single blends of propane using air as the diluent.

(3) Gases for NO_x analyzer shall be single blends of NO named as NO_x, with a maximum NO_2 concentration of 5 percent of the nominal value, using nitrogen as the diluent.

(4) Fuel for the evaporative emission enclosure FID shall be a blend of 40±2% hydrogen with the balance being helium. The mixture shall contain less than 1 ppm equivalent carbon response. 98 to 100 percent hydrogen fuel may be used with advance approval by the Administrator.

(5) The allowable zero gas (air or nitrogen) impurity concentrations shall not exceed 1 ppm equivalent carbon response, 1 ppm carbon monoxide, 0.04 percent (400 ppm) carbon dioxide and 0.1 ppm nitric oxide.

(6) "Zero grade air" includes artificial "air" consisting of a blend of nitrogen and oxygen with oxygen concentrations between 18 and 21 mole percent.

(7) The use of precision blending devices (gas dividers) to obtain the required calibration, as defined below, is acceptable, provided that the calibration curver they produce name a calibration gas within 2 percent of its certified concentration. This verification shall be performed at between 15 and 50 percent of the full scale concentration of the range and shall be included with each gas calibration incorporating a blending device. Alternative procedures to verify the validity of the analyzer calibration curves generated using a gas divider are acceptable provided the procedures are approved in advance by the Administrator.

(b) Calibration gases shall be traceable to within 1 percent of NBS gas standards, or other gas standards which have been approved by the Administrator.

(c) Span gases shall be accurate to within 2 percent of true concentration, where true concentration refers to NBS gas standards, or other gas standards which have been approved by the Administrator.

[42 FR 22994, June 28, 1977, as amended at 43 FR 52900, Nov. 14, 1978; 54 FR 2121, Jan. 19, 1989]

§ 86.114-94 Analytical gases.

(a) *Analyzer gases.* (1) Gases for the CO and CO_2 analyzers shall be single blends of CO and CO_2 respectively using nitrogen as the diluent.

(2) Gases for the THC analyzer shall be:

(i) Single blends of propane using air as the diluent; and

(ii) Optionally, for response factor determination, single blends of methanol using air as the diluent.

(3) Gases for the methane analyzer shall be single blends of methane using air as the diluent.

(4) Gases for the NO_x analyzer shall be single blends of NO named as NO_x, with a maximum NO_2 concentration of 5 percent of the nominal value, using nitrogen as the diluent.

(5) Fuel for FIDs and HFIDs and the methane analyzer shall be a blend of 40 ±2 percent hydrogen with the balance

416

Environmental Protection Agency

§ 86.115-78

being helium. The mixture shall contain less than one ppm equivalent carbon response. 98 to 100 percent hydrogen fuel may be used with advance approval by the Administrator.

(6) The allowable zero gas (air or nitrogen) impurity concentrations shall not exceed 1 ppm equivalent carbon response, 1 ppm carbon monoxide, 0.04 percent (400 ppm) carbon dioxide, and 0.1 ppm nitric oxide.

(7) "Zero grade air" includes artificial "air" consisting of a blend of nitrogen and oxygen with oxygen concentrations between 18 and 21 mole percent.

(8) The use of precision blending devices (gas dividers) to obtain the required calibration, as defined below, is acceptable, provided that the calibration curves they produce name a calibration gas within 2 percent of its certified concentration. This verification shall be performed at between 15 and 50 percent of the full scale concentration of the range and shall be included with each gas calibration incorporating a blending device. Alternative procedures to verify the validity of the analyzer calibration curves generated using a gas divider are acceptable provided the procedures are approved in advance by the Administrator.

(b) Calibration gases (not including methanol) shall be traceable to within one percent of NIST (formerly NBS) gas standards, or other gas standards which have been approved by the Administrator.

(c) Span gases (not including methanol) shall be accurate to within two percent of true concentration, where true concentration refers to NIST (formerly NBS) gas standards, or other gas standards which have been approved by the Administrator.

(d) Methanol in air gases used for response factor determination shall:

(1) Be traceable to within ±2 percent of NIST (formerly NBS) gas standards, or other standards which have been approved by the Administrator; and

(2) Remain within ±2 percent of the labeled concentration. Demonstration of stability shall be based on a quarterly measurement procedure with a precision of ±2 percent (two standard deviations), or other method approved by the Administrator. The measurement procedure may incorporate multiple measurements. If the true concentration of the gas changes by more than two percent, but less than ten percent, the gas may be relabeled with the new concentration.

[56 FR 25773, June 5, 1991, as amended at 60 FR 34342, June 30, 1995]

§ 86.115-00 EPA dynamometer driving schedules.

Section 86.115-00 includes text that specifies requirements that differ from § 86.115-78. Where a paragraph in § 86.115-78 is identical and applicable to § 86.115-00, this may be indicated by specifying the corresponding paragraph and the statement "[Reserved]. For guidance see § 86.115-78."

(a) The driving schedules for the EPA Urban Dynamometer Driving Schedule, US06, SC03, and the EPA New York City Cycles are contained in appendix I of this part. The driving schedules are defined by a smooth trace drawn through the specified speed vs. time relationships. They each consist of a distinct non-repetitive series of idle, acceleration, cruise, and deceleration modes of various time sequences and rates.

(b) The driver should attempt to follow the target schedule as closely as possible (refer to § 86.128-00 for additional cycle driving instructions). The speed tolerance at any given time for these schedules, or for a driver's aid chart approved by the Administrator, are as follows:

(b)(1) through (c) [Reserved]. For guidance see § 86.115-78.

[61 FR 54891, Oct. 22, 1996]

§ 86.115-78 EPA urban dynamometer driving schedule.

(a) The EPA Urban Dynamometer Driving Schedule and the EPA New York City Cycle are listed in appendix I of this part. The driving schedules are defined by a smooth trace drawn through the specified speed vs. time relationships. They each consist of a distinct nonrepetitive series of idle, acceleration, cruise, and deceleration modes of various time sequences and rates.

(b) The driver should attempt to follow the target schedule as closely as possible. The speed tolerance at any

417

Calibration Gases (not including methanol) shall be traceable to within one percent of NIST (formerly NBS) gas standards, or other gases as approved by the Administrator

New Standards to Support the Automobile Industry

Compound	Current SRMs	New Standards
Methane	1.0 ppm to 100 ppm	0.1 ppm to 0.5 ppm
Propane	0.25 ppm to 500 ppm	0.05 ppm to 0.2 ppm
Carbon Monoxide	10 ppm to 0.08 %	0.2 ppm to 5 ppm
Carbon Dioxide	0.5 % to 16 %	0.01 % to 0.1 %
Nitric Oxide	5 ppm to 3000 ppm	0.01 ppm to 1.0 ppm
Zero Air	NA	Detection Limit

Red text = Significant research involved

Stationary Sources

- Clean Air Act: Title IV
  - Power Plants -> Stack Emissions
  - EPA rules allowing emissions trading
    - Sulfur Dioxide, Nitric Oxide
    - EPA Protocol Gas Standards -> Requires “NIST Traceability”
- NIST Programs
  - Gas SRM and NTRM program
    - Partners: EPA and the specialty gas industry
    - Infrastructure: Primary Gas Standards
- Global Warming Gases emission trading program?

Standards for Mercury Emissions

EPA to regulate mercury emissions from coal fired power plants (Title II of the Clean Air Act of 1990)

- Original publication of regulations: December 2003
- Cap and Trade proposal issued February 24, 2004
  - 30 % reduction by 2008

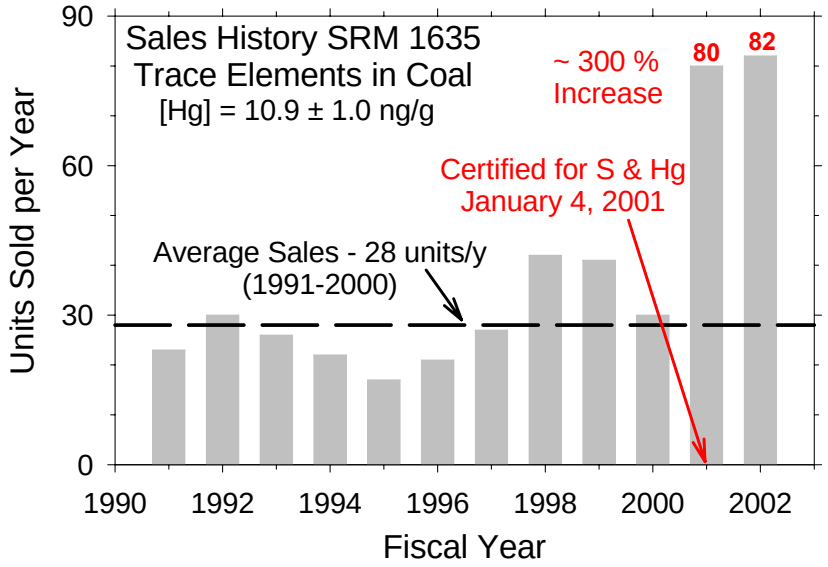
NIST Project Objectives

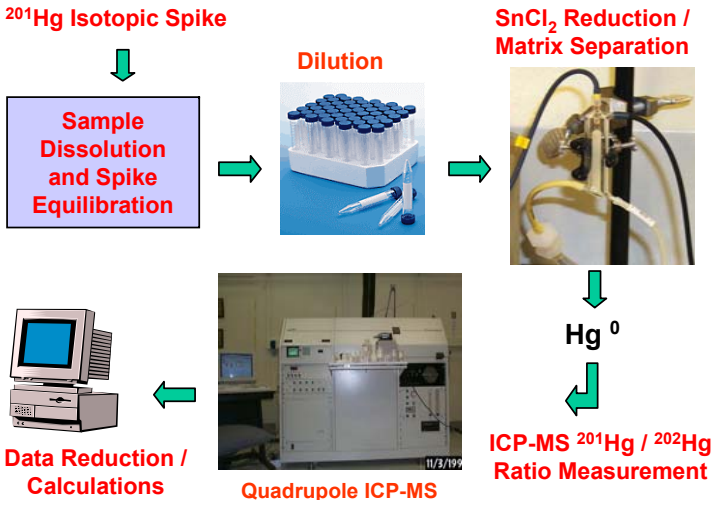
- **Provide traceability in elemental mercury emissions monitoring**
  - *Add Hg values to suite of existing Coal SRMs*
  - *Develop new gas mixture SRMs with NIST certified elemental mercury concentrations*

Certification of Mercury in Fossil Fuel SRMs by ID-CV-ICP-MS

Value added to existing SRMS

	ng/g of Hg	
SRM 1632c	93.8 ± 3.7	Bituminous
SRM 2682b	108.8 ± 2.9	Subbituminous
SRM 2683b	90.0 ± 3.6	Subbituminous
SRM 2684b	97.4 ± 4.7	Bituminous
SRM 2685b	146.2 ± 10.6	Bituminous
SRM 2692b	133.3 ± 4.1	Bituminous
SRM 2693	37.3 ± 7.7	Bituminous

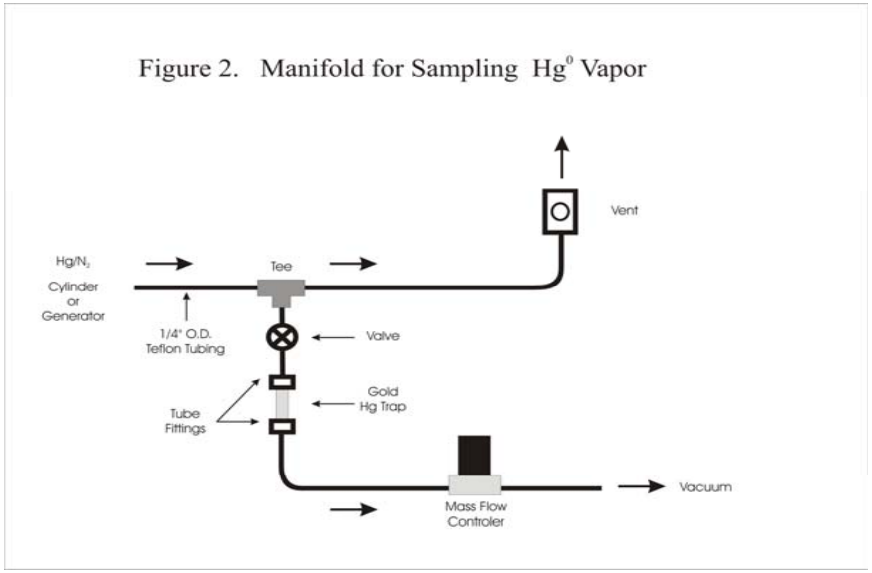




New method developed to meet industry need for low level Hg standards in coals

Mercury in Nitrogen Gas Standards

New Method: The first step is to develop a NIST traceable method for determining Hg^0 in nitrogen from two sources gas cylinders mercury generators (calibrators). This will be followed by the development of a NIST traceable standard for Hg^{++} in a flue gas.



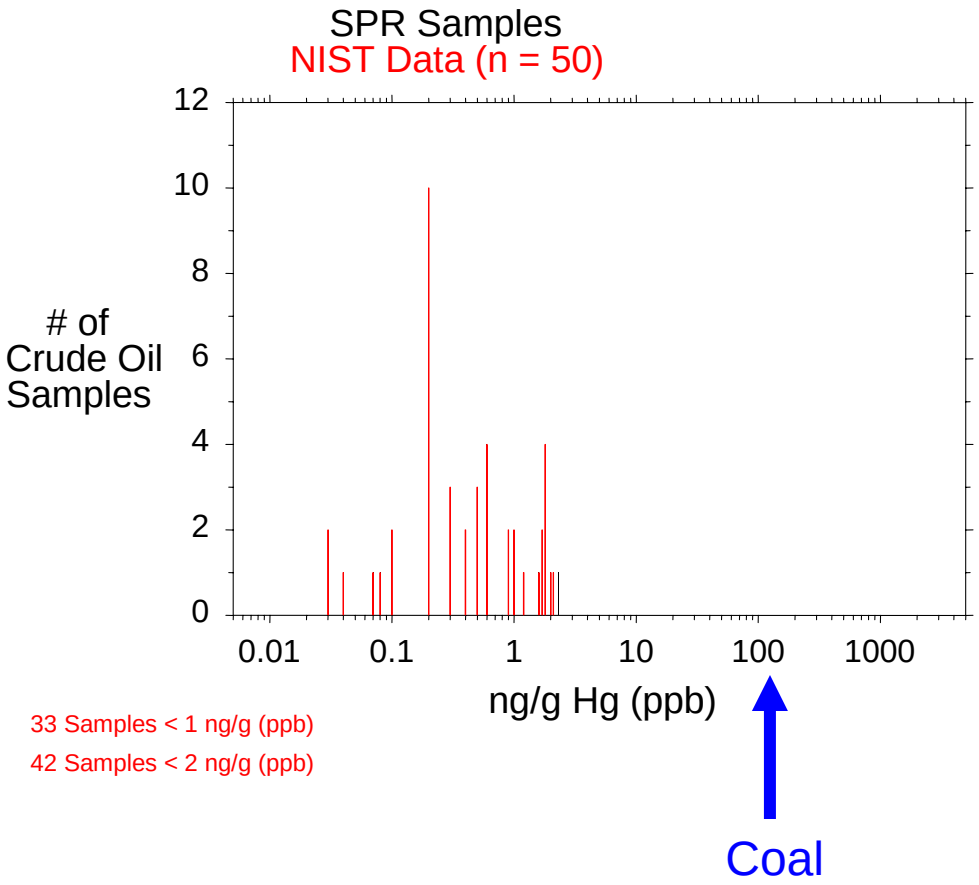
Mercury Concentration of Cylinder Gas Mixtures

Cylinder Number	Concentration Hg (µg/m³)	Expanded Uncertainty	Percent Relative
CC-162841	2.13	0.14	6.6 %
CC-162896	2.50	0.16	6.4 %
CC-162918	2.25	0.16	7.1 %
CC-162789	5.99	0.36	6.0 %
CC-165910	6.31	0.38	6.0 %
CC-162915	4.48	0.28	6.3 %
CC-162824	21.4	1.3	6.0 %
CC-162881	22.8	1.4	6.0 %
CC-162911	22.9	1.4	6.0 %
CC-162828	55.6	3.4	6.1 %
CC-162887	64.9	3.8	5.9 %

Three sets of three cylinders each containing Hg^0 vapor in nitrogen were analyzed by NIST to provide traceable calibration gas mixtures. The nominal concentrations of Hg^0 in the sets are 2 µg/m³,5 µg/m³ and 20 µg/m³.

Calibration: SRM 3133 Mercury Standard Solution

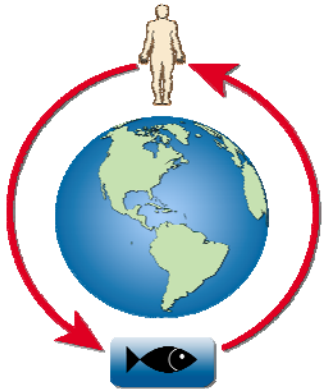
Hg in Crude Oil Samples from the U.S. Strategic Petroleum Reserve



Hg concentrations much less than typical values found in U.S. coal.

Oceans and Human Health Initiative

To provide science and biotechnology for evaluating and understanding linkages between costal development, the condition of the marine ecosystems, and public health.



NIST will support OHHI efforts for:

- **Detecting, identifying and determining the sources of human pathogens in coastal waters.**
- **Identifying and quantifying emerging chemical contaminants in coastal waters and assess their potential effects.**
- **Assessing the health status of key marine organisms using genomic technology (oyster and shrimp).**
- **Monitoring and assessing coastal environmental quality and associated public health threats.**

Pharmaceuticals in the Environment

Pharmaceuticals enter the environment primarily through treated and untreated waste (human excretion, landfill and agricultural run-off, disposal of expired medications)

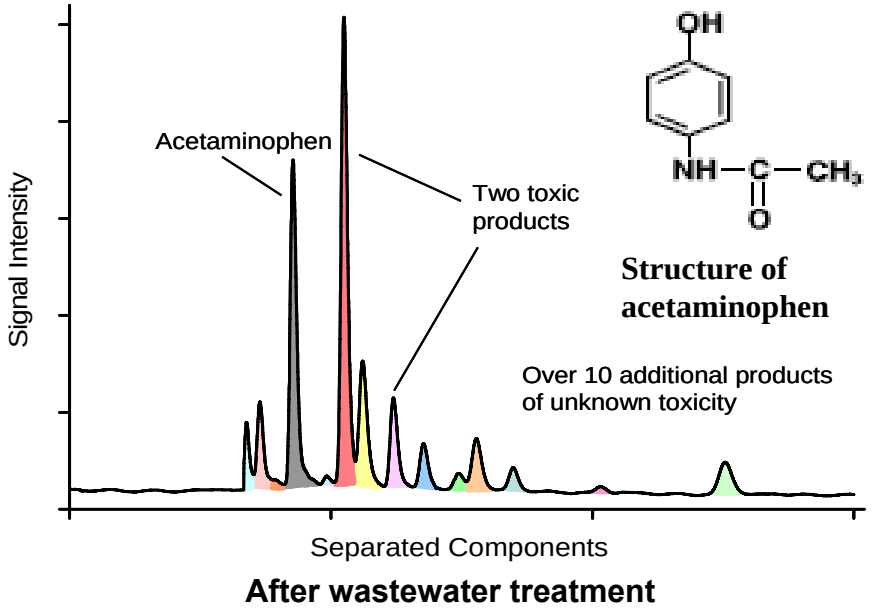
Continuous release results in pseudo-persistence in the environment

Some of the most frequently detected anthropogenic compounds in US streams are pharmaceuticals: acetaminophen (analgesic), erythromycin and sulfamethoxazole (antibiotics), estriol (estrogen); frequency of detection > 15 %

They are of environmental and human health concern because of their bioactivity, e.g., metabolic/endocrine disruption, bacterial resistance

Environmental Fate of Pharmaceuticals and Personal Care Products

- **Research into the fate and effects of pharmaceuticals and personal care products in the environment is rapidly increasing.**
- **Characterization of pharmaceuticals and other emerging contaminants is an important component of the Center of Excellence in Oceans and Human Health within the HML.**
- **Current research is aimed at identifying environmentally relevant chemical species to be monitored and developing trace analytical methods for their determination in water, sediments, and sewage sludge.**



After wastewater treatment

NIST Mission and Strategies for Success

- **Mission:** *To promote U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology – in ways that enhance economic security and improve the quality of life for all Americans*
  - *NIST is well positioned – at the nexus of science and industry – to advance this mission in support of industry and national needs*
- **Implementation Strategies:**

1) Help the U.S. to drive and take advantage of the increased pace or technological change
2) Foster more efficient transactions in the domestic and global marketplace by promoting more effective development and use of standards by manufacturers and the service sector
3) Address selected critical national needs *assigned* to NIST

Proposed Center of Excellence for Chemical Nanomanufacturing

- Chemical V2020 and Council for Chemical Research formed consultative committee with NNI to help implement Nanomaterials by Design Roadmap

- Formed WGs and had workshop (Feb 05) to identify specific industry needs (semiconductor and chemical industry particpated). The following broad areas were identified
  - Manufacturing Unit Operations
  - Real-time Measurement Science/Metrology
  - Modeling and simulation
  - Synthesis

A National program in Chemical Metrology is a great investment that pays significant dividends to the National economy and Quality of Life through underpinning

- Transactional efficiency in National and International Trade
- Fact-based Environmental Decision-Making
- Assessment Food Safety and Nutritional Content
- Healthcare Decision-Making
- National Security
- Innovation and Industrial Competitiveness

Thanks for your attention !!!

For further information:

Contact: willie.may@nist.gov

or visit us at www.cstl.nist.gov