QUALITY ASSURANCE ASPECTS OF THE HUMAN HEALTH STUDIES DURING PHASE II OF THE NORTHERN CONTAMINANTS PROGRAM (1998-2003)

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ABSTRACT

For the past decade, the Northern Contaminants Program (NCP) has supported an Interlaboratory Quality Assurance (QA) Program that assessed the quality, reliability and comparability of measurement data being generated within NCP research projects. During Phase II of the NCP (1998 to 2003), increasing emphasis was placed on immediate human health and safety issues associated with contaminants in traditionally harvested foods for Northern people, and toxicological and epidemiological studies intensified. This report details how the internal and external quality control measures being implemented in the human health laboratories of the NCP adequately addressed data quality and comparability. These measures include having sound quality management systems, the use of reference materials, interchange of standards and samples, and participation in external intercomparison programs. This report also shows how participation in the NCP Interlaboratory QA Program, the CTQ Interlaboratory Comparison Programs, the AMAP Ring Test and the First Nations and Inuit Health Branch Mercury in Hair Interlaboratory Program ensure that acceptable and known levels of precision and accuracy are generated for the measurement of contaminants such as OCs, PCBs, heavy metals, and methylmercury in biological fluids and human tissue samples.

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INTRODUCTION

Like all research and monitoring programs, the Northern Contaminants Program (NCP) requires an ongoing quality assurance (QA) program that provides assurance to its managers of the quality, reliability and comparability of measurement results being generated within its research projects. During Phase I of the NCP, considerable attention was devoted to identifying contaminants and their sources, and monitoring the pathways, trends and fate of substances of concern in the Arctic environment. Phase II, however, has had more focus on immediate human health and safety issues associated with these contaminants in traditionally harvested foods for Northern people. Therefore, to assess and prioritize the changing QA needs of the NCP, two surveys were conducted during 1998. By evaluating the analytical programs and capabilities of the laboratories and organizations that were contributing measurement data to the NCP, the first survey identified what measurements were being made, which laboratories were conducting these measurements, and what quality control procedures were already in place (Stokker et al, 1999a). The second survey reviewed the suitability of a number of external interlaboratory programs that would be pertinent to the QA needs of the NCP. In this report, several interlaboratory programs were identified as being suitable replacements for NCP-run intercomparison studies on human tissue samples, and recommendations were made for

Table 1. Laboratories that have contributed measurement data to NCP human health studies

AXYS Analytical Services Ltd. Sidney, BC	*organic contaminants in biological fluids and human tissues*
Centre de Toxicologie du Quebec (**CTQ**) CHUQ/CHUL Ste-Foy, Quebec	*metals and organics in biological fluids and human tissues;* *toxicological and epidemiological measurements*
Centre for Indigenous Peoples' Nutrition and Environment (**CINE**) McGill University, Macdonald-Campus Ste-Anne-de-Bellevue, Quebec	*nutrients, metals and organic contaminants in country foods, (occasionally blood and human tissues);* *toxicological and epidemiological measurements*
First Nations and Inuit Health Branch (**FNIHB**) Health Canada, Ottawa	*metals, PCBs, OCs in blood, serum, urine and hair*
Envirotest Laboratories Edmonton, Alberta	*metals and organics in biological fluids and tissues*
Bureau of Chemical Safety Health Protection Branch **Health Canada**, Ottawa	*risk assessment studies*
Food Research Division Residue Laboratory **Health Canada**, Ottawa	*organic contaminants in blood and adipose tissue*
Toxicology Research Division Health Protection Branch **Health Canada**, Ottawa	*toxicological studies of contaminants and their metabolites*
National Wildlife Research Centre (**NWRC**) Canadian Wildlife Service Environment Canada, Ottawa	*metals and organics in biotic fluids and tissues*
Saskatchewan Research Council (**SRC**) Saskatoon, SK	*radionuclide measurements (radiochemical and radioactivity measurements)*

the continued participation by the health laboratories in these QA programs (Stokker et al, 1999b).

Table 1 provides a listing of the Canadian laboratories who have contributed data to human health studies of the NCP over the last several years. At the onset of Phase II of the NCP, a review of the QA/QC procedures being conducted in the NCP health laboratories indicated that the data quality of their NCP measurements was being adequately addressed by their in-house quality control procedures, by comparison of standards and methodologies between collaborative partners, and by participation in several intercomparison programs that addressed the measurement of contaminants in human tissue samples such as blood and urine. The internal and external quality control procedures being implemented in these facilities is described below, followed by brief descriptions of the three Canadian intercomparison programs that support their human health measurements. Lastly, the data quality for the quantification of contaminant and nutrient intake by Northerners is described.

INTERNAL QUALITY CONTROL ACTIVITIES

Human health studies supported by the NCP that incorporate an analytical measurement component have included analyses ranging from contaminant measurements in biological fluids (blood, urine, milk) to the measurement of dietary nutrients, hormones and biomarkers in human, primate and other tissues. Because the NCP QA Program does not conduct intercomparisons on human tissue samples, it is imperative that good QA/QC

Table 2. Interlaboratory programs for human health issues in which NCP laboratories participate

Program	Matrices	Analytes
Organic and inorganic contaminants:		
BLLRS	blood	lead
CDCP	blood	lead
CFIA	fish tissue	mercury
CTQ: AMAP Ring Text	blood plasma	Congener PCBs and OC pesticides
CTQ Interlab Comparison Program	blood, serum, urine	Al, As, Cd, Cr, Cu, F, Hg, Pb, Se, Zn
CTQ Interlab Comparison Program for ICP-MS	Blood, urine, serum, hair	Al, Be, Bi, Cd, Co, Cu, Cr, Hg, Mn, Mo, Ni, Pb, Sb, Se, Sn, Sr, Te, Ti, Tl, V, W, Zn
FNIHB: Interlab mercury QA program	hair	mercury
GLRP	blood serum	Hg; pesticides and PCB congeners
GSOEM	blood plasma	Congener PCBs, OC pesticides
GSOEM	urine, blood	arsenic, manganese, mercury, creatinine
NCP	tissues	Toxaphene, OCs and PCBs, heavy metals, methylmercury
QUASIMEME	tissues	PCBs and organochlorines
State of New York Dept. of Health	blood, ZPP	lead
World Health Organization	breast milk	contaminants
Wisconsin State Laboratory of Hygiene	blood, ZPP	lead
WIAQC	water, serum	aluminum
Clinical and bio-monitoring:		
AAB: TDM		valproic acid, carbamazepine, diphenylhydantoin, ethosuximide, phenobarbital, primidone
CAP: Serum Alcohol	blood serum	acetone, ethanol, isopropanol, methanol
CAP: Toxicology	serum, urine	general toxicology
CAP: Forensic Urine Drug Testing	urine	amphetamines, cannabinoids, cocaine, phencycladine, opiates
FIOH: organic solvent metabolites	urine	Muconic acid, phenol, trichloroacetic acid, 2.5-hexanedione
GSOEM	urine	cotinine
GSOEM	urine	Hippuric acid, mandelic acid, methylhippuric acid, phenylglyoxylic acid, trichloroacetic acid, phenol, pentachlorophenol, 2.5-hexanedione, hydroxypyrene
SQBC		acetaminophen, diphenylhydantoin, phenobarbital

Acronyms:
AAB - American Association of Bioanalysts (USA)
AMAP - Arctic Monitoring and Assessment Programme
BLLRS - Blood lead laboratory reference system (Centre for Disease Control, Atlanta, USA)
CAP - College of American Pathologists (USA)
CDCP - Centre for Disease Control & Prevention (USA)
CFIA - Canadian Food Inspection Agency
CTQ - Quebec Toxicology Centre
FIOH - Finland Institute of Occupational Health (Finland)
FNIHB - First Nations and Inuit Health Branch Laboratory Services, Health Canada
GLRP - Great Lakes Research Program, (MDCH/Labs, USA)
GSOEM - German Society for Occupational and Environmental Medicine (Germany)
NCP - Northern Contaminants Program (Environment Canada)
QUASIMEME - Quality Assurance for Marine Environmental Monitoring in Europe, (UK)
SQBC - Quebec Society of Clinical Biology
WIAQC - Worldwide Interlaboratory Aluminum Quality Control (France)

programs be implemented in each facility conducting biological monitoring or health risk related studies. A review of the quality management systems in the key health laboratories of the NCP shows that the organizational structure, responsibilities, procedures, processes and resources used are well-documented and suited to the analytical programs conducted at each facility. Internal quality control procedures employed include the use of control standards to monitor calibration accuracy and stability, appropriate CRMs and RMs to monitor method accuracy, duplicates to monitor method precision, analyte or surrogate spikes to monitor method recovery, and solvent and method blanks to assess for contamination. In addition, participation in the NCP intercomparisons on standards and biotic tissues, as well as a number of external intercomparison programs that address the analysis of human tissues and other health related matrices, ensure comparability with other laboratories and among different research projects of the NCP. Table 2 provides a list of these external interlaboratory programs.

A wide variety of reference materials (RMs) and certified reference materials (CRMs) are used on a regular basis by the NCP laboratories. For the data quality assurance of human tissue analyses, some of these health-related RMs and CRMs are listed in Table 3. In-house reference materials have also been developed by CTQ and FNIHB within their own interlaboratory programs including blood serum for PCBs and metals, and hair samples for mercury analysis.

Table 3. Reference materials used for data quality assurance in NCP human health studies

RM/CRM code	Supplier	Matrix	Analytes
CRM-188	BCR	milk powder	OC pesticides (spiked)
CRM-397	BCR	hair powder	total mercury
CRM-450	BCR	milk powder	PCB congeners
CRM-463	BCR	fish powder	total mercury
IAEA-085 & IAEA-086	IAEA	hair powder	heavy metals, total mercury, methylmercury
NIES No. 13	NIEH	hair powder	total mercury, methylmercury
SRM-966	NIST	blood	toxic elements
SRM-968c	NIST	human serum	retinoids, tocopherols, carotenoids, cholesterol
SRM-1544	NIST	frozen diet composite	fatty acid, cholesterol, proximate
SRM-1588a	NIST	cod liver oil	PCB congeners, OC pesticides, α-tocopherol
SRM-1589a	NIST	blood serum	PCB congeners, OC pesticides, dioxins/furans
SRM-1945	NIST	whale blubber	PCB congeners, OC pesticides
SRM-2383	NIST	baby food composite	vitamins, proximate, minerals
AMIB-1701, -1702, -1703	Promochem AB (Sweden)	lyophilized human blood	lead, cadmium, chromium, manganese

Acronyms:

BCR - Community Bureau of Reference, Belgium
IAEA - International Atomic Energy Agency, Austria
NIEH - National Institute For Environmental Health, Japan
NIST - National Institute of Standards and Technology, USA

EXTERNAL DATA QUALITY ASSURANCE

Northern Contaminants Interlaboratory Quality Assurance (QA) Program

The primary objective of the Northern Contaminants Interlaboratory Quality Assurance (QA) Program is to provide assurance to NCP managers and researchers of the quality, reliability and comparability of measurement results being generated within the NCP studies. Several intercomparison studies are conducted annually to address the quality of data being generated for heavy metals, methylmercury, and POPs, including PCB congeners, organochlorine (OC) pesticides and toxaphene. Due to the focus of NCP Phase II on country foods, a significant portion of NCP contaminant measurements have been on environmental and biotic (wildlife) tissues. Therefore, the check samples used in the NCP QA intercomparisons have included standard solutions, environmental materials and tissues from Arctic biota. Sample descriptions and laboratory performance in these studies are detailed in the quality assurance chapter of the *Canadian Arctic Contaminants Assessment Report II* (Stokker, 2003). While the current NCP QA program does not include human tissues as check samples, many of the health laboratories have participated in the studies by analyzing the injection-ready standard solutions and/or the wildlife tissue samples, where feasible. In addition, their participation in the NCP QA program is complemented by participation in several excellent external QA programs that directly address human tissue measurements using biological fluid and tissue check samples. Two of these Canadian QA programs are described in more detail below.

Centre de Toxicologie du Quebec Interlaboratory Comparison Programs

Although there have been several laboratories that have provided human tissue measurements to the NCP (refer to Table 1), much of the work has been conducted at the Centre de Toxicologie du Quebec (CTQ). This laboratory is the reference laboratory in human toxicology for the Province of Quebec. It is accredited by the Standards Council of Canada (SCC) under ISO/IEC 17025. Their expertise is in the determination of heavy metals and persistent organic pollutants in biological fluids and tissues. Human health samples for the NCP research program have included blood, urine, milk, placental and adipose tissue, and hair.

In 1979, in order to support its internal quality control needs as well as to provide a measure of comparability with other international toxicology laboratories, CTQ developed an Interlaboratory Comparison Program for laboratories conducting measurements of toxic trace metals in blood and urine. The check samples are prepared, whenever possible, by pooling specimens obtained from exposed workers or patients. This meets the need for matrix-matching that cannot be optimally achieved with most commercial reference materials which are often either freeze-dried and/or spiked with the analytes of interest. A parallel program, called the ICP-MS Comparison Program, addresses the comparability of analytical clinical laboratories using inductively-coupled plasma mass spectrometry (ICP-MS) to analyze for trace metals in biological samples (blood, urine, serum and hair). At present, more than 200 laboratories world-wide participate in these programs for one or more toxic substances. In table 4, the distribution frequency, cost, and the selection of parameters being assessed in these studies are detailed.

Table 4. Intercomparison studies available from Centre de Toxicologie du Quebec

Name of scheme:	**Interlaboratory Comparison Program** for trace metals in biological fluids	**ICP-MS Comparison Program** for trace metals in biological samples	**AMAP Ring Test** for PCBs and OCs in plasma
Type of proficiency testing study:	Laboratory Comparison	Laboratory Comparison	Laboratory Comparison
Target group:	Analytical clinical laboratories	Analytical clinical laboratories using ICP-MS instrumentation	Analytical laboratories
Matrices:	Human urine, Human whole blood, Human serum	Human urine, Human whole blood/serum, Human hair	Serum/plasma
Analytes:	*Urine* Total As, Non-dietary As, Cd, Cr, Cu, F, Hg, Pb, Se, Zn *Whole blood* Cd, Hg, Pb *Serum* Al, Cu, Mn, Se, Zn	Ag, Al, As, Ba, Be, Cd, Co, Cr, Cu, Hg, Mn, Mo, Ni, Pb, Pt, Sb, Se, Sn, Te, Tl, U, V, Zn	PCB congeners: # 28, # 118, #138, # 153 # 170. # 180 OC pesticides: p,p'-DDE, p,p'-DDT oxychlordane Beta-HCH
Concentration:	Physiological and pathological	Physiological and pathological	Physiological
Sample distribution:	3 samples per round	3 samples per round (usually 1 urine, 1 blood or serum and 1 hair)	3 samples per round
Period of time:	6 rounds/year	3 rounds/year	3 rounds/year
Fee:	Annual : US $150 registration and US $160 per control material	Annual : US $210	Annual : US $210

More recently, as a reference health laboratory for the Arctic Monitoring and Assessment Program (AMAP), the CTQ became a provider of annual intercomparison studies on the analysis of selected POPs in blood. This program, known as the AMAP Ring Test (Weber, 2002) is mandatory for laboratories providing analytical results for PCBs in blood to the AMAP. Details of the frequency, cost, and specific analytes for the AMAP Ring Test intercomparison studies are provided in table 4. Participants are provided with frozen human blood plasma samples spiked with various levels of the PCB and OC analytes. At the close of each study, they receive a summary report with their laboratory performance clearly detailed. In the first run of this intercomparison program, twenty-six laboratories provided results, but the data were generally not normally distributed. While there was good correlation between related analytes, poor performance was noted at concentrations <0.5 μg/L. In the second run, most analytes and the majority of results from the twenty-five reporting laboratories were within ±20% of their assigned values in the study. Examples of the performance of three different laboratories over two runs of this program are shown in figures 1-3. Each figure is a modified Youden plot (Youden, 1959) where the results for each parameter are plotted against their assigned value in the test sample. In Figure 1, the laboratory clearly provided consistent, accurate results for each parameter in each run. In Figure 2, the laboratory demonstrated a systematic error or bias in the first run with a dramatic improvement in their results in the second run. Figure 3 illustrates the results for a laboratory with random variations in their analyses on both runs 1 and 2.

Thus, as a provider of data quality assurance to the NCP, the interlaboratory and intralaboratory quality control procedures for this facility were reviewed (CTQ, 1999). Consistent with their SCC accreditation to ISO 17025, these procedures were found to be well documented and adequately address the data quality of measurements produced in this laboratory.

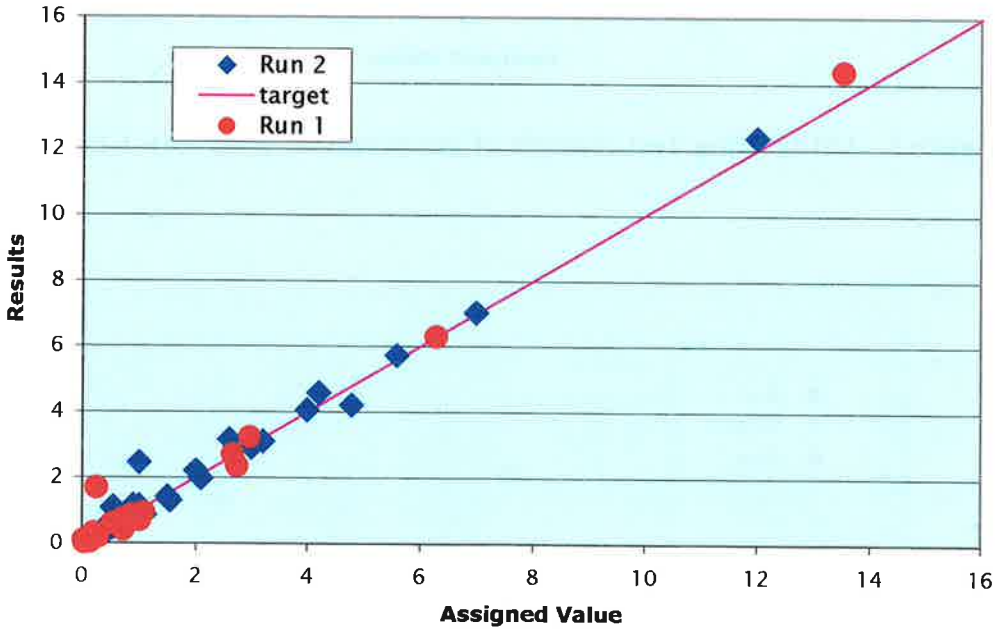

Figure 1. AMAP Ring Test example of a proficient laboratory

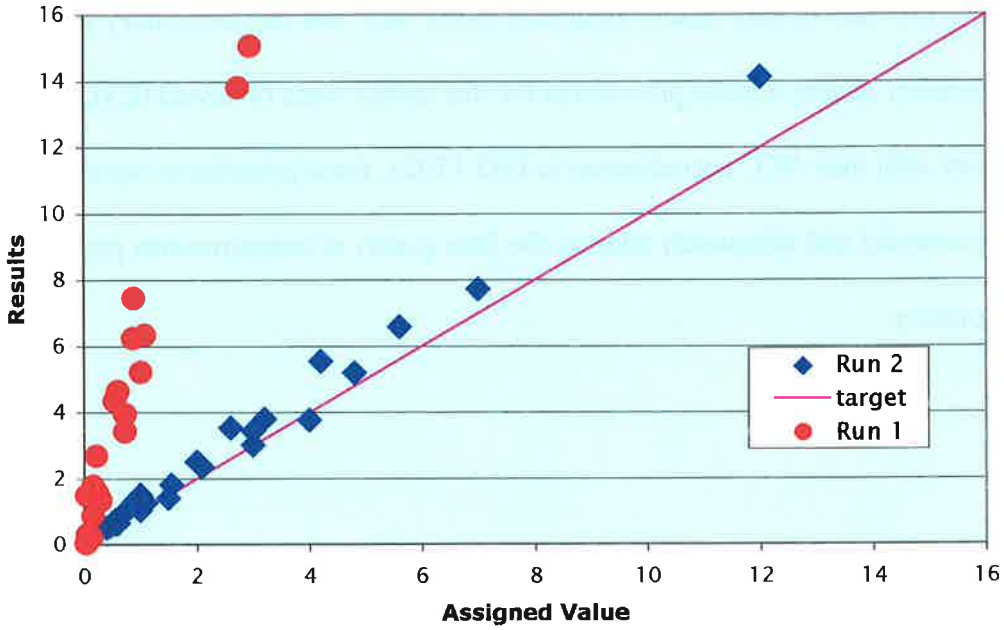

Figure 2. AMAP Ring Test example of improvement from Run 1 to Run 2

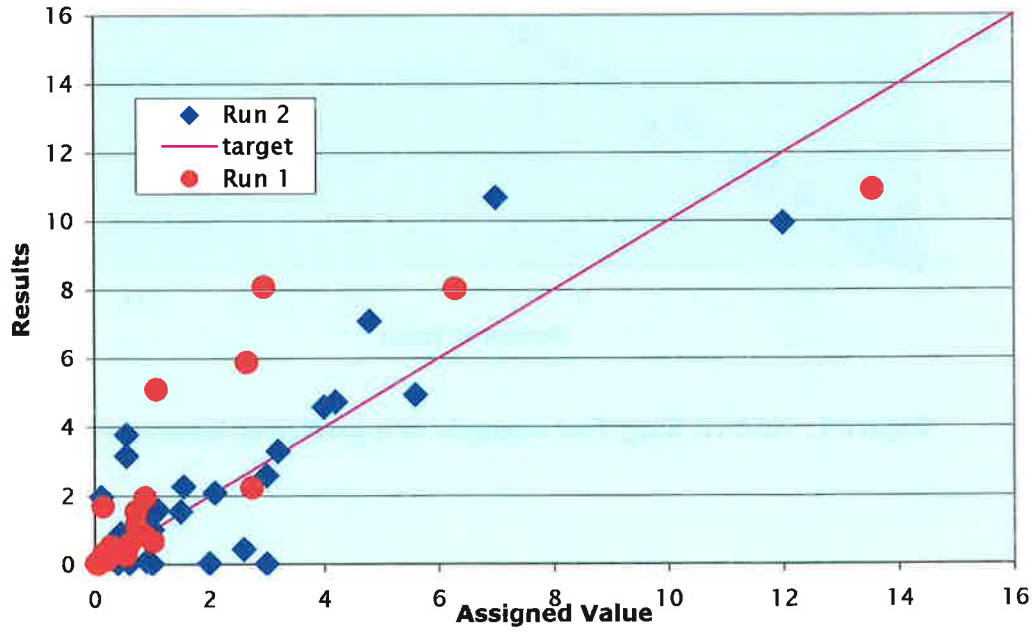

Figure 3. AMAP Ring Test example of random variations

Hair Mercury Quality Control Program.

Health Canada's First Nations and Inuit Health Branch Laboratory Services (FNIHB) offers analytical testing services for Total PCBs (as Aroclor 1254 and 1260), 35 PCB congeners, 34 organochlorinated pesticides (OCs), total mercury, inorganic mercury and organic mercury (Health Canada, 2001). Human health samples include biological fluids such as blood, serum and urine, and tissues (hair samples). This laboratory is proceeding toward accreditation by the Standards Council of Canada (SCC) for the above tests. Along with developing a quality management system that follows ISO Guide 17025 (Standards Council of Canada, 2000), they have participated on a regular basis in the NCP QA program for mercury analyses in biotic tissues.

Health Canada's FNIHB has also conducted a mercury in hair interlaboratory QA/QC program since 1990 (Gill, 2002) in which more than thirty laboratories from ten countries have participated. The check samples were prepared from hair specimens from the Canadian population and assessed for suitability in the intercomparison study by replicate measurements of total mercury and inorganic mercury. To assess homogeneity, the FNIHB laboratory analyzed six replicates of each sub-sample and consistently produced measurements with a repeatability of better than 10%. In fact, more than 90% of these homogeneity measurements produced a repeatability of better than 5%. These results not only verify the homogeneity of the sub-samples produced, but are also an indication of good in-house precision at the FNIHB. Figure 4 illustrates a comparison of the homogeneity test mean from the FNIHB laboratory with the consensus mean from the

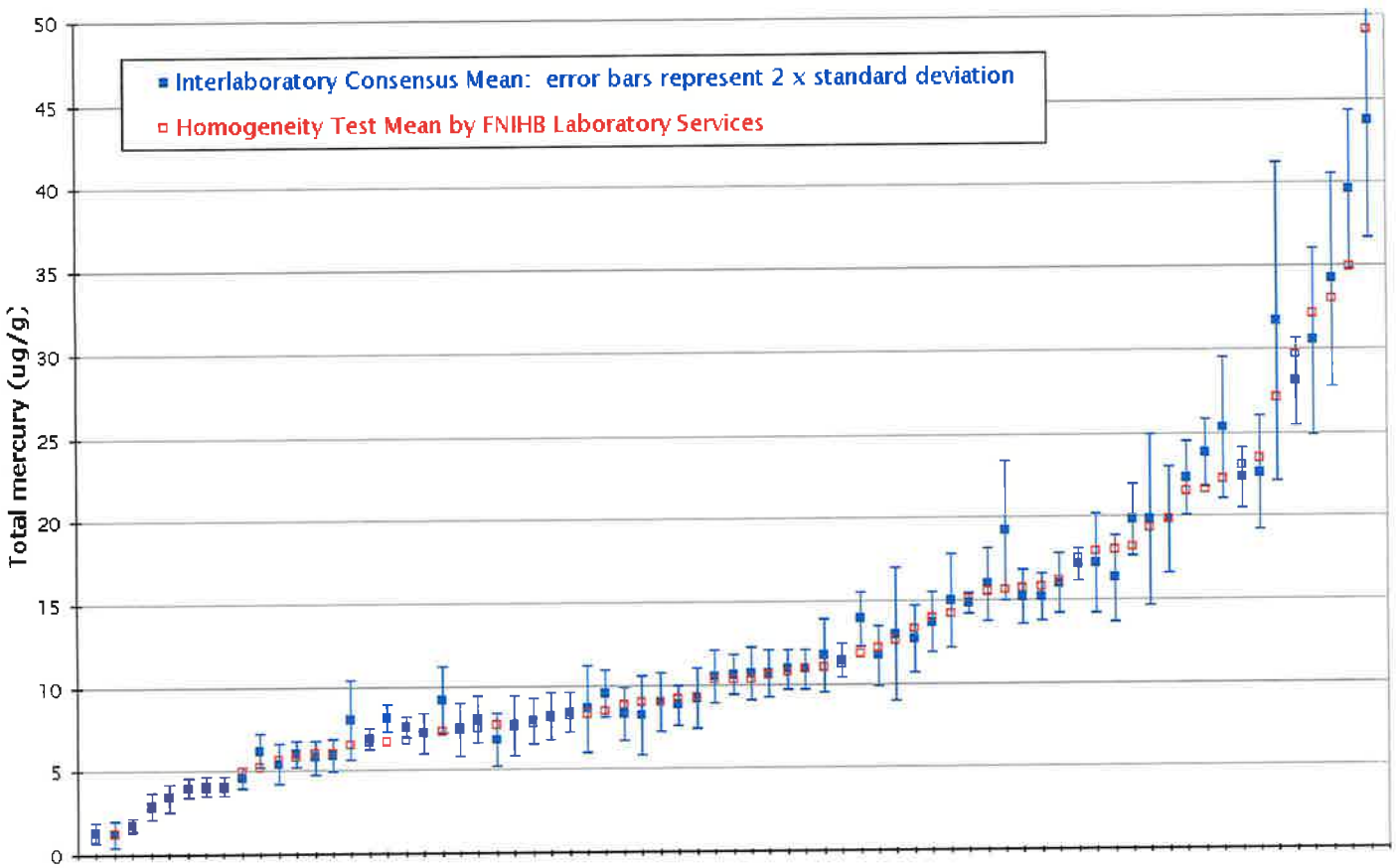

Figure 4. FNIHB homogeneity test means and the consensus means for total mercury in each intercomparison sample, 1990-2000. Samples are plotted from lowest to highest concentration (i.e. not in chronological order).

participants in the studies. In twenty-four studies conducted from 1990-2000, 95% of the participating laboratories, using their own in-house techniques, produced results that agreed well with the FNIHB results from the respective studies (Gill et al, 2002). From the plot of results presented in Figure 4, it can be clearly seen that the FNIHB has consistently produced reliable data for total mercury in hair.

DIETARY SURVEYS AND MEASUREMENTS

Along with the chemical measurement of contaminants in their environment, their food and their tissues, an equally important aspect to monitoring the health of Northerners is the determination of their dietary intake of both nutrients and contaminants. This area of NCP research has been addressed by several multi-year projects conducted by scientists at the Centre for Indigenous Peoples' Nutrition and Environment (CINE), a multi-disciplinary research and education resource for Indigenous Peoples. The research and education activities conducted at CINE focus on the concerns of Aboriginal Peoples regarding the health and integrity of their traditional food systems incorporating the various issues related to ecosystem, contaminants, health and culture. Their scope of work within NCP includes evaluating the nutrient content and contaminant levels in country foods, conducting dietary surveys, risk:benefit studies, and toxicological studies, and developing and distributing educational materials to northern communities. For the generation of NCP measurement data, CINE's laboratory focuses primarily on food samples, with less emphasis on the routine analysis of hair, blood and urine. Since their methodologies for contaminants in traditional Northern foods are similar to those being

conducted by wildlife laboratories, CINE's data quality is regularly monitored by their participation in the Northern Contaminants Interlaboratory Quality Assurance Program for both POPs and heavy metals.

CONCLUSION

At the onset of Phase II of the NCP, an assessment of the analytical programs and internal quality control procedures of the NCP health laboratories indicated that the data quality of the measurements generated in these laboratories was being adequately addressed. More recently, a review of the QA/QC procedures being followed in the NCP's key health laboratories show that they have sound quality management systems in place that continue to address their data quality needs. These procedures include traceability and comparability checks on standards, samples and methodologies, good documentation of policies, procedures and protocols, and regular participation in external interlaboratory QA programs. As well as generating comparable results in the NCP Interlaboratory QA Program on standards and biotic tissues, many of these laboratories also routinely participate in external intercomparison programs on human tissue samples, such as CTQ's Interlaboratory Comparison Program and FNIHB's Hair Mercury Quality Control Program. As these laboratories continue their research and monitoring measurements on human health issues into Phase III of the NCP, their continued participation in the above three intercomparison programs is strongly recommended.

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