GUIDANCE FOR LABORATORY BIOMONITORING PROGRAMS

Developing Biomonitoring Capabilities

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APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES®

Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

Acknowledgments

This is an update of APHL's 2012 biomonitoring guidance.

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1. INTRODUCTION

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PURPOSE OF THIS GUIDANCE

This guidance provides technical information to members of the National Biomonitoring Network (NBN) and other state, local and territorial laboratories engaged in human biomonitoring. The aim of this document is to advance the science, quality and use of biomonitoring in public health practice. This is part of APHL's commitment to further develop the NBN.

APHL's work in this area began in 2009 with enactment of APHL's first five-year plan to create a network of public health laboratories with enhanced biomonitoring capacity. This was the basis for the subsequent development of the NBN and additional collaboration with partners and federal agencies. One such joint effort with specific relevance to this guidance is work with the Council of State and Territorial Epidemiologists (CSTE) in developing the guidance document, *Biomonitoring in Public Health: Epidemiologic Guidance for State, Local, and Tribal Public Health Agencies*,[1] which serves as a companion to this guidance.

If you are interested in sharing information about your biomonitoring project or would like more information about CDC's National Biomonitoring Program, please contact APHL at EH@aphl.org. Visit aphl.org to learn more about our biomonitoring activities.

1 CSTE. Biomonitoring in public health: Epidemiologic guidance for state, local, and tribal public health agencies. 2012. Accessed June 2019. www.cste2.org/webpdfs/BioMonISFINAL.pdf

AUDIENCE

This guidance is for staff in state or local public health or environmental laboratories and their public health partners involved in the design and implementation of biomonitoring programs and studies. The content was developed for professionals working in analytical laboratories who are either new to biomonitoring or bring previous experience to their efforts. It is assumed that users of this guidance have an understanding of good laboratory practices and basic principles of analytical chemistry. A background in epidemiology is not necessary, but basic knowledge and access to epidemiologic expertise is beneficial and recommended.

While the laboratory may not have a role in all of the activities described in this document, the range of efforts is included to provide an overview of the entirety of biomonitoring-related work conducted by public laboratories.

GOALS

The goals of this guidance are to:

- Describe key elements of biomonitoring studies and the roles of the study team members that carry out these activities
- Identify key stakeholders and how to engage them and obtain input into the study process
- Outline the role of public health laboratories in these studies including necessary infrastructure and expertise
- Provide examples from peers to inform future biomonitoring activities

IN THIS GUIDANCE

- **Biomonitoring and Public Health.** This section covers: definition of biomonitoring, components of biomonitoring studies, role in public health and the federal response (the Laboratory Response Network and the NBN.
- **Study Team and Advisory Panel.** This section reviews a biomonitoring study's core team members and, when involved, the role of advisory panels for state biomonitoring programs and biomonitoring studies.
- **Community Engagement and Communication.** Presented here is a definition of the broad term "community" and insights about ways to engage with the community and various partners.
- **Laboratory Infrastructure.** This includes the components that make a laboratory function: the facilities, equipment, information technology, laboratory personnel and quality management system.
- **Biomonitoring Study Design.** Covered here are the components of a study, from goals and objectives to study design steps, provisions to protect human subjects and population selection and study sample selection.
- **Biomarker Selection.** This covers types of biomarkers, matrix, properties of the chemical and pharmacokinetics, biomarker specificity, analytic specificity and sensitivity and feasibility considerations.
- **Study Protocols and Plans.** This section reviews the analytical method, participant selection and recruitment, specimen collection and storage and handling, data security, reporting and communications, data analysis, evaluation and protection of human research participants.
- **Analytical Protocol and Methodology.** This section reviews initial considerations in analytical method selection, specimen collection and analytic testing
- **Preparing and Communicating Results.** Covered here are laboratory results reporting, results interpretation and communication of results.

2. BIOMONITORING & PUBLIC HEALTH

IN THIS SECTION

- About Biomonitoring
- Components of Biomonitoring Studies
- Role of Biomonitoring in Public Health
- Development of the National Biomonitoring Network

ABOUT BIOMONITORING

Human exposure to environmental chemicals can occur from multiple sources, such as air, water, soil, food and consumer products. Biomonitoring is the assessment of individual and population exposures to environmental contaminants by measuring the concentration of chemicals and or their metabolites in human specimens, such as blood, urine, hair, or saliva. Biomonitoring identifies and quantifies chemicals and elements in the human body to provide scientific evidence of the degree of exposure to a particular product or chemical. This information, when combined with subsequent trend analysis, improves our understanding of the relationship between exposure to environmental chemicals and their impact on health.

More specifically, the data from biomonitoring studies are useful to:

- Establish baselines for prioritizing and conducting research on health effects
- Identify exposure sources
- Support risk assessment and management
- Help decision makers create evidence-based public health and environmental policies and target limited public resources to reduce unusual or emerging exposures
- Assess the efficacy of a public health intervention, as in the removal of lead from gasoline and indoor smoking restrictions

CHECKLIST: COMPONENTS OF A BIOMONITORING STUDY

- ☐ Define the goals of the study.
- ☐ Engage community early in the study design process.
- ☐ Choose the appropriate biomarker in the appropriate matrix at a sufficient level of sensitivity.
- ☐ Identify resources needs and sources of potential funding.
- ☐ Establish a collaboration among chemists, epidemiologists, toxicologists, and other relevant public health scientists in the development of the study design and to analyze and communicate biomonitoring data.
- ☐ Include communications specialists and policy advisors on the study team as appropriate.
- ☐ Produce reliable and valid and laboratory data.
- ☐ Develop an effective communication plan that involves reporting of study progress, reporting individual results (if appropriate) and aggregate data, and facilitates access to public health staff or medical professionals for results distribution and interpretation.

The technology and instrumentation used for biomonitoring testing have a lot in common with environmental testing, the latter of which examines chemicals in water, soil and air. Biomonitoring data can complement environmental monitoring data by measuring how much of the environmental contaminant is found in the body. However, biomonitoring and environmental testing differ in certain respects. First, biomonitoring data measure exposure across all environmental sources,[1] providing a more accurate picture of human exposure than estimates based solely on environmental measurements. Biomonitoring also presents a unique set of challenges, including the requirement that laboratories receive approval for clinical testing of human specimens. Assaying clinical matrices also involves unique requirements such as the safe handling of potentially infectious materials, different interferences and possibly the quantification of metabolites. However, the greatest difference between biomonitoring and environmental testing involves the interpretation of clinical findings, the results of which must then be effectively communicated to the individual and, as appropriate, the wider community.

Multiple biomonitoring studies have identified the presence of widely used chemicals in human blood, urine or tissues. One such study is the CDC's *National Report on Human Exposure to Environmental Chemicals*,[2] and its determination of, for example, the presence of bisphenol A and flame retardants. These types of national studies are important first efforts in answering critical environmental health questions. However, they do not provide targeted or regional information, health effects information, or exposure sources that can be used at state and local levels. A network of biomonitoring programs across the nation can fill this gap by providing state and local public health organizations with the tools necessary to investigate environmental health questions and problems in their respective communities.

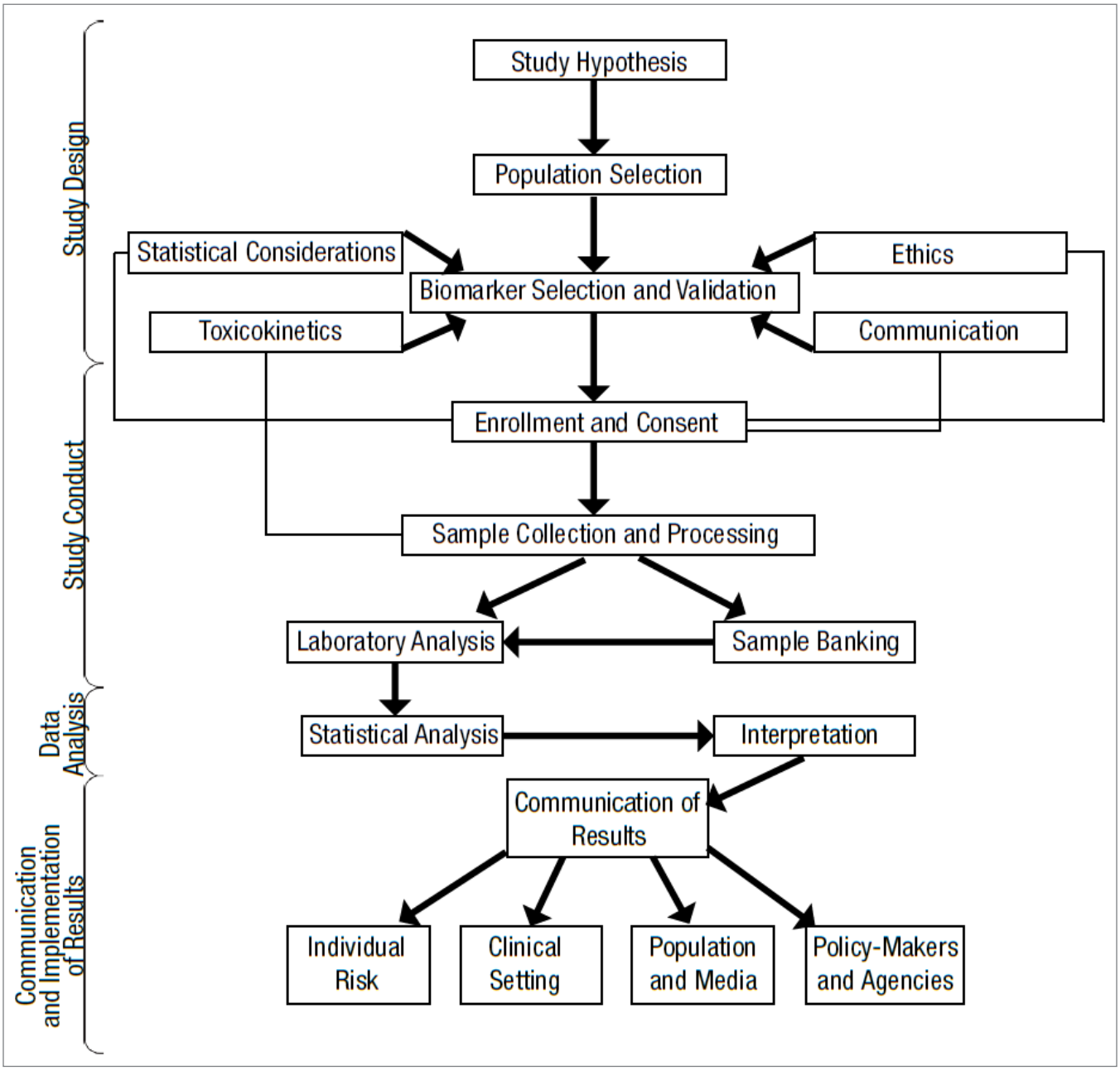
1 CDC. Fourth report on human exposure to environmental chemicals. 2009. Accessed June 2019. www.cdc.gov/exposurereport/

2 CDC. National Report on Human Exposure to Environmental Chemicals. 2017. Accessed June 2019. www.cdc.gov/exposurereport/index.html

COMPONENTS OF BIOMONITORING STUDIES

Biomonitoring studies are multi-step, multidisciplinary undertakings. Laboratory scientists can provide valuable information and insight during each phase of the project. The Committee on Human Biomonitoring for Environmental Toxicants at the National Research Council has developed the following algorithm to describe the essential stages of a biomonitoring study.[1] More information on the components of biomonitoring studies and how to conduct them are provided in this guidance.

Figure 1. Human biomonitoring for environmental chemicals[1]



1 National Research Council of the National Academies. *Human Biomonitoring for Environmental Chemicals*. Figure 4-1, page 86. Washington, DC: The National Academies Press. 2006. www.nap.edu/read/11700/chapter/6#86

ROLE OF BIOMONITORING IN PUBLIC HEALTH

Biomonitoring studies can be used by public health agencies in conducting disease investigations in their public health surveillance work; assessing chemical exposures in a potentially exposed and at-risk population; and responding to emergency exposures. Each is discussed below.

Public Health Surveillance

Public health surveillance compiles and interprets health-related data needed for planning, implementation and evaluation of public health practice. Biomonitoring studies can support surveillance work as these data detect and measure spatial or temporal differences in population exposure as a way to evaluate the efficacy of public health actions to reduce a known exposure. Data can also be used to determine baseline levels of population exposure to contaminants. Used together with individual or community-level health information, the results can help to determine both the association between exposure and disease and evaluation the effectiveness of policies and interventions to address the health-related impact of the contaminants. Some states collect biomonitoring surveillance data, like mandatory registries (i.e., databases) based upon physician and laboratory reports of various biological measures (e.g., blood lead, pesticide poisonings).

In the United States, CDC's National Health and Nutrition Examination Survey (NHANES) routinely collects nationally-representative data on the health and nutritional status of the US general population, including exposure to chemical substances. NHANES uses a cross-sectional sample of a defined population. Data are collected from approximately 5,000 representative individuals per year through interviews, physical exams and clinical tests. Environmental chemical analytes are measured in blood, serum, and urine from NHANES participants (per two-year survey period). These data are reported in the *National Report on Human Exposure to Environmental Chemicals*.[1]

Targeted Public Health Investigations

The discovery of environmental contamination, or a cluster of disease with a possible chemical exposure origin, can trigger public concerns and a public health investigation. Biomonitoring activities can:

- Measure the range and distribution of the exposure in the community
- Determine whether exposures are above a reference level or different than unexposed populations
- Determine whether a public health response is required.

Exposure Events and Emergency Responses

In instances of acute exposure to a toxic substance, investigation methods used are similar to a disease outbreak investigation. The role of biomonitoring in response to such an emergency exposure would be to evaluate clinical measures in individuals and support diagnosis of poisonings and assess the need for medical treatment.

An emergency response would require exposed individuals to be rapidly identified and referred to a clinical setting for specimen collection, processing, analysis, patient diagnosis and follow-up by medical professionals. State health professionals would provide necessary laboratory or toxicology support. Epidemiologists will then track outcomes over the course of the response and design follow-up investigations.

1 CDC. *National Report on Human Exposure to Environmental Chemicals*. 2017. Accessed June 2019. www.cdc.gov/exposurereport/index.html

DEVELOPMENT OF THE NATIONAL BIOMONITORING NETWORK

Laboratories operate at federal, state and local levels and conduct varied biological and chemical assessments. This infrastructure has evolved in recent decades to create a national network of laboratories and build their capacity to conduct biomonitoring studies. Two major initiatives are described below.

Laboratory Response Network

The Laboratory Response Network (LRN)[1] was established in 1999 by CDC and other key partners (including the Federal Bureau of Investigation and APHL) as a network of laboratories that can effectively respond to biological and chemical threats and other public health emergencies. LRN includes state and local public health, veterinary, military, and international labs.

In 2003, the LRN expanded its mission from only testing for biological threat agents to testing for chemical threat agents. The chemical component of the LRN, referred to as the LRN-C,[2] has worked to build a network capable of responding to chemical threats. The LRN-C consists of 62 public health laboratories throughout the US and its territories as well as a laboratory at CDC.

The 62 LRN-C laboratories have designated "levels" that correlate with their ability to perform certain tasks during emergency events.

- Level 3 laboratories work with hospitals and first responders to collect, package and ship clinical samples to other laboratories for testing.
- Level 1 and 2 laboratories test samples for toxic chemicals, metals and some chemical warfare agents.
- Level 1 laboratories test for additional chemical warfare agents, maintain surge testing capacity, and serve as backup to CDC during large-scale emergencies.

The level 1 and 2 laboratories have the instrumentation, knowledge and personnel necessary to conduct most biomonitoring studies. They are available to states who wish to implement biomonitoring. States that lack the capability to develop their own biomonitoring capacity can consult or partner with level 1 and level 2 states to initiate biomonitoring studies.

National Biomonitoring Network

In 2009, APHL developed the first National Biomonitoring Five-Year Plan to establish a network of public health laboratories able to provide accurate human exposure data to inform public health decisions through biomonitoring. This work resulted in the formation of the National Biomonitoring Network (NBN),[3] an interconnected system of government laboratories working with public health partners to advance the science of human biomonitoring. The NBN aims to harmonize biomonitoring data for use in routine public health practice by establishing quality standards, mentoring nascent programs and enhancing analytical capability and capacity through technical assistance.

Guided by a multi-disciplinary Network Steering Committee (NSC), the NBN developed an organizational framework, membership criteria, and guidance related to program and study design, quality management and analytical measurements. To facilitate the production of these resources, the NSC established interdisciplinary workgroups of subject matter experts. Important challenges remaining for the NBN are to define data standards and to identify an appropriate national repository for biomonitoring data.

1 APHL. Laboratory Response Network aphl.org/LRN

2 APHL. Laboratory Response Network for Chemical Threats. aphl.org/LRN-C

3 APHL. National Biomonitoring Network. aphl.org/NBN

Throughout its development, the NBN has taken a systems approach to provide high-quality data for use in public health practice. Many challenges were encountered in developing practices, policies and materials that provide consistency but afford flexibility to adapt to emerging needs, technology and concerns. By providing guidance, technical training, examples and templates for analytical and epidemiological practices and opportunities for collaboration and interaction, the NBN addresses some of these challenges and is working towards solutions for others. Currently, 17 laboratories are members of the NBN.

NBN GOALS

1. Advance the science of biomonitoring.
2. Encourage the use of biomonitoring in addressing environmental health questions.
3. Ensure quality practices, which will help produce comparable biomonitoring data.

Internationally, biomonitoring networks are forming. While their objectives may differ, understanding their structure, advantages and limitations will inform the NBN and provide opportunities for cross-network collaboration.

RESOURCES

APHL Environmental Health Program
aphl.org/EH

APHL Biomonitoring Module
vimeo.com/showcase/4767908?video=258108654

National Biomonitoring Program (CDC)
www.cdc.gov/biomonitoring/index.html

***National Report on Human Exposure to Environmental Chemicals* (CDC)**
www.cdc.gov/exposurereport/

National Health and Nutrition Examination Survey (NHANES, CDC)
www.cdc.gov/nchs/nhanes/

***Improving the Collection and Management of Human Samples Used for Measuring Environmental Chemicals and Nutrition Indicators* (CDC)**
stacks.cdc.gov/view/cdc/53206/cdc_53206_DS1.pdf

***National Biomonitoring Plan* (2015)**
aphl.org/docs/default-source/technical/eh_national_biomonitoring_plan.pdf

***Biomonitoring in Public Health* (CSTE)**
www.cste2.org/webpdfs/BioMonISFINAL.pdf

Agency for Toxic Substances and Disease Registry (ATSDR, CDC)
www.atsdr.cdc.gov/

US Environmental Protection Agency
www.epa.gov/

Interstate Technology Regulatory Council
www.itrcweb.org/

3. STUDY TEAM & ADVISORY PANELS

IN THIS SECTION

- **Core Study Team Members**
- **Additional Expertise**
- **Advisory Panels**

The most successful biomonitoring activities are those that involve collaboration among public health and other partners working to answer a defined environmental health question. This is true whether it is a study team (those responsible for conducting a hands-on study), an advisory panel formed in the state to provide an additional level of input and oversight or an advisory panel that provides input into the design and implementation of a biomonitoring study.

This section contains a description of the study team, followed by information on forming and maintaining an advisory panel for biomonitoring programs and studies.

CORE STUDY TEAM MEMBERS

The need for a multi-disciplinary approach is essential regardless of the intended purpose of the biomonitoring activity. This effort can be population-based surveillance, targeted exposure assessment, disease investigation or emergency response. For smaller targeted studies, one person can potentially play multiple roles in the project if they have the necessary expertise and experience.

Expertise necessary to develop and implement a well-designed biomonitoring study includes epidemiology, exposure science, analytical chemistry, statistics and toxicology. Additional skills are needed to communicate and interpret biomonitoring information to individual participants as well as to the larger community. Ideally, study design and execution are jointly conducted by the core team.

Below is a summary of each area of expertise to include in a core study team.

Epidemiologists

Epidemiologists design biomonitoring studies with input from team members in other public health disciplines. As the leader in design efforts, the epidemiologist develops study hypotheses and specific aims and determines the appropriate study type (e.g., longitudinal, cross-sectional, cohort, case-control). Epidemiologists oversee study design and collaborate with exposure scientists, statisticians, analytical chemists and toxicologists during the study design phase to develop a scientifically sound plan for the biomonitoring activity.

Epidemiologists and exposure scientists work jointly to:

- Identify study populations
- Develop questionnaires
- Write protocols for recruitment of participants
- Analyze data
- Report results

The epidemiologist monitors the overall execution of the study protocol throughout the duration of the study, often as the principal investigator or as co-investigator. Overseeing daily adherence to protocols is a critical function of the epidemiologist for ensuring the validity of inferences drawn from the resulting data. Reporting of the results is also typically the responsibility of epidemiologists.

Analytical Chemists

Analytical chemists are on the core team as they are responsible for ensuring the quality of the analytical measurements used in biomonitoring activities. The chemist works with toxicologists to identify the appropriate biomarker(s), considering not only the pharmacokinetics of the analyte(s), but also the feasibility of measurement. The chemist determines and validates the appropriate analytical methodology for

CORE STUDY TEAM: KEY ROLES

Epidemiologist
Study design and hypothesis generation

Analytical Chemist
Chemical analysis plan and determination and biomarker selection

Toxicologist
Assess routes of exposure, toxicity and biomarker selection

Biostatistician
Sample size determination, data analysis plan and execution

Physician
Medical oversight or consultation to the study, order clinical tests, discuss individual results with participants

Field Sampling Staff
Subject recruitment, administer survey, obtain consent, collect and handle samples

Communication Specialist
Convey tailored information to the community, policy makers, stakeholders and subjects

measuring the target biomarker(s) and writes standard operating procedures (SOPs) for the study. The chemist works with the study design team to develop sample collection, processing and shipping protocols to ensure valid samples are obtained for the laboratory analysis. These processes are particularly important if the target biomarkers are ubiquitous environmental contaminants or environmental degradates (e.g., bisphenol A, triclosan, parabens). The chemist offers specific training to specimen collectors and in some instances may assist in the collection process.

During the analytical portion of the study, the chemist measures the concentration of environmental chemicals or their metabolites in clinical specimens and monitors multiple quality assurance indicators to verify the integrity of the data generated. The chemist may be responsible for reporting and interpreting findings along with appropriate reference ranges (if available) to environmental health professionals and/or clinicians. These data may be used in conjunction with survey information to provide answers to environmental health questions.

Toxicologists

Toxicologists determine the appropriate biomarkers for measurement after considering available environmental data and opportunities for exposure. Important factors that influence this determination include potential route(s) of exposure, duration of exposure (acute vs. chronic) and metabolism, compartmentalization, and elimination (i.e., half-life) of the analyte(s) within the body.

Biomarker selection is finalized after consultation with the epidemiologist and chemist to assure practicality of specimen collection as well as the analytical capability and capacity of the laboratory. The toxicologist is also responsible for the determination of critical values and action levels. The toxicologist plays an active role in the analysis and interpretation of all study data to ensure that statistical inferences and conclusions are biologically plausible.

Field Sampling Staff

Field sampling staff are responsible for subject recruitment. Depending on the number of subjects that must be recruited, this may be one person or a team. These individuals should have experience in community outreach. Field sampling staff are also responsible for administering the survey to participants, including obtaining consent. They also collect, process and ship/transport samples.

Biostatisticians

Biostatisticians provide input in both the study design and data analysis phases of a biomonitoring activity. During the design period, the statistician calculates the minimum sample (population) size needed to adequately address the environmental health questions. Following data collection, the statistician recommends appropriate statistical method(s) for data analysis and is responsible for data management and analysis. After data analysis, the biostatistician assists in results interpretation.

Physicians

Physicians provide medical oversight or consultation to a study, order clinical tests and, most importantly, are available to discuss individual results with participants. Physicians with a specialty in medical toxicology, occupational medicine or pediatrics, and those with training in epidemiology are especially helpful in interpreting medical risks and conveying this information to patients. Physician also provides critical diagnostic information and analysis in studies that include biomarkers of effect (i.e., a measurable change in an organism that can be associated with a resulting health outcome).

Communication Specialists

Communication specialists provide expertise and support in communicating with a broad range of audiences about all aspects of the study. They provide information on study goals, progress of the study and the results. They may also assist in the recruitment of subjects. This may take the form of disseminating information about the study through various methods, organizing community meetings, and contacting community leaders, policy makers, and other stakeholders to introduce them to the study. These professionals may come to the study from the health department or other local government agency, academia, or the private sector.

ADDITIONAL EXPERTISE

Depending on the biomonitoring activities, recruiting additional professionals to the team may be beneficial.

Occupational Health

Many exposures to toxic chemical substances occur in work settings. Specialists in occupational health and occupational medicine evaluate environmental exposure. If a study is focused on work place exposure, referral of participants to an occupational health expert may be necessary.

The Association of Occupational and Environmental Clinics (AOEC),[1] which is supported by CDC/ATSDR and the National Institute for Occupational Safety and Health, has developed educational and referral tools, including a directory of occupational and environmental clinics. AOEC's main goals are to assist in identifying, reporting and preventing occupational and environmental health hazards and their effects and to help locate high-quality clinical services for people with work- or environmental-related health problems. Additionally, CDC maintains a list of State Health Department Occupational Safety and Health Contacts.[2]

Pediatric Environmental Health

Specialized resources for children are available through Pediatric Environmental Health Specialty Units (PEHSU). The PEHSU Network[3] of regional centers offers expertise relevant to the assessment of environmental exposures in pediatric patients and a range of appropriate medical treatment services.

PEHSUs are academically based, typically at university medical centers. Because environmental factors have a variety of impacts on the health of children and reproductive age adults, the network has experts in pediatrics, allergy/immunology, neurodevelopment, toxicology, occupational and environmental medicine, nursing, reproductive health and other specialized areas. Network members provide advice on prevention, diagnosis, management and treatment of environmentally-related health effects in children.

1 The Association of Occupational and Environmental Clinics. aoec.org/

2 CDC. State Health Department Occupational Safety and Health Contacts. January 15, 2019. Accessed June 2019. www.cdc.gov/niosh/statosh.html

3 Pediatric Environmental Health Specialty Units Network. www.pehsu.net/

STATE ADVISORY PANEL: BIOMONITORING CALIFORNIA'S SCIENTIFIC GUIDANCE PANEL

The Scientific Guidance Panel (SGP) was established by legislation as part of the California Environmental Contaminant Biomonitoring Program (or Biomonitoring California). Panel members are appointed by the Governor or the California Legislature and have expertise in a wide range of disciplines, including epidemiology, exposure assessment, toxicology, bioethics, and maternal and child health. The SGP provides input on the design and implementation of all aspects of the program. One of the Panel's major responsibilities is to recommend chemicals that are priorities for biomonitoring in the state.

The Office of Environmental Health Hazard Assessment (OEHHA) is responsible for convening three SGP meetings per year and ensuring compliance with the Bagley-Keene Open Meetings Act. This includes posting an agenda in advance and offering the public ample opportunity to comment. The public is encouraged to join the meetings in person or online (the meetings are live streamed).

OEHHA works with the California Department of Public Health (CDPH) and the Department of Toxic Substances Control (DTSC), the other two departments involved in conducting this program, to develop appropriate SGP meeting topics. Some recent sessions include:

- Biomonitoring California's Environmental Justice Activities - Perspectives from Community Organizations
- Community Exposure to Air Pollutants - A Role for Biomonitoring
- Measuring Exposures to PFASs (perfluoroalkyl and polyfluoroalkyl substances) in California
- Community Exposures to Metals - Perspectives from County Health Departments

Each meeting also includes a program update by CDPH, the lead agency for Biomonitoring California, and an open public comment period, during which the audience can address any program topic.

Panel members volunteer their time and receive reimbursement only for travel-related expenses. Significant staff resources are required to manage all aspects of convening three meetings per year, including:

- Handling logistics (e.g., scheduling meeting dates, booking rooms, setting up a webinar, contracting with a transcriber, coordinating Panel member travel, managing email contact list, sending meeting announcements).
- Preparing scientific documents to support the Panel's deliberations.
- Developing staff presentations and working with guest speakers.
- Posting meeting materials online in compliance with state accessibility requirements.
- Coordinating with the SGP Chair to facilitate the meeting.
- Developing a summary of the Panel's input and recommendations.

RESOURCES

For examples of the make-up and activities of state biomonitoring advisory panels, visit the websites of:

California
biomonitoring.ca.gov/scientific-guidance-panel

Minnesota
www.health.state.mn.us/communities/environment/biomonitoring/advisorypanel/index.html

ADVISORY PANELS

Advisory Panel: Program Level

Convening an advisory panel is an effective way for biomonitoring programs to get regular, structured input from an informed group of stakeholders. In some states, advisory panels are a legislative requirement.

An advisory panel has various functions for a state biomonitoring program. Besides providing guidance on components of studies, such as selection of chemicals to analyze, communities to involve in studies and priorities for the program, the panel can also help with interpretation of results and identifying effective dissemination activities.

The mission and purpose of the advisory panel can vary. Roles include:

- Help guide important decisions during the planning and execution of a biomonitoring study
- Support scientific rigor
- Build support for a specific biomonitoring study
- Strengthen credibility of biomonitoring with the public and other key audiences

EXAMPLES OF ADVISORY PANEL MEMBERS

- Academic scientists
- Public health representatives
- Representatives from other health disciplines
- Environmental agencies
- Local industry groups
- Community groups
- Regulatory members
- Public representatives

Including public representatives on the panel can serve to increase the credibility and transparency during the design and planning phases of a study. These representatives can also provide insight into how to effectively disseminate results so that they will be understandable and meaningful to the public.

To ensure the effectiveness of an advisory panel, appropriate budgeting and staffing to support panel activities are necessary.

Advisory Panel: Study Level

Formal and informal processes for obtaining community input into the design and implementation of a study can be critical to its success. Such advisory groups provide a vehicle for enlisting community members as equal partners in the study design process and for offering input throughout the study. Key participants in such groups include local health departments, policymakers, community-based organizations and representatives of the target population.

Community representatives can provide important perspective on community concerns and values that can potentially impact the study. This local knowledge and participation aids in the design of the study to ensure it simultaneously meets the needs of the community and the investigator or agency. In addition, community members can be helpful in communicating the goals and limitations of the study to others in the community, encouraging participation and aiding in communication efforts throughout the study. More information on community engagement is provided in next section, Community Engagement and Communications.

4. COMMUNITY ENGAGEMENT & COMMUNICATIONS

IN THIS SECTION

- Roles of the Community
- Understanding Community Engagement
- Communicating with Policymakers about Biomonitoring

The "community" is a term that refers to members of the public and key constituencies. They have a role in biomonitoring studies as stakeholders who have specific insights, concerns and expertise to share. Their roles include providing input on priority issues and the design of the study. They can also be partners recruiting participants and in the delivery of study results to the broader community. Below are insights on the role of the community in biomonitoring studies.

Community includes individuals and groups who are most affected by exposures to chemicals (sometimes called stakeholders). Community also refers to various partners with an interest in biomonitoring activities at the state and local level.

- Stakeholders have a role in providing input and building community support for the study. They may not have a direct role in the study.
- Partners include academic institutions, state agencies other than the one conducting the program, local public health agencies, policymakers, non-governmental organizations (NGOs), community-based organizations, business organizations and the medical community. Partners may work directly with biomonitoring program staff on project planning, implementation and results communication. They may have a clear role, and often a funded relationship, in these activities.

ROLES OF THE COMMUNITY

Stakeholders and partner agencies can play varied roles in a biomonitoring study. Below are examples.

Build Support

The community, if adequately informed and involved, can build public awareness and understanding of the biomonitoring study and manage expectations of what study results can provide. This type of involvement can also help the study to achieve higher participation rates within the target population(s) to be studied.

Provide Input in the Study

The community can provide input on study design, outreach and recruitment, study implementation and guidance on interpreting results.

Communicate Results

The community, especially affected individuals, can help the study team in developing the most effective ways to communicate biomonitoring results so that they are understandable and accepted.

Specific Types of Involvement

Various partner organizations can contribute significantly to biomonitoring studies (see Roles of Select Partners). These partners can also provide resources not available to the public health laboratory, including access to data, target analyte information and patient samples. They can provide access to community groups that can provide support to the study. Laboratories should work with these organizations and share information about their planned projects. This can be accomplished, for example, by working with environmental health program directors and state epidemiologists to establish relationships with various partners.

ROLES OF SELECT PARTNERS

Local Public Health

Local health departments can identify local history and culture, help reach communities of interest, offer communications support and provide data.

Environmental Protection Agencies

The US Environmental Protection Agency (EPA), state and local environmental agencies can assist in gathering data on environmental exposures, permissible limits (if applicable) and regulations regarding some chemicals.

Poison Control Centers

These centers are a potential resource for biomonitoring studies, especially those related to emergency response. They often track trends in poisonings and have yearly surveillance data. The American Association of Poison Control Centers[1] produces an annual report with statistics and information on poisonings in that calendar year and has information on some common chemicals and guidelines for patient management. Additionally, certified poison control centers have medical toxicologists who may be helpful as collaborators during the design, planning and interpreting results.

Local Medical Providers

Local healthcare providers are important partners for patient management, specimen collection and identification of targeted study participants. Medical toxicologists in hospitals or private practices can assist in interpreting the biomonitoring data.

National Environmental Public Health Tracking Network (NEPHTN)[2]

NEPHTN is a system of integrated health, exposure, and hazard information and data from a variety of national, state, and city sources. Currently, 23 state and local health departments have received funding from CDC to participate in the network and are collecting data on hazards in the environment. These health departments are examining trends in the environment and health using surveillance techniques. States in the network can serve as resources for laboratories starting or expanding biomonitoring projects and programs. For those laboratories not located in a network state, they can reach out to neighboring network states, their local public health department or a local university.

1 American Association of Poison Control Centers. aapcc.org/

2 National Environmental Public Health Tracking Network ephtracking.cdc.gov/

UNDERSTANDING COMMUNITY ENGAGEMENT

Most biomonitoring studies in public health settings include community engagement and public participation to provide an effective mechanism for health departments and communities to exchange information, concerns and resources. The laboratory may or may not be directly engaged in community engagement.

Community engagement starts with effective communications. CDC/ASTDR's Principles of Community Engagement (Second Edition, 2011)[1] describes community engagement as:

> "The process of working collaboratively with and through groups of people affiliated by geographic proximity, special interest, or similar situations to address issues affecting the wellbeing of those people. It is a powerful vehicle for bringing about environmental and behavioral changes that will improve the health of the community and its members. It often involves partnerships and coalitions that help mobilize resources and influence systems, change relationships among partners, and serve as catalysts for changing policies, programs, and practices."

Effectively conveying information to the community serves to engage affected individuals, policymakers, other stakeholders and the general public. Their understanding and support can help ensure that a study is successfully executed and appropriate interventions are implemented. However, clear delivery of information is only part of the equation. Equally important is listening and meaningful involvement. This will help the community buy into and value proposed biomonitoring activities. In turn, the study team will be better positioned to understand and act upon the community's priorities, concerns and needs.

Community engagement must also recognize and respect the diversity of the community. Awareness of the cultural differences and subpopulations within a community is critical in planning, designing and implementing approaches to engaging a community.

COMMUNICATING WITH POLICYMAKERS ABOUT BIOMONITORING

Legislators and other policymakers are key audiences for information about biomonitoring studies—both before and after the investigation. They are part of the community, but they also represent the community.

Legislators should be informed about studies that involve their constituents. They will want to know if their constituents will be recruited since they may get questions from the community about the study. Legislators also may be able to help with outreach and recruitment of members of their community. They often have regular newsletters and can include information about the study or participate in video interviews

While reaching out to policymakers and legislators about a study may not be an explicit role for laboratories, they can integrate information about biomonitoring into their general efforts to educate policymakers. For examples, laboratory tours can include details about biomonitoring activities.

Working through the public health agency's legislative relations office is an effective way to reach policymakers. During the legislative session, it can be useful to have short program updates ready in the event interest or questions arise. Longer legislative reports can also be effective ways to convey information and may be required by state statute. For these types of written documents, communications best practices are important, including using plain language, keeping messages simple and focusing on the public health importance of findings. For example, the California Environmental Contaminant Biomonitoring Program[2] produces a legislative report, executive summary and one-page legislative highlight report. It may also be possible to be invited to testify before relevant committees (i.e. health, environment committee).

1 CDC. Principles of Community Engagement, Second Edition. 2011. Accessed June 2019. stacks.cdc.gov/view/cdc/11699

2 State of California. Biomonitoring California Reports. Accessed June 2019. biomonitoring.ca.gov/biomonitoring-california-reports

REACHING OUT TO THE COMMUNITY: NEW HAMPSHIRE'S TARGETED ARSENIC AND URANIUM PUBLIC HEALTH STUDY

Upon receiving a CDC grant to carry out the Targeted Arsenic and Uranium Public Health Study, the study team developed a study plan that included strategies for reaching out to communities to recruit participants. The team relied on "old school" methods as well as social media. Both methods had minimal costs other than staff time.

Members of the study team were responsible for promoting the study in communities and recruiting participants. None of them had extensive experience in communications. therefore, they relied upon the department's Public Information Office, which provided advice and support in disseminating messages.

Press releases played a key role in promoting the study. An initial press release announced the CDC grant and outlined the purposes of the study. The story was picked up by the AP wire service and many New Hampshire newspapers. Two additional press releases resulted in online articles and radio coverage, including New Hampshire public radio. The press releases also resulted in news about the study being posted on town websites and social media pages.

A next step by the study team was to send a letter to policymakers in towns to alert them to the study. They wanted to be proactive in informing policymakers about the study and the activities that might involve their constituents. The letter also requested help in recruiting participants and offered to provide a briefing for selectmen at town meetings. This helped get the word out in the community.

Social media played a major role in building awareness about the study. The team regularly made announcements through social media. When a state legislator retweeted, it greatly increased the reach of the program. The health department's YouTube channel was helpful for posting webinars highlighting the program. Town meetings were posted on YouTube and then linked to other social media activities. Early on in the process, the program started using #biomonitoringNH.

At the conclusion of the study, the team held three public meetings to share findings. These one-hour meetings included a 30-minute presentation, with attention to ensuring effective communication of technical information to lay people, and 30 minutes for questions from the audience. A follow up survey that was emailed to participants indicated that the information provided was useful to participants.

Team members emphasize the importance on learning how to effectively communicate with the community. This is especially important for scientists communicating with the general public. CDC Plain Language Guidelines are essential for distilling scientific information for the lay population. When developing materials, the team asked, "What would Nana understand?" Since focus groups were not in the budget, they tested materials on other staff and family members. The team sought to keep all their communications with the public at an 8th grade reading level.

- Recommendations for other programs in terms of communications with the community include:
- Work closely with the Public Information Office.
- Look for examples of effective communications and adopt these methods (e.g., graphics that simplify concepts).
- Follow what is trending on social media and look for promotion opportunities.
- Follow CDC on social media and learn from their promotion activities (i.e., apply them to your work).
- Take advantage of CDC online trainings on effective communications.

WAYS TO ENGAGE THE COMMUNITY

Provide for Early and Ongoing Involvement

Involve the community in early planning stages. Inclusion of community representatives on advisory panels is a common method for gaining citizen input, support and participation. They can also provide important perspectives on community concerns and values that will aid in the design of a study that meets the needs of the community as well as the investigator or agency.

Develop a Communications Plan to Specify Types of Involvement

A communications plan is part of the study design and should be based on the principles of risk communication and health communication. Stakeholders and partner agencies should be included in the development of the plan and resources should be allocated to communications activities. The plan should specify communication of study goals and objectives, intended audiences, communication methods and products to use, time lines and required resources. While the plan addresses communications with the broader community, it should also specify whether individual participants will receive their own results prior to releasing any aggregate data and outline that process.

Identify and Use Effective Messengers

Conveying information, especially when it is complicated or threatening, is often made easier by selecting the right messengers. The best messengers are those with a deep knowledge of the community who are trusted sources of information. Community health workers can be especially effective as they are trained and often come from the community they serve. Local public health agencies or other community organizations typically have on-the-ground community public health experience. They also have staff with expertise in clinical medicine and public health, connections to local communities and staff with language skills. The latter can be especially important for biomonitoring studies focusing on immigrant, refugee and/or minority communities. There may be mistrust of government agencies and partnering with community-based health organizations can facilitate access and break down barriers.

Involve Community Members in Study Activities

Community agencies and individuals can conduct outreach about a study, recruit participants and maybe even assist with sample collection. They can assist in educating participants about exposure to chemicals and appropriate responses and communicate study results to the broader community.

RESOURCES

Principles of Community Engagement **(CDC/ASTDR)**
stacks.cdc.gov/view/cdc/11699

Community Involvement Resources (CDC/ASTDR)
www.atsdr.cdc.gov/community-engagement-playbook/php/about/index.html

Human Biomonitoring of Environmental Chemicals, Communicating the Results, Interpretations, and Uses of Biomonitoring Data to Nonscientists **(National Academies Press)**
www.nap.edu/read/11700/chapter/8

5. LABORATORY INFRASTRUCTURE

IN THIS SECTION

- Facilities
- Equipment
- Information Technology
- Laboratory Personnel
- Quality Management System

Adequate and appropriate laboratory facilities, equipment, information technology (IT) infrastructure and personnel are necessary to support biomonitoring activities. Below is an overview of the infrastructure needs. For more detailed information, the Laboratory Response Network for Chemical Threats (LRN-C)[1] has developed a series of guidance documents related to emergency response activities that may be relevant to biomonitoring studies.

1 APHL. Laboratory Response Network for Chemical Threats. aphl.org/LRN-C

FACILITIES

FACILITIES ESSENTIALS

- Biosafety and Chemical Safety
- Clean Rooms
- Waste Disposal
- Backup Power
- Laboratory and Data Security

Biosafety and Chemical Safety Considerations

Engineering controls are design principles and the use of devices that protect workers from unnecessary exposure to pathogens, chemicals and radiological hazards. Engineering controls are part of an overall Exposure Control Plan that describes the way risk is managed to minimize exposure to blood borne pathogens and other organisms that might be present in biological specimens. Examples of biosafety controls include controlled air flow (negative air pressure) and use of biosafety cabinets and splash shields. Depending on the desired level of protection and the potential risk, various levels of biosafety may be needed, from biosafety level 1 (BSL-1) to BSL-4 (reserved for work with the most dangerous pathogens). Most of the biomonitoring work will be conducted in BSL-2 laboratory space.

Equally important is minimizing workers' exposure to chemical substances and solvents. The use of chemical hoods, proper chemical storage and signage are only some of the elements of an effective chemical hygiene plan. All personnel working on biomonitoring studies should be familiar with their laboratory's chemical hygiene plan, follow universal precautions, and use appropriate personal protective equipment (PPE) when working with biospecimens. Additional information can be found in the Occupational Safety and Health Administration (OSHA)'s standards related to laboratories[1] and CDC's *Biosafety in Microbiological and Biomedical Laboratories (*5th Edition).[2]

Clean Rooms

Clean rooms may be necessary to minimize contamination background in blanks, standards, quality control materials and study specimens. This is especially important when measuring elements and chemical compounds of interest at very low concentrations in human tissues. For example, Class 100 to 10,000/1,000 clean rooms have been used effectively for controlling contamination for analysis of trace elements by Inductively-Coupled Plasma Mass Spectrometry (ICP-MS). Whether a Class 100 or 1,000 or 10,000 clean room is necessary depends on what level of background contamination can be tolerated. For example, some laboratories have a Class 100 room for preparation of specimens, standards, and blanks, then transport prepared specimens to an instrument for analysis residing in a Class 10,000 room or uncontrolled laboratory setting.

Waste Disposal

Special considerations are necessary for the handling of mixed waste and radioactive materials. Suitable containers should be made available along with training on how to properly dispose of waste and to manifest the waste for proper disposal in accordance with state and federal laws.

Backup Power

An emergency generator bridged with an uninterrupted power supply (UPS) system, is ideal to assure continued instrument operation. If no emergency power is available, a UPS system to allow a suitable time for the instrument to be powered down without being subject to potentially damaging power surges and other severe problems that might occur from a power failure should be considered.

1 OSHA. Laboratory Safety Standards. www.osha.gov/SLTC/laboratories/index.html

2 CDC. Biosafety in Microbiological and Biomedical Laboratories, 5th Edition. 2018. Accessed June 2019. www.cdc.gov/labs/bmbl/

Laboratory and Data Security

Given the nature of the specimens being handled and the implications of the investigations, laboratory and data security must be addressed. Individual laboratories will need to determine the appropriate level of security for their application. At a minimum, security should include restricted access to all laboratory and survey data, specimens and laboratory facilities. These restrictions may be accomplished in a combination of ways including:

- Technology-based methods: proximity card access, biometric fingerprint or retinal readers, electronic surveillance and alarms
- Policies and procedures: sample tracking, chain of custody, inventory control, data privacy
- Data privacy issues should be part of the initial project planning and are discussed in more detail in Biomonitoring Study Design

EQUIPMENT

Analytical Instrumentation

Analytical instrumentation used in biomonitoring must be sufficiently sensitive and specific to detect the analyte of interest in human tissues such as blood and urine. The instruments chosen should provide the best sensitivity possible within reasonable cost to assure the detection limits adequate for the intended purpose(s) of the study can be attained. Instruments used for biomonitoring measurements should not be used for extremely dirty or contaminated samples. The following guidelines may be used as a starting point for selecting the appropriate instrumentation/technology for a given analyte or analyte class.

> **Note:** The platforms discussed below are recommendations, and this is not an all-inclusive list. Alternative instrumentation that meets a given laboratory's performance standards should be used, as appropriate, for the intended purpose(s) of the study. CDC's National Center for Environmental Health (NCEH) Division of Laboratory Sciences (DLS)[1] has developed some methods, outlined in the testing portion of this guidance document, for these classes of compounds.

When new instrumentation is purchased, consideration should be given to the instrumentation (vendor, model type) used by existing biomonitoring laboratories to facilitate bringing methods up and validating them in a reasonable amount of time. As with any instrumentation, service contracts past the duration of a standard one-year manufacturer warranty are recommended. This helps to ensure the instrument is well maintained and is brought online quickly if a problem occurs.

Clinical Chemistry Equipment

Clinical chemistry equipment is also needed, such as centrifuges, shakers, vortex equipment, autodilutors and other similar equipment. Refrigerator and freezer capacity is required for the storage of standards, isotopes and specimens.

Refractometer

Biomonitoring measurements in urine are commonly corrected for urine dilution by specific gravity or creatinine correction. Specific gravity is determined using a relatively inexpensive refractometer. NHANES reports both volume-based and creatinine corrected urinary concentrations. An in-house or vendor capability for urine creatinine analysis is

1 CDC, Division of Laboratory Sciences. www.cdc.gov/nceh/divisions-offices/about-division-laboratory-sciences.html

necessary to match the published CDC data. Measurements in blood/serum may be normalized for lipid content.

Table 1. Analytical platforms for biomonitoring analytes

ANALYTE	INSTRUMENTATION
Trace elements (including some radionuclides)	ICP-MS (Laboratories who are LRN-C Level 1 or 2 already have an ICP-MS instrument that can be used for biomonitoring. ICP-MS instruments require argon as the plasma gas and other gases such as hydrogen, helium or ammonia, as needed, for collision cell applications. Speciation for elements such as arsenic may also be desirable. Speciation will require a high-performance liquid chromatography (HPLC) system and associated software)
Volatile organic compounds and metabolites	• Gas chromatography – mass spectrometry (GC/MS) or gas chromatography-tandem mass spectrometry (GC-MS/MS) • LC/MS/MS for metabolite
Semi-volatile and non-volatile compounds and metabolites (soluble in relatively polar solvent mobile phases)	Liquid chromatography-tandem mass spectrometry (LC- MS/MS)

Sample Preparation Equipment

Sample preparation equipment such as microwave digestion and hot blocks may be necessary for elemental determinations. Solid phase extraction and other extraction techniques (e.g., liquid-liquid extraction) should be available for organic analyses.

INFORMATION TECHNOLOGY

Information technology (IT), both hardware and software, is an integral part of instrumentation and data processing required for the analyses of biomonitoring specimens. Modern analytical instruments include computer systems to collect and evaluate data. Interfaces are needed to transmit these data to a laboratory information management system (LIMS) for a centralized and secure repository of specimen data and associated management, tracking, analysis and reporting functions. See the appendices for more general information on LIMS.

LABORATORY PERSONNEL

Biomonitoring testing activities require specific skills and capabilities. The technology and instrumentation are similar to those used in environmental testing/laboratories so training in environmental health is recommended. Other essential skills include training in the safe handling potentially infectious clinical specimens and working with challenging biological matrices. Additionally, as test results may be used for diagnostic purposes (as opposed to research only), the laboratory and laboratory personnel must meet federal requirements for clinical laboratories, commonly known as Clinical Laboratory Improvement Amendments (CLIA).[1] CLIA requirements differ based on the type of testing provided. Virtually all biomonitoring labs would fall under the "high complexity" category and "toxicology" subcategory. Alternate accreditation through the College of American Pathologists (CAP) or the International Organization for Standardization (ISO) may meet the CLIA requirements through reciprocity agreements.

1 Clinical Laboratory Improvement Amendments. www.cdc.gov/clia/

Table 2. Personnel-related experience, skills and professional development or training required to participate in biomonitoring studies (high complexity testing)

EXPERIENCE/SKILLS	REQUIREMENT
Education	• Laboratory personnel must be appropriately qualified to perform high complexity testing under CLIA '88 regulations • Analysts should have a BS or BA in chemistry, biology or related scientific field or appropriate amount of course-work required for high complexity testing required by CLIA '88
Computer Proficiency	• Laboratory Information Systems (LIMS) • Statistics calculations and spreadsheet software such as Microsoft Excel
Instrumentation Training	• Necessary for GC-MS, LC-MS, LC-MS/MS, ICP-MS, HPLC-ICP-MS, ICP-MS/MS and other related platforms necessary to test human tissues for analytes of concern • Formal training may be provided by the instrument vendor or by an analyst proficient in the use of the instrumentation • CDC offers analyte-specific training, which includes some instrumental component in various formats (e.g., in person or online) • Training on site-specific methods and procedures should be provided internally by each laboratory
Analytical Training Regularly updated	• Basic understanding and knowledge of analytical chemistry principles and capability to verify and validate test methods. Analytical accuracy and precision, selectivity and specificity are examples of necessary parameters that must be properly set for any analytical method used for biomonitoring purposes • Continuing education related to analytical chemistry, toxicology and epidemiology (e.g., conferences, vendor presentations, webinars)
Human Subject Protection & Data Confidentiality Training	• Laboratories must fulfill requirements for data privacy training and adhere to policies and practices for approval of studies involving human subjects (Institutional Review Board and/or Human Subjects Review) • Completion of the certification course offered by the National Institutes of Health (NIH) Office of Extramural Research for Protecting Human Research Participants is recommended for all investigators responsible for biomonitoring study design and execution and is required by law for any study conducted with or supported by federal funds
Safety Training	• Training in chemical and biological safety is required based on individual laboratory requirements and federal regulations • At a minimum, blood-borne pathogens training, hazardous waste disposal and chemical safety training are required • Familiarity with OSHA regulations and good laboratory practices are necessary • Radiation safety training is required, if applicable
Interdisciplinary Training Highly recommended to enhance study team participation	• Epidemiology • Statistics • Toxicology • Risk communications (especially if staff is engaging with community members or the media)

Worker Safety Program

An ongoing worker safety program is essential given the interaction with human biological samples. Appropriate immunizations should be offered to staff (e.g., hepatitis B for work with blood) based on each laboratory's policy and exposure control plans. Required personal protective equipment (PPE), such as gloves, safety glasses, and lab coats, should be provided, such as gloves and face shields. Exposure control measures (e.g., biosafety cabinets, splash shields) should be utilized. More information on biosafety can be found in CDC's *Biosafety in Microbiological and Biomedical Laboratories* (5th Edition).[1]

Additionally, laboratory staff working with chemical hazards should be aware of ongoing safety issues and attend regular worker safety trainings as required by their state. Laboratory staff should always use fume hoods and standard PPE when working with chemicals.

QUALITY MANAGEMENT SYSTEM

A quality management system (QMS) describes how laboratories perform internal audits to ensure acceptable performance. It assures the integrity and traceability of laboratory results. The internal audits may focus on a specific area of the quality system and may be conducted by laboratory quality assurance (QA) officers, senior management or others from within the laboratory. The QMS guides a laboratory in implementing an overall quality policy that encompasses quality assurance (QA, plans that guide laboratory activities) and quality control (QC, measures to ensure compliance); both are required elements of the overarching QMS.

A description of a QMS, and how those elements are implemented to assure quality testing results, should be included in the laboratory's quality management plan (QMP). The US Centers for Medicare and Medicaid Services (CMS) has developed an instructive quality management plan template.[2]

QMS DEFINITIONS

Quality Assurance (QA)

QA incorporates those planned and systematic laboratory activities that guarantee the accuracy and defensibility of testing results. The quality manual, SOPs and documentation are essential components of a QA program. The quality manual refers to the master document of the laboratory quality policy and serves as the primary resource for laboratory information. Laboratory staff are responsible for ensuring adherence to the laboratory quality manual, QA plan and SOPs. Other supplementary records (e.g., instrument logbooks, reporting forms) are also critical components in a QA program.

Quality Control (QC)

QC refers to a measuring process used to check a result and provide assurance that all activities are performing within predetermined limits. QC procedures that ensure that the laboratory results are of required quality include instrument calibration, use of reference materials, repeated analyses, and sample and reagent blank analyses.

1 CDC. Biosafety in Microbiological and Biomedical Laboratories, 5th Edition. 2018. Accessed June 2019. www.cdc.gov/labs/bmbl/

2 CMS. XLC Artifacts and Templates. 2019. Accessed June 2019. www.cms.gov/research-statistics-data-and-systems/cms-information-technology/xlc/artifacts.html

Elements of the QMS

In summary, some of the essential elements of a QMS include:

Document Control System

A document control system assures the traceability of all records from sample collection, sample receipt, preparation and analysis of the sample, reporting of results and disposal of the sample. Controlled documents are tracked to ensure analysts are in possession of the current version of the document and following up-to-date procedures. SOPs are an example of a controlled document.

Staff Training

The QMS describes how staff are trained and qualified to perform testing and how they maintain competency and proficiency through demonstrations of capability and performance testing.

Conformance and Corrective Actions

The QMS also describes and documents how the laboratory handles non-conformances such as quality control failures and subsequent corrective actions that resolve the issue.

Equipment

Additionally, the QMS includes management of equipment, supplies and inventories, finances and budgeting, and providing training and continuing support of staff.

Essential Elements in a QA Program

There are three major issues that should be addressed in QA programs: traceability, uncertainty and proficiency testing. As summarized in *What Defines a Laboratory Quality System?*,[1] they are described as follows:

Traceability ensures that the measurement results can be related to a reference through a documented and unbroken chain of comparisons. This can be done by testing a certified reference material and comparing the results with the certified value. The reference material's certified value is usually reported with **uncertainty** given the comparison is of statistical significance.

Proficiency testing is an assessment of a laboratory's ability to identify and accurately measure the analyte(s) of interest, in the selected clinical matrix. Regular, successful participation in an externally managed proficiency testing program is preferred. If external programs are not available, alternate methods of demonstrating profiency include inter-laboratory comparison exercises or round-robins and/or analysis of blinded samples.

Accreditation

Accreditation is an audit of the laboratory conduct by an accreditation body or an external organization. It is not an assessment of the overall quality of the laboratory's activities but does certify that the laboratory has the capability to produce quality data.

The process documents the technical competence of a laboratory against a set of accepted standards. In the United States there are multiple accreditation organizations. For clinical testing these include but are not limited to: CAP, CLIA, and ISO Accreditation, The process can take anywhere from several months to multiple years depending on the laboratory's experience, activities and quality practices.

1 Dai, SY. What defines a laboratory quality system? Food Safety Magazine. October/November 2013. Accessed June 2019. www.foodsafetymagazine.com/magazine-archive1/octobernovember-2013/what-defines-a-laboratory-quality-system/

GENERAL REQUIREMENTS FOR THE COMPETENCE OF TESTING AND CALIBRATION LABORATORIES: ISO/IEC 17025:2005

The International Organization for Standardization (IOS)'s ISO/IEC 17025:2005 specifies the general requirements for the competence to carry out test and/or calibrations, including sampling. It covers testing and calibration performed using standard, non-standard and laboratory methods.

Find the full document on IOS's website: www.iso.org/standard/39883.html

6. BIOMONITORING STUDY DESIGN

IN THIS SECTION

- Study Design Steps
- Developing Goals and Objectives
- Protection of Human Subjects & Other Ethical Considerations
- Population Selection and Study Sample

There are many components, or steps, in designing a biomonitoring study, some of which will happen concurrently. Even with extensive up-front planning, it is often necessary to make modifications during the course of the study. During this initial planning phase, the laboratory should identify sufficient resources (time and staffing) to ensure the study design is achievable within the designated time line. As noted in this document, partner and community participation in the study design process is strongly encouraged and may require additional time and resources to coordinate.

STUDY DESIGN STEPS

Key study components, in which the laboratory must be involved in the design, include the following items. They are covered in more detail in the sections that follow:

- **Section 6:** Study goals and objectives; protection of human subjects; other ethical consideration; population selection and study sample
- **Section 7:** Biomarker selection
- **Section 8:** Study protocols and plans
- **Section 9:** Analytical protocol and methodology
- **Section 10:** Preparing and communicating results

There are other important study components where the laboratory is not deeply involved. However, it can be helpful to involve laboratory staff in the planning and/or review of the components. These include:

- Enrollment and consent methods
- Survey development
- Communications plan

DEVELOPING STUDY GOALS AND OBJECTIVES

The study goals address the overall purpose of the study. They must be carefully crafted to ensure that they clearly identify the intent of the study and what it hopes to achieve. The specificity of the goals is dependent on the type of study conducted.

Surveillance studies may have broad goals in terms of identifying exposure in the general population. Targeted investigations sample a specific population, such as a community's exposure to environmental contamination. Studies determine if biological exposures are elevated above a reference level and if public health interventions are necessary. Emergency response investigations are conducted in response to an exposure event to evaluate clinical measures in exposed individuals and support diagnosis of poisonings. These investigations also determine the need for medical treatment.

Goals should be established with a sound understanding of the impacted community. In particular, engaging the targeted community and gaining their buy in for the goals of the study is critical to study success.

For some studies, goals and objectives are determined by the sponsoring agency or funder. These agencies may also have significant input into design of the study and may impose restrictions in terms of the activities that can be carried out.

Objectives are more specific than goals and may address process (specific actions to be taken) or expected outcomes. They serve as a guide to implementation of the various study components and are a measure that the study is accomplishing what the researchers set out to do.

PLANNING A BIOMONITORING STUDY: NEW JERSEY'S ASSESSMENT OF ENVIRONMENTAL EXPOSURE OF PREGNANT WOMEN TO TOXIC METALS

In 2017, the New Jersey Department of Health/Environmental Chemical Laboratory Services received a grant from CDC to assess lead and mercury exposure in pregnant women in New Jersey. The study design was a very methodical process given the complexities of working with a population with many risk factors (e.g., expectant mothers, fetuses, low income, minority, immigrant). The laboratory had all the expertise, staff, resources and equipment in place to test the samples. The challenging part was engaging stakeholders and partners, ensuring compliance with human subject requirements and addressing ethical considerations.

As the study team worked to finalize the study design, it became apparent that what happened after the testing took place would require significant attention and partner engagement. These tasks included ensuring that they women were connected to healthcare, identifying the source of contamination and conducting remediation. Over the course of more than two years, the study team worked with community partners to ensure that protocols were in place to address exposure and follow up with participants in terms of treatment and remediation. Key to this follow up was the work of local health departments and poison control centers in providing education, home inspections and case management. The study team reached out to these key players to ensure their collaboration. In particular, the local health department had funding to cover the costs of abatements and temporary lead-safe housing that study participants would be able to access.

After reaching out to various prenatal clinics and OBGYN practices, the study team connected with University Hospital in Newark. The hospital serves a robust population of pregnant women and agreed to collect the samples during the first prenatal visit and provide medical care to address exposure as needed. The study team worked with hospital staff to resolve the issue of obtaining consent from patients. Given the proposed number of women to be tested (over 2,000), obtaining consent in compliance with requirements would take significant staff resources that were not available. To address this, the head of the OBGYN department designated the testing as a standard of care given the serious health impact of exposure to lead and mercury to both mother and fetus. The testing became a regular part of the care offered to all patients receiving prenatal care. Study staff provided training to hospital staff about the study, the health implication of exposure to lead and mercury and how to collect the samples. In addition, the team connected with the department of pediatrics at the hospital since it would play a role in the treatment of exposed infants.

The study team also had to address how to handle results. HIPAA requirements prohibit laboratory staff from directly contacting participants to provide results. Instead, the hospital provided results to the local health department, which followed up with patients.

Key Lessons

- Establish partnerships as soon as possible as these will impact the design of the study. Maintain regular communication with these partners concerning their potential roles. This will help to finalize protocols early in the process, which results in more efficient implementation.
- Conduct meetings in person. This facilitates communications that may be helpful in identifying other partners necessary to the study.
- Given that biomonitoring involves human subjects, be mindful of ethical considerations and HIPAA requirements. Do not make assumptions.
- Consult with the CLIA project officer early in the process to ensure that study protocols are in compliance.

PROTECTION OF HUMAN SUBJECTS: KEY CONSIDERATIONS

Essential to the design of a biomonitoring study is ensuring the protection of the study's participants. This is basic ethical concern. Many biomonitoring investigations are considered public health surveillance, not research studies, so do not usually require full IRB review. However, compliance with human subjects review is an essential aspect of biomonitoring investigations. There are federal regulations[1] related to the protection of human subject in research studies; consult your institution's policies or procedures for guidance. As part of any study, investigators are required to develop a Protection of Human Research Participants Plan.

Consent Procedures

There are different circumstances under which consent from participants must be obtained. If the biomonitoring study requires personal information from the prospective participants, Informed consent must be obtained. Consent must be conducted prior to enrolling the participants into the study. Usually the field team schedules a face-to-face meeting with a prospective participant and explains the study procedures. The individual is required to sign the consent form if they agree to participate. In some cases, consent by phone or mail is also acceptable. A sample consent form is included in the appendices.

If secondary use of specimens or follow-up with participants is anticipated, consent documents must secure permission for future contact and continued storage and use of specimens beyond the study period. If original consent does not include the information about secondary use, consent must first be obtained prior to the use of the samples for analysis.

Consent is not required for blind samples that are provided to the laboratory for analysis (i.e., personal identifications have been removed prior the use by the laboratory testing).

Risks and Benefits

Risks and benefits of biomonitoring for participants should be clearly identified and explained so participants can make an informed choice.

- Risks generally refer to individual health risks such as the potential for injury or infection or pain from an invasive procedure. Other risks are often included, such as the potential for heightened anxiety from a procedure, discomfort, inconvenience and costs.
- Benefits should clearly state how the participant benefits, such as medical treatment, counseling or follow-up to identify and remove sources of exposure. If they are provided, incentives (monetary or gifts) should be described in the protocol but generally are not considered benefits of participation.

Confidentiality Procedures

Protection of data privacy is paramount. With few exceptions, biomonitoring necessarily requires the collection of individually-identifiable health information that will be classified as private or confidential. All staff that require access to private data must be trained on the laws governing the protection of data privacy and data practices that are applicable in their jurisdiction. The Collaborative Institutional Training Initiative (CITI) program focuses on ensuring the public's trust in research activities through the provision of high-quality, peer-reviewed, online educational activities for researchers and study staff. Training information is available from the IRB office overseeing each study. The certificate of training from CITI must be submitted to the IRB.

1 Evergreen State College, Who Must Apply for Human Subjects Review? Accessed September 2019.

Standard protocols should include password-protected systems on all computers and locked cabinets for maintaining files. State laws generally include severe penalties for release of private data on individuals. Participants should receive absolute assurance of the protection of their individual health information and that no identifying information will be released.

De-identification of specimens in the laboratory is often recommended to protect privacy. With de-identification, personal identifiers are maintained by investigators in a database and linked by an individual study identification code to the laboratory results.

A different type of privacy protection is anonymization of specimens: identifiers are permanently severed from all information about the source of the specimen and results cannot be traced back to the individual. Anonymization is not appropriate for biomonitoring in a public health context as it limits the use of the data for understanding health effects, prevents informing individuals of their results and prevents delivery of an intervention that could potentially protect individuals at risk.

If a sample is determined to require sample tracking, that is, ensuring that the specimen can be traced to the original donor, the field sampling staff must initiate the process. If appropriate, the laboratory should implement a chain of custody protocol. More information about such procedures as well as a sample chain of custody form are in the appendices.

Other Ethical Considerations

Given the involvement of human subjects, researchers must take steps to minimize risk, either physical or psychological, to participants. There are also community-level considerations since contamination may result in stigmatization or have and economic impact on the community and its residents. Strict protocols related to obtaining informed consent and careful attention to protecting privacy and confidentiality is imperative in biomonitoring studies

Biomonitoring studies assess exposure levels of chemicals that could be potentially harmful. Given this, individual results obtained during a study should be communicated to participants in a manner that is easy to understand and describes the extent of the risk. This is even more imperative when concentrations exceed established reference or population-wide levels. Some IRBs or jurisdictional rules require that results be made available to all study participants. Protocols should be in place to help participants access treatment if exposure is detected.

Biomonitoring of community exposures has led to discussions of the rights of communities as research subjects.[1] In study planning with the community, researchers will need to incorporate community values and consider how the project may potentially harm or benefit the community as a whole. The potential for unintended economic, social and political consequences to the community should be addressed.

POPULATION SELECTION AND STUDY SAMPLE

Considerations in the identification and selection of a study population include the purpose of the study, type of chemical exposure of interest (exposure scenario) and whether biomonitoring will address past or only current exposures. In turn, sampling criteria should include a description of the following items:

Target Population

The sample should provide a frame of reference for the population of concern. Ideally, the study population should be representative of the target population by age, sex, race/ethnicity or any other characteristics considered to be important.

1 Blumenthal DS. A community coalition board creates a set of values for community-based research. Prev Chronic Dis. V.3(1). www.ncbi.nlm.nih.gov/pubmed/16356369

Selection Methodology

Selection of the study population will determine whether findings can be generalized to the general population. If the study population is self-selected, then findings probably cannot be generalized. Additionally, significant non-participation will hinder the ability to generalize to the general population. This information will feed into the data analysis protocol.

Random sampling within the defined target population is the preferred method for selecting participants in order to minimize selection bias. Clear and unbiased criteria for recruiting and selecting participants will aid the random selection process. Convenience sampling can result in selection bias and data may not be generalizable to a larger population. If convenience sampling is used, the characterization of the sample should be clearly described to avoid misinterpretation.

Matching can improve internal validity of study results. This involves selecting one or two non-exposed or non-diseased (i.e., control population) individuals for every exposed or diseased one. Matching typically involves selecting individuals who are similar in all relevant characteristics (such as age, sex, and race/ethnicity), differing only by whether they are exposed or diseased.

Sample Size

The sample size identifies the number of study participants necessary to be able to achieve adequate statistical power to allow for detection of meaningful differences in outcomes. Generally, the smaller the group, the larger the variation due to inter-individual difference, resulting in more uncertain results.

RESOURCES

Federal Policy for the Protection of Human Subjects ('Common Rule') (HHS)
www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Human Subjects Research (NIH)
grants.nih.gov/policy/humansubjects.htm

Human Subject Training and Resources (NIH)
grants.nih.gov/policy/humansubjects/training-and-resources.htm

The Belmont Report: Ethical Guidelines for the Protection of Human Subjects (HHS, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research)
www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Preserving Public Trust: Accreditation and Human Research Participant Protection Programs (Institute of Medicine)
www.nap.edu/catalog/10085/preserving-public-trust-accreditation-and-human-research-participant-protection-programs

Ethical and Policy Issues in Research Involving Human Participants (National Bioethics Advisory Commission)
bioethicsarchive.georgetown.edu/nbac/human/overvol2.pdf

WORKING WITH PARTNERS TO ACCESS TARGET POPULATION: VIRGINIA'S BIOMONITORING STUDIES

External partners play an essential part in participant recruitment for Virginia's biomonitoring program. Currently conducting two CDC-funded studies, the program has depended heavily on partners to reach potential participants. Working to establish these types of partnerships was time consuming but ultimately resulted in access to the necessary study population.

Virginia is a large and diverse state with rural/agricultural areas, mountains, coastal areas and large cities. For a study assessing exposure to toxic metals and perchlorate in the general population, the state faced the daunting task of developing a cost- and (staffing) time-effective strategy for recruiting participants from across the state. The study needed to identify sites with large numbers of potential participants who would be willing to participate and provide urine samples. Community colleges were identified as an ideal venue. In Virginia, community colleges are independent, so each of the 23 potential partners had to be approached separately. Each community college had different rules in terms of, for example, engaging with students on campus and completing IRB reviews. After the study team engaged in negotiations, 18 community colleges partnered in the study. This provided coverage for most of the state.

A study focusing on exposure of firefighters to toxic combustion products sought to assess exposure to cyanide and polycyclic aromatic hydrocarbon (PAH) metabolites. Given that this study has clear benefits for the population studied, the team did not anticipate any challenges in recruiting. This was not the case. It took four years to identify a fire department that would participate in the study.

While the study team often found fire departments and unions receptive to the study, things stalled at the municipal level, where questions of liability were a major consideration. One of the first municipalities to participate agreed only if a waiver was signed by participants.

As often happens, a chance encounter—networking during an APHL meeting—had a significant impact on recruitment activities. An APHL colleague from another state mentioned a professor in Community and Environmental Health at a local university who had worked with fire departments. The study team reached out to the professor, and he was able to connect them with additional municipalities, which resulted in additional participants. This is an example of how identifying a trusted partner can assist in the advancement of a project.

With this study, there seemed to be a reluctance among municipalities to be the first to sign up. Once one participant agreed, more were receptive. In addition, these new partners served as effective recruiters in terms of reaching out to their peers (other jurisdictions) and encouraging their participation.

Key Lessons

- For population studies, look for an entity that has wide coverage. While each community college had to be approached separately, there were enough similarities in their requirements that allowed for a common protocol.
- Know that there are multiple levels of approval and the information and messages provided at each level differ. The approach and messages for a fire chief are very different from the approach to a city attorney.
- Leverage relationships with those that sign on for a study. They are effective advocates with their peers.
- Network with colleagues outside of the jurisdiction. They may know of contacts that can facilitate necessary connections.

7. BIOMARKER SELECTION

IN THIS SECTION

- **Types of Biomarkers**
- **Selection of Biomarkers**
- **Feasibility Considerations**

Biomarkers are measures of environmental exposures or their effects intrinsic to the receptor. This is in contrast to environmental measurements, which measure environmental media as a mean of estimating internal exposure to a receptor.

TYPES OF BIOMARKERS

There are three types of biomarkers:

- Biomarkers of exposure
- Biomarkers of effects
- Biomarkers of susceptibility (e.g., genotypes and phenotypes)

A biomarker of exposure measures a contaminant or its metabolites in human biological tissues. Biomarkers of effect measure the biological outcome associated with a specific environmental exposure.

Biomarkers of susceptibility are indicators of the natural characteristics of an organism that make it more susceptible to the effects of an exposure to a chemical. (**Note:** Discussion of these biomarkers is beyond the scope of this document.)

SELECTION OF BIOMARKERS

The decision regarding which substance and biomarker that will be investigated must be made early in the study design as it greatly influences the selection of the specimen type to be collected. Laboratory scientists and chemists should work closely with epidemiologists, exposure scientists and toxicologists to determine the study biomarker(s) as their scientific understanding and input is essential at this phase. Specifically, several variables need to be thoughtfully considered prior to reaching a decision including:

- Properties of the chemical of interest
- Biomarker specificity
- Available analytic methods
- Feasibility

Appropriate biomarkers are selected based on the concern of environmental exposure and the purpose of the study. For example, some studies intend to determine biological level of a single pollutant for a subpopulation who are potentially exposed to a known source of contaminant. Other studies aim to gather surveillance information of multiple pollutants for the general population. For these types of biomonitoring studies, biomarkers of exposure should be selected. If the purpose of biomarker collection is to link internal body burden to an adverse health effect, there are multiple considerations. Biomarkers of effect are specific to the health outcome of interest. A biomarker of exposure could be used to establish the association between exposure and health effects.

Matrix

Biomarkers in different clinic matrices can be selected for a study. The most common clinical matrices are urine, blood, serum and saliva. Other matrices are also used such as hair, nails, breast milk and adipose tissue, but these clinical matrices present additional challenges related to specimen collection and interpretation of the analytical results. There may be special analysis techniques or specimen handling for the less common biospecimens. Consideration should also be given to the potential effects of the biological matrix on the concentrations of the target biomarkers.

Properties of the Chemical and Pharmacokinetics

Investigators must understand the properties of the chemical of interest and factors governing the absorption, distribution, metabolism and excretion of the analyte. Investigators must research potential routes of exposure with respect to differences in uptake. These differences may affect storage and pharmacokinetics in the body, making one specimen type preferable over another. Rates of analyte metabolism may also influence specimen selection. For example, some organic compounds are readily metabolized and, therefore, it may be preferable to measure the metabolite in urine rather than the parent compound in blood.[1] As a very general rule, persistent chemicals are generally measured in blood, while non-persistent chemicals (or their metabolites) are measured in urine. Another important consideration is whether the biomarker has been measured at the appropriate time, the critical life stage of interest, and the disease's induction and latency characteristics. Depending upon the pharmacokinetics of the compound, a sample might represent exposures that occurred yesterday, in the past month or in the past decade. Suspected time of exposure is especially relevant. If many years have passed since the exposure occurred and exposure is no longer occurring, biomonitoring serves little purpose. Substances with short half-lives may not be feasible to measure unless the timing of exposure is known and is recent or if the exposure is frequent or ongoing such that the biomarker will likely be continuously present.

1 National Research Council of the National Academies. Human biomonitoring for environmental chemicals. Washington DC. 2006. www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals

It is also useful to understand inter-individual variability in pharmacokinetics of the chemical and to collect any such information that may impact biomarker concentration (e.g., age, body build, health status, concurrent exposures). Information on how concentrations vary over time within the same individual is also important, especially for one-time biomarker collection. The selected biomarker and media should adequately reflect body burden and if not, additional metabolites and/or specimens in alternative media should be collected.

Resources on biomarker and sample selection are listed below.

Biomarker Specificity

The biomarker should be specific to the chemical(s) of interest, particularly if one of the intentions is to elucidate potential pathways and sources of exposure. Certain metabolites may be common to several parent compounds. For example, 3-phenoxybenzoic acid is a metabolite common to several pyrethroid insecticides, some of which are more commonly found on food while others are usually found in residential settings. Further, certain metabolites may also be environmental degradates, which can obfuscate interpretation of results. For example, the environmental degradation of the insecticides chlorpyrifos and chlorpyrifos-methyl results in the formation of the same chemicals as does human metabolism. Therefore, by measuring the metabolite 3,5,6-trichloro-2-pyridinol (TCPy) in urine, one cannot distinguish whether exposure was to chlorpyrifos or chlorpyrifos-methyl or to TCPy itself.

Analytic Specificity and Sensitivity

Available analytical methods must be evaluated to determine the robustness of the method and whether its detection limits will result in data suitable to answer the study questions. The limit of detection may be more of an issue for evaluating “background” or “environmental” levels of a biomarker compared to levels anticipated to occur from occupational exposure or community exposure to a known point source of contamination. The sensitivity, specificity and potential for false-positive or false-negative results must be considered.

FEASIBILITY CONSIDERATIONS IN BIOMARKER SELECTION

Feasibility is also a consideration in the selection of biomarkers. Analytic costs, laboratory precision and accuracy, ease of collection, invasiveness, the requisite volume of sample needed for analysis and the stability of the compound are all factors in assessing feasibility.

Laboratory Capacity

Investigators should consider two critical questions:

- Does the laboratory have the capability, analytical instrumentation, necessary skills, and capacity to perform the method in the allotted timeframe?
- Will the data generated be directly comparable to those in the literature or will additional post-analysis calculation be required?

The laboratory must demonstrate method validation to address these questions and provide pilot data before initiating a study.

Sample Selection

While theoretically any tissue type can be used for biomonitoring purposes, in practice, the ease and non-invasiveness of obtaining a specimen is a major consideration in study design. For these reasons, whole blood, serum and urine are most commonly used. These matrices may be collected in a relatively non-invasive manner while still providing specimens appropriate for a measurement of a wide range of organic and inorganic moieties. Less common but sometimes used specimens include hair, fingernails, breast milk, adipose and other tissues. While hair and fingernails may initially appear to be good choices, they are prone to exogenous contamination and may require tedious sample cleanup to be viable. The remaining sample types are far less easy to obtain from study participants, each presenting their own unique analytical challenges. As a practical consideration, non-invasively collected matrices typically result in reduced collection costs and increased participation rates.

BIOMARKER SELECTION: INPUT FROM THE LABORATORY

The New York State Department of Health's research-intensive public health laboratory, the Wadsworth Center, is an example of how laboratories can provide input on the selection of biomarkers and appropriate matrices as well as sample collection methods. The Wadsworth Center collaborated with the New York City (NYC) Department of Health and Mental Hygiene on the design of the NYC Health and Nutrition Examination Survey (NYC HANES). Laboratory experts helped NYC epidemiologist design collection protocols to assess exposure to a range of environmental contaminants.

One of the key analytes included in NYC HANES was mercury. In the initial 2004 study, exposure to inorganic mercury, which is rapidly cleared from the body, was assessed by analyzing urine for total mercury. Laboratory staff worked with the study team to develop appropriate protocols for handling of samples, including using the appropriate preservative for mercury and certified the collection vials used, to ensure the quality and integrity of the samples.

Laboratory input continued during the sample analysis, when analytical staff identified extremely high levels of mercury in the urine of one participant. The metals laboratory director notified NYC health department staff, which followed up with the participant, who had been using a skin lightening product brought to the US from the Dominican Republic. The skin lightening product contained very high levels of mercury. The health department subsequently identified stores and importers associated with production and distribution of skin care products and conducted a public education campaign in Spanish and English.

The laboratory also identified higher levels of mercury in blood samples from Asian participants and foreign-born Chinese. Laboratory analysis of blood samples for total mercury is generally reflective of organomercury compounds (e.g., methyl-mercury), indicating exposure through diet that was subsequently associated with consumption of fish or shellfish. This also resulted in an educational campaign targeting this population.

Both interventions appeared to have had a positive impact as a follow up NYC HANES study in 2014 documented reduced levels for both blood and urine mercury among study participants.

Learn More

McKelvey W, Gwynn RC, Jeffery N, Kass D, Thorpe L, Garg RK, Palmer CD, Parsons PJ. A biomonitoring study of lead, cadmium and mercury in the blood of New York City adults. Environmental Health Perspectives. 2007 October; 155(10):1435-1441.

McKelvey W, Jeffery N, Clark N, Kass D, Parsons PJ. Population-based inorganic mercury biomonitoring and the identification of skin care products as a source of exposure in New York City. Environmental Health Perspectives. 2011 February; 119 (2):203-209.

McKelvey W, Alex B. Chernov C, Hore P, Palmer CD, Steuerwald AJ, Parsons PJ, Perlman SE. Tracking declines in mercury exposure in the New York City adult population, 2004-2014. J Urban Health. 2018; 95:813–825.

8. STUDY PROTOCOLS & PLANS

IN THIS SECTION

Study Protocols

- Analytical Method
- Participant Selection and Recruitment
- Specimen Collection
- Specimen Storage and Handling
- Data Security
- Participant Protection
- Reporting and Communications

Plans

- Data Analysis
- Evaluation
- Protection of Human Research Participants

STUDY PROTOCOLS

Detailed, written protocols covering every aspect of the study design are critical for biomonitoring studies. Written protocols provide reference documents that guide how the study is conducted (which can often go over several years) and ensure that key elements in the design are maintained. The project epidemiologist monitors adherence to study protocol and documents protocol or procedural changes that can occur during the study. This is necessary because changes in participant recruitment and data collection protocols have the potential to significantly affect the interpretation and validity of the results.

More information on protocols and SOPs can be found in the CLSI document *Quality Management System: Development nd Management of Laboratory Documents* (Sixth Edition).[1]

Following is a brief description of the primary protocols needed for management of a biomonitoring study.

1 CLSI. Quality Management System: Development and Management of Laboratory Documents (Sixth Edition). 2018. Accessed June 2019. clsi.org/standards/products/quality-management-systems/documents/qms02/

Analytical Method Protocol

This provides a blueprint to the overall study design by describing analytic methodology and data needs to address overall research questions. This includes sample size determination. A thorough description of analytical protocol and methodology is provided in Section VIII.

Participant Selection and Recruitment Protocols

These describe the specific methods to be used by study staff for sampling and selecting participants from a target population, making contact with participants (by phone, mail, or other means), and obtaining informed consent. Recruitment protocols include methods for tracking the number of people who are eligible and consent to participate, as well as non-participants, people in the study population who are determined to be ineligible, refuse to participate, or cannot be contacted.

Documentation of Selection and Recruitment Protocols, or Changes in Protocols

These protocols address the validity of inferences that are drawn from the study results. Protocols include attachments of study materials such as letters to participants, informed consent documents, questionnaires and other data collection instruments. Protocols should be in compliance with the latest HHS standards for data collection[1] on race, ethnicity, sex, primary language and disability status.

Specimen Collection Protocols

These provide detailed step-by-step instructions regarding how, where and when specimens are to be collected, processed, preserved and transported to the laboratory. Laboratory personnel work with the epidemiologist to write procedures for field staff and instructions for participants on specimen collection. In some situations, laboratory personnel may train field staff in specialized specimen collection procedures to ensure the integrity of the sample for testing. This is particularly important if the target biomarkers are ubiquitous environmental contaminants or environmental degradates (e.g., bisphenol A, triclosan, parabens). More information is provided in Section VIII.

Specimen Storage and Handling Protocols

These ensure that unless specimens are being stored for other uses, there are procedures for when and how specimens will be destroyed at the end of the study. Conditions and length of storage time should be documented. It is strongly recommended to include field blank samples (e.g., high-purity solvent(s) placed in a sample container and processed as a biological specimen) in the protocols for the collection and/or processing of biological specimens for programs/studies with a current or potential biomonitoring component. More information is provided in Section VIII.

Data Security Protocols

These describe methods for ensuring data security and privacy protection, data cleaning and aggregation analysis methods, and define the specific study outcomes (e.g., geometric mean, standard deviations, and percentiles).

Participant Protection Protocols

These identify and address any legal or ethical issue, and describe methods for minimizing privacy risks to participants, especially among vulnerable groups.

1 DHHS, ASPE. HHS Implementation Guidance on Data Collection Standards for Race, Ethnicity, Sex, Primary Language, and Disability Status. 2011. Accessed June 2019. aspe.hhs.gov/basic-report/hhs-implementation-guidance-data-collection-standards-race-ethnicity-sex-primary-language-and-disability-status

Reporting and Communications Protocols

These address plans for interpreting and communicating results with multiple audiences including participants, community members, legislators, media representatives, and medical providers. Reference populations or health-based reference values should be specified for the interpretation of findings. A protocol for the rapid communication of results and referral to medical follow-up should also be specified.

PLANS

Data Analysis Plan

The data analysis plan should describe what information (e.g., demographics, medical history, biological samples) is collected, its sources, what data collection methods are used and how these methods were validated.

A data analysis plan has multiple components. As described below, they may include statistical methods, sampling plan design and quality control.

Statistical Methods

Statistical analysis of data is done in three major steps: data preparation, descriptive analysis and inferential analysis. A data analysis plan describes appropriate statistical methods for each study question with both descriptive analysis (characterizing the study population) and inferential analysis for each hypothesis to be tested. The statistical plan should obtain statistical consultation during all phases of the study, including the early planning stages. For each study question, the plan should include a clear statement of:

- Dependent variables, independent variables and covariates
- Analytical outcomes, statistical models, sampling frame, sample size calculations
- Test methods for determining variable distributions, central tendency and variability
- Comparisons by pre-determined strata

Potential sources of measurement error, selection bias and confounders should also be identified. A plan for minimizing and controlling such errors is recommended to strengthen the validity of results. If identified early in the process, some errors may be minimized with changes in the study design.

Sampling

The sampling plan should ensure achieving adequate sample size for meaningful analysis. Thus, the data analysis plan should include appropriate sampling methods. Other measures can be taken to avoid biased results, including:

- Use same/similar sources and procedures for the groups being compared
- Mask investigators to the exposure status of a subject so that they make unbiased decisions when assessing the outcomes (or vice versa depending on the study design)
- Identify clearly what measures are used for defining exposure and outcome/disease for both accuracy and comparability

Laboratories should work with epidemiologists or statisticians to ensure they have robust data. The appendices have more information on statistical analysis.

Data Quality Assurance and Control

The data analysis plan should also include specific, data-related QA/QC measures for all data collection procedures. This includes protocols for handling data for:

- Assuring protection of confidential personal identifiers
- Recording and keeping track of data from multiple sources
- Checking for completeness and accuracy of data collection/abstraction
- Developing a data element dictionary

Evaluation Plan

An evaluation plan evaluates the processes and outcomes of the proposed study using a variety of measures and indicators, with evaluation activities conducted throughout the study period. The model commonly used for study evaluation for community-engaged studies is the Logic Model. More information on this model can be found in the WK Kellogg Foundation's Logic Model Development Guide.

Biomonitoring studies usually include two components, the technical/research component and the public health action (PHA) component. Each requires different evaluation strategies. The evaluation plan should address both.

Evaluation Plan for Research

As shown in **Table 1**, research evaluation may address, for example:

- Adherence to the IRB-approved protocols for subject recruitment
- Effectiveness of approaches for subject recruitment
- Completion of proposed sampling tasks, sample and data analyses within the projected time frame

COMMON EVALUATION QUESTIONS

Research Component

- Are the exposures elevated for certain populations?
- What are the causes of the exposure?
- What are the factors that may affect the exposure?

Public Health Action Component

- Are the recruitment methods effective?
- Are the results and findings effectively disseminated to the community members and public?
- Are the community outreach and education goals achieved?
- Are the exposures reduced?

Table 1. Sample logic model summarizing research efforts and evaluation plan

GOALS/AIMS	INPUTS	ACTIVITIES	OUTPUTS	OUTCOMES
• Determine the biological levels of target analytes • Determine the potential causes of the exposure • Determine the major factors that may affect the exposure	• Study Team • Advisory committee • External partners • Lab equipment and supplies • Other resources • Funding	• IRB material preparation • QA/QC plan • Study protocols • Supply purchasing • Subject recruitment • Sample collection • Sample analysis • Data analysis • Publication preparation • Report preparation	• Biological levels of target analytes • Demographic characteristics information about potential sources of exposure • Information of the factors that may affect exposure	• Database for future health effects assessment • Reduction plan or other study plan to advance public health science

The evaluation plan can measure outputs for these and other evaluation questions. Examples of outputs include:

- Completion of consent forms before sampling as a measure of compliance with IRB protocols
- Response rate for subject recruitment approaches, feedback from community members on their effectiveness
- Adherence to QA/QC for sampling, sample and data analysis based on completeness of sampling and sample analysis records
- Valid number of samples that are collected
- Completeness and accuracy of the target analyte(s) concentration database and questionnaire database
- Study questions are adequately answered with confidence
- Number of publications and education materials produced

Evaluation data can be used to modify or improve study protocols/procedures.

PHA Evaluation Plan

The PHA evaluation plan evaluates:

- Effectiveness of PHA activities to translate and disseminate the findings from the proposed study to community members
- Effectiveness of PHA activities to educate community members on the potential sources of exposure, the associated health risks and how they might reduce their personal exposure to environmental contaminants

The logic model in **Table 2** summarizes PHA activities and how they are linked to the expected results. Besides the information and data that will be generated through the study, such as subject number and the retention rate, other data can be generated through a survey to evaluate the PHA.

Table 2. Sample logic model summarizing PHA efforts and evaluation plan

GOALS/AIMS	INPUTS	ACTIVITIES	OUTPUTS	OUTCOMES
• Recruitment rate and retaining rate • Community meetings attending rate and outcome • Reception and responses about the results and findings • Change in awareness and behavior related to exposure	• Study team • Advisory panel • External partners • Other resources • Funding	• Community meetings • Home visits • Phone calls • Publication/ educations materials preparation • Report preparation	• Education materials • Publication • Report	• Increase in awareness of exposure and public health • Reduction in exposure • Partnership with community and stakeholders

Protection of Human Subjects Plan

With all studies that involve human subjects, the lead investigator is responsible for knowledge of and compliance with state and federal laws that protect the rights of participants in health research. Information about the training, ethical guidelines and federal laws governing human subjects can be found on multiple websites (see Resources below). In all activities involving human subjects, a review must be conducted to protect participant rights. Many biomonitoring activities are considered public health investigations not research studies, Only projects that determined to be research studies require Institutional Review Board (IRB) review, and adherence to highly specific practices related to human subjects protection, data privacy protection and ethical practices. IRB requirements may vary from state-to-state.

ITEMS FOR IRB APPLICATION

- Form of consent
- Study protocols
- Questionnaires (if any)
- Study flyer
- Phone script for subject recruitment
- Other documents that will be used by the participants

Study protocols must be established and approved by the IRB prior to starting the project. Investigators are strongly advised to consult with their IRB for a determination of whether a given project is deemed to be research or public health practice, as this determination is subject to interpretation, and different IRB application are required depending on the determination.

A key part of compliance is to develop a clear consent form for participants. The consent form should include descriptions of the study objectives, study approach, specific sample and data collection procedures, how the data collected from the participants will be used, the benefits and risks for participants from the study and how personal information will be protected. The form should be clear and easy to understand by a person that does not have a scientific background (e.g., use lay terms). See appendices for an example of a consent form.

RESOURCES

Federal Policy for the Protection of Human Subjects ('Common Rule') (HHS)
www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html

Human Subjects Research (NIH)
grants.nih.gov/policy/humansubjects.htm

Human Subject Training and Resources (NIH)
grants.nih.gov/policy/humansubjects/training-and-resources.htm

The Belmont Report: Ethical Guidelines for the Protection of Human Subjects (HHS, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research)
www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

Preserving Public Trust: Accreditation and Human Research Participant Protection Programs (Institute of Medicine)
/www.nap.edu/catalog/10085/preserving-public-trust-accreditation-and-human-research-participant-protection-programs

Ethical and Policy Issues in Research Involving Human Participants (National Bioethics Advisory Commission)
bioethicsarchive.georgetown.edu/nbac/human/overvol2.pdf

9. ANALYTICAL PROTOCOL & METHODOLOGY

IN THIS SECTION

- **Initial Considerations in Analytical Method Selection**
- **Specimen Collection**
- **Analytic Testing**

Biomonitoring has many unique method validation challenges. One is biomonitoring measurement, which often involves detection at very low levels (e.g., parts per billion) that are near the limit of detection. Biomonitoring also has the potential to introduce contamination of samples. For example, materials to draw blood or specimen containers may also contain the analyte of interest. Materials used in the lab (e.g., paper towels, hand soaps) may contain the chemical of interest and result in contamination; pesticides sprayed outside the laboratory building may be tracked into the labs, volatilize, and result in contamination; exposing serum to air by repeatedly opening the vial may introduce PBDE-containing dust and falsely elevate results. These are a few examples that have caused measurement inaccuracies. For a laboratory performing biomonitoring measurements, it is imperative to consider such sources of external contamination. Pre-screening of materials may be necessary to avoid contaminating samples and biasing analytical results.

Notably, the laboratory's quality management system and protocols should address these challenge areas. Additional challenges related to analytical method selection are discussed throughout this section.

INITIAL CONSIDERATIONS IN ANALYTICAL METHOD SELECTION

While selecting an analytical method may seem to be the responsibility of the laboratory, epidemiologists can also provide invaluable insights to address the following questions and lead to the best method choice.

Table 1. Questions to consider in analytical method selection

STUDY COMPONENT	QUESTIONS
Biomarker	• Which biomarker has been selected?
Analyte(s)	• What is/are the analyte(s) of interest? • Is there a priority basis for the analytes? • What concentration range is appropriate?
Matrix	• What matrix is required by the project or available from previously collected samples? • What matrix is best suited for the analyte(s) of interest and helps to answer the project question? • Is the sufficient sample volume to reach the desired level of sensitivity?
Quantitation	• How are the data going to be used? • Will they be used for trend analysis, identification, and quantification? • Does the method need to be qualitative or quantitative?
Instrument Availability	• What instrumentation is currently available in the laboratory? • Can additional instrumentation be acquired?
Special Criteria	• What other criteria need to be considered? Are there special sample collection requirements such as preservation or specific collection containers? • What storage or processing conditions must be addressed? • Is the sample volume appropriate for all the analytes to be tested?

METHODOLOGY RESOURCES

CDC *Fourth National Report on Human Exposure to Environmental Chemicals*
Includes an appendix with a list of peer-reviewed methods: www.cdc.gov/exposurereport/index.html

CDC NHANES Peer-reviewed Biomonitoring Articles
www.cdc.gov/exposurereport/biomonitoring_articles.html

CDC's LRN-C Website (Members Only)
Includes SOPs for network methods.

National Center for Biotechnology Information
This and other search engines can be used to find peer-reviewed publications: www.ncbi.nlm.nih.gov/

NBN Member Profiles (Members Only)
Profiles provide information regarding individual laboratory capabilities and allow searching by analytes, method and analytical platform.

SPECIMEN COLLECTION

Biological specimen collection must ensure the integrity of the specimen and the validity of the resulting data. As described below, considerations include use of appropriate methods for specimen collection equipment, storage and shipping. These should be specified in specimen collection protocols. Laboratory personnel should work with an epidemiologist and other public health workers to document procedures for field staff and instructions for participants for specimen collection. In some situations, laboratory personnel may train field staff in specialized specimen collection procedures to ensure the integrity of the sample for testing. More information is available in CDC/NCEH/DLS's *Improving the Collection and Management of Human Sample Used for Measuring Environmental Chemicals and Nutrition Indicators.*[1]

Specimen Containers/Tubes Used for Biomonitoring

Biomonitoring studies often involve measuring chemicals at extremely low levels in order to gather meaningful data on exposure. Care must be taken to ensure containers are compatible with the specimen and the analytes of interest and no positive or negative interferences are encountered. Containers, including lids, must be constructed of a material that does not contain or interact with (i.e., absorb) the analytes being measured. Contamination from the containers used for specimen collection and storage can introduce a bias in laboratory measurements and affect the results and conclusions of a study.

The suitability of a given lot of containers must be assured by the laboratory prior to the collection of specimens. This is particularly important when the laboratory is measuring a chemical or metabolite common in the environment or that could potentially leach from specimen containers. For example, trace elements such as lead or mercury are biologically active at very low concentrations and are ubiquitous in the environment. Per- and polyfluoroalkyl substances (PFAS) and phthalates can be present in some plastic materials and may leach into the specimen. Some containers used by clinical/medical laboratories are certified to be free of certain chemicals and are commercially available from lab supply distributors.

Laboratory quality control testing of lots of containers used for specimen collection is highly advisable for all methods. The screening procedure must assure that when specimens are collected and stored following the laboratory protocol, the contamination introduced by the containers themselves or any preservatives remains negligible (i.e., below the detection limit of the analytical method). Pre-cleaning (acid-washing, solvent rinsing) of collection materials may be indicated for some analyses. However, this may not always happen. Ideally, collection vessels should be archived for future target testing at a later date.

Assessing Integrity of Samples: Collection Blanks

A collection blank can be used to estimate the extent of contamination introduced in the field. It is a blank or empty specimen container from the same lot as the specimen containers used to collect specimens from study participants. Blanks frequently used in monitoring include:

- **Field Blank:** A field blank (or empty container) is transferred to the sampling site for the purpose of determining ambient contamination levels in the field and in the laboratory.
- **Laboratory Blank:** This blank is analyzed to ensure laboratory reagents and equipment are free from contamination. Analyte-free matrix, synthetic matrix or deionized water may be used in place of a participant specimen for blank determination.

Collection blanks may be collected alongside regular samples and must be subjected to all of the steps and manipulations to which study specimens are subjected.

1 CDC. Improving the Collection and Management of Human Sample Used for Measuring Environmental Chemicals and Nutrition Indicators. 2008. www.cdc.gov/biomonitoring/php/public-health-strategy/

Specimen Collection Procedures

Proper collection of specimens for testing is essential to assure that the results are representative of biomarker concentrations in the specimen and reflective of the body burden of the participant. Use of specimen collection instructions and field blanks is recommended.

The Clinical and Laboratory Standards Institute (CLSI)[1] publishes consensus standard procedures for the collection, handling and processing of clinical specimens. However, the CLSI standards do not consider challenges unique to biomonitoring studies. Biomonitoring studies often measure environmental chemicals and/or metabolites in clinical specimens at levels below clinical significance. Therefore, contamination from external sources at the time of collection must be minimized through careful specimen collection and strict adherence to study collection protocols. This is especially important in non-clinical settings such as private homes or community settings where biomonitoring specimens may be collected for convenience purposes.

Specimen collection instructions should be written with input from laboratorians, public health workers, healthcare providers (phlebotomists, nurses, physicians) and others involved in the collection. Community members should also be involved to ensure that the process is sensitive to the needs of the community. Step-by-step directions (i.e., collection protocol) should be detailed and address:

- Sample containers
- Contamination prevention
- Processing
- Labeling
- Information collected from the participant
- Storage prior to transportation to the laboratory

In cases of self-collection, instructions for study participants should be written in plain language without scientific or medical terminology and should include a phone number to direct questions.

Collection staff must be trained to follow these procedures in order to minimize the likelihood of exogenous contamination and to ensure the integrity of specimens during transport.

SPECIMEN COLLECTION RESOURCES

APHL Biomonitoring Module (APHL)
vimeo.com/showcase/4767908?video=258108654

Collection and Management of Human Samples (CDC)
www.cdc.gov/biomonitoring/php/public-health-strategy/

Consensus Standard Procedures for Collection, Handling and Processing of Clinical Specimens (CLSI)
clsi.org/media/1430/ep17a2_sample.pdf

Specimen Collection—Blood and Urine (NHANES)
www.cdc.gov/nchs/nhanes/spu-specimens/index.html

1 Clinical and Laboratory Standards Institute. clsi.org/

Specimen Identification and Documentation

Proper specimen identification is necessary to link laboratory results to demographic, dietary and/or lifestyle information collected for the purpose of the study. This requirement is less stringent, but still important, when a study purpose is purely range-finding (i.e. designed to determine the range of concentrations of a particular chemical in a given population).

Specimen identification in biomonitoring studies must be accomplished without the direct use of participant names or other personally identifiable information. Unique identification numbers may be generated through the use of a laboratory information management system (LIMS) or through other means. A key linking the laboratory generated identifiers to the participant should be kept by the principal investigator or other essential study personnel. Barcoding of specimen vials and laboratory submission forms is recommended for identification and efficient tracking of specimens and associated paperwork in the laboratory. Additionally, consider specimen storage conditions when selecting labels, especially if specimens will be stored at extremely low temperatures such as -20 °C or -80 °C.

Standardized forms (hard copy or electronic) and protocols are essential to ensure that all required information is collected and transmitted with the sample. This may include study subject name or ID code, date of birth, date collected, specimen type, dietary habits and demographic information.

Shipping to the Laboratory

If samples are mailed, they must comply with all local, state and federal regulations. If samples are known to include pathogens, they must comply with the federal regulations listed below.

Packaging and shipping of hazardous materials is tightly regulated internationally and domestically. Adherence to hazardous material shipping regulations is the sole responsibility of the shipper. Supplies and specimens must be packaged in accordance with the regulations appropriate for the associated hazards, mode of transportation and destination. Refer to the links in the text box for more information on shipping hazardous materials. Other regulations may apply.

The study protocol should address any shipping issues and take into account the type of samples. Training should be provided to all study staff in terms of handling and shipping of samples.

Specimen Storage and Banking

Laboratory protocols for storage, handling and disposition of specimens (including disposal of specimens not stored for future use) must be in place prior to commencement of the study. Specimens must be stored under suitable conditions to avoid target analyte and matrix deterioration. Optimal storage conditions will vary depending on the matrix and analytes studied. Analyte stability studies should be researched or performed to assess the suitability of a chosen analyte and storage method.

SHIPPING REGULATIONS

International

International Air Transport Association and International Civil Aviation Organization have guidelines for the international transport of dangerous goods or hazardous materials by air.[1]

Domestic

The US Department of Transportation regulates transport of hazardous materials by all modes of transport except for the US Mail.[2]

The US Postal Service or US Mail Regulations that affect the transport of hazardous materials in the US mail, including Division 6.2 materials, are codified in the Code of Federal Register (38 CFR) and published in the Domestic Mail Manual.[3]

1 IATA International Transport Guidelines. www.iata.org/publications/dgr/Pages/index.aspx

2 Transportation, 49 CFR § 100-185 (2019) www.ecfr.gov/cgi-bin/text-idx?sid=585c275ee19254ba07625d8c92fe925f&c=ecfr&tpl=/ecfrbrowse/Title49/49cfrv2_02.tpl

3 USPS Domestic Mail Manual. pe.usps.com/text/dmm300/601.htm

Room temperature storage may be appropriate for some matrices (e.g., hair or nail clippings). However, refrigerated or frozen storage is commonly employed for the majority of common clinical matrices such as urine, whole blood and serum. Storage at temperatures below freezing (-20˚C or -80˚C) is generally recommended for long-term storage and for temperature-sensitive analytes such as those speciated by oxidation state.

The above storage guidelines are widely followed even though there is limited information regarding their applicability in relation to the stability of many analytes that may be selected for biomonitoring studies. The effects of temperature variations during transport and prolonged storage and freeze/thaw cycles on the stability of many analytes have not been studied. Temperature must be closely monitored. These effects remain particularly concerning when plans include long-term storage or specimen banking.

ANALYTICAL TESTING

Cost, feasibility and quality control procedures factor into selection of an analytical method. Another important consideration is the comparability of data, especially for surveillance activities where the results will be compared with reference values or with national estimates (e.g., NHANES).

Analytical method development and validation generally follows the steps in the diagram below.

Figure 1. Validation process flow chart

ANALYTICAL PROTOCOL

An analytical protocol outlines the procedures a laboratory must follow to ensure that information collected in the study is accurate and bias free. The laboratory might develop its protocol as the study method is being developed. This may involve adapting an existing published method. Alternatively, the laboratory may develop and document a new and novel method. Pre-analytical work is necessary before finalizing the protocol to establish the suitability of the method with regards to, for example, linearity of analyte response, precision and accuracy of the measurement, sensitivity, matrix interferences, recovery, carryover and stability.

SOPs serve as essential laboratory documents. SOPs are crafted specifically for each study and guide the study team in their activities. A well written, detailed SOP is important to ensure operations are carried out correctly, consistently and in a reproducible manner leading to consistent defendable results.

SOP writing begins as the method is being developed and may involve adaptation of an existing published method or documentation of a new and novel method. Pre-analytical work is necessary before finalizing the SOP to establish the suitability of the method with regards to linearity of analyte response, precision and accuracy of the measurement, sensitivity, matrix interferences, recovery, carryover, stability, etc.

At a minimum, an SOP should contain detailed information on the following:

- Safety Precautions for Biological Hazards and Chemical Hazards
- Procedures for Collecting, Labeling, Storing and Processing of Specimens
- Criteria for Specimen Rejection (if applicable)
- Limitations of the Method including Interferences
- Equipment and Instrumentation
- Detailed step by step procedures
- Preparation of Reagents, Calibrators (Standards) and Quality Control Samples
- Calibration, Calibration Curves, Acceptance Criteria and Calibration-Verification Procedures
- Calculations
- Interpretation of Results
- Quality Control (QC) Procedures
- Proficiency testing
- Reference Ranges (Normal Values) and Critical-Call Results (Panic Values) if known
- Test-Result Reporting System; Protocol for Reporting Critical Calls (If Applicable)
- References

Analytical Standards

Certified primary chemical standards and reference materials are available for many analytes of interest to biomonitoring researchers. However, not all are available from commercial sources as catalog items. In some cases, calibration standards and quality control materials will need to be custom ordered or prepared within the laboratory from pure materials.

A second standard should be obtained from a different source or, if a second source is not available, a different lot number from the vendor of the primary standard should be purchased to serve as an independent verification of the primary standard. Internal standards should be used to normalize instrument response and correct for drift or to account for losses during sample preparation. For analyses where analytes are determined via mass spectrometry, isotopically labeled analytes may be used as internal standards. Store all standards and quality control materials under appropriate conditions to avoid degradation of analytes or changes in the solutions due to evaporation of solvent or other processes.

Method Validation (Internal)

Method validation is necessary to confirm that the analytical method is suitable to detect, identify and reliably measure the target compounds in the designated matrix. The completed validation demonstrates and documents that all facets of the method are in control. See the appendices for a Clinical Method Validation.

Method Validation Plan

A method validation plan should be in place. Typically, this plan serves to ensure:

- **Accuracy and Precision:** This deals with the matrix, the analytical technique and the quality of the analytical standards. A method validation plan would collect sufficient numbers of analyses of matrix-based samples by different analysts to allow for the determination of intra- and inter-day precision and accuracy. The QC characterization may serve as a source for this data.
- **Selectivity and Specificity:** This is the confidence that the measured signal is due to the analyte of interest without influence from other sample components. Selectivity may be established through various means including, for example, ion pattern/ratio, retention time, wavelength of light absorbed or emitted. Selection depends on the analytical technique used for measurement. Selectivity should be established with control materials and actual field samples to properly determine if all interferences have been eliminated or identified and compensated for.
- **Sensitivity:** This is established through the determination of the limit of quantification (LOQ) and limit of detection (LOD). The LOD may be determined through a number of procedures based on the signal to noise ratio of calculation of the standard deviation of multiple measurements of a signal. See the Clinical and Laboratory Standards Institute (CLSI)'s EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline.[1] Another reference for the determination of LODs can be found in *Quality Assurance of Chemical Measurements*.[2] The LOQ is commonly set as a multiple of the LOD or as the concentration of the lowest calibration standard used to generate the calibration curve. Results below this level may be reported as non-detect (ND) or less than the value of the LOQ (< LOQ) or qualified to indicate increased uncertainty in the measurement. A method detection limit (MDL) will measure lower levels of the analyte. Lower MDLs are often required to compare background or environmental exposure levels of an analyte with levels that are anticipated to occur from occupational or community exposure to a known source of contamination.
- **Stability of the Chemical In and Out of Matrix:** There are several types of stability that need to be addressed: freeze-thaw stability, short-term stability at room temperature, long-term stability in storage conditions and stability of the chemical in solution as opposed to matrix.
- **Analytical Versus Reporting Range:** The analytical range is the lower calibration level to the upper calibration level. The reporting range is the validated ability to dilute a sample that is above the calibration range to bring it down to within the calibration range.

1 CLSI. EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. 2012. clsi.org/media/1430/ep17a2_sample.pdf

2 Taylor, JK. Quality Assurance of Chemical Measurements. Lewis Publishers. Chelsea, Michigan. 1987. 78-84.

Ongoing Review of Method Validation

There are several ways to ensure the integrity of method validation.

- **Update Protocols as Needed:** Method validation protocols should be reviewed at least annually and revised whenever necessary due to changes in the procedure, equipment, extension to a new sample matrix or other significant change. If significant changes are made to a method, it may be necessary to revalidate the protocol to ensure that accuracy, precision and sensitivity have been maintained. New equipment should be verified by comparison studies with analysis of split samples on the existing and new instrumentation when possible. The NBN is finalizing multiple approaches for harmonization of laboratory biomonitoring measurements.
- **Staff Training:** Analysts must demonstrate competency in the method prior to analyzing study samples. Initial competency may be established through training by an experienced analyst (i.e., performance of the method under the guidance of a competent analyst and analysis of samples of known concentration). The samples may consist of certified reference materials (CRMs), fortified matrix, previously analyzed PT samples or other samples for which the concentration of analyte has been well established.

Pre-validation Testing

Testing must be completed to demonstrate that the proposed method is applicable to the analyte of interest in the given matrix. These parameters should be evaluated prior to the more rigorous formal validation to demonstrate that the proposed/intended method will meet the criteria for the quantification of the analyte in the matrix.

LRN-C PRE-VALIDATION TESTING PROTOCOL

Establish the response versus analyte concentration relationship and the dynamic range of the relationship. Most measurement techniques will result in a linear response with respect to analyte concentration. It is important to demonstrate this relationship and determine the range of concentrations for which this is the case.

Ensure that the instrument sensitivity meets the requirements for the analysis. Once the dynamic range has been determined, this demonstrates that the method will perform satisfactorily at analyte concentrations relevant to exposure studies.

Determine precision and accuracy of the method. Precision and accuracy must be demonstrated for each analyte throughout the calibration range. This is usually accomplished through the repeated analysis of quality control samples or standard solutions at the low, middle and high ends of the calibration curve.

Evaluate the sample preparation portion of the method to ensure analyte recovery. Certified reference materials or other samples of known analyte concentration are extracted and analyzed to ensure that the analyte is quantitatively recovered during sample extraction.

Determine if interferences are present that depress or enhance analyte response. Analytical interferences may be evaluated through the analysis of blank matrix and blank matrix with a known amount of analyte added.

Determine the potential for carryover between samples. The potential for carryover is evaluated by analyzing samples containing the analyte of interest followed by blank samples or solvent.

Ensure the analyte is stable under storage conditions. Analyte stability should be evaluated in both the unextracted sample as well as the extract if applicable. Repeated extraction of a sample over time and repeated analysis of an extracted sample over time should result in similar answers if the analyte is stable.

Note: If a published analytical method serves as the basis for the SOP, some of the steps may be omitted.

Quality Control Samples

Quality control (QC) and proper laboratory techniques help ensure that biomonitoring study results are valid and scientifically defendable. QC also enhances the confidence with which data from different sources may be compared.

Quality control samples analyzed with each analytical batch are a continuous indicator of accuracy and precision of the instrumental portion of the method. Consistent QC results address potential quality issues like build-up of materials in the instrument or environmental conditions like humidity or room temperature fluctuations that can lead to instrument drift and erroneous results. QC materials must be well characterized and stable so QC data can be tracked over time. Following are considerations when preparing QC samples.

- Quality control samples are typically comprised of the same matrix as the study specimens and have concentrations of target compounds in the low, medium and/or high range of the assay calibration.
- If available, CRMs or standard reference materials (SRM) should be used to prepare QC samples.
- CRMs may not exist for many biomonitoring analytes of interest. In such cases, QC materials can be prepared in the laboratory using a blank matrix (see below), fortified with the appropriate amount of the chemicals of interest. Optimally, the solutions used to fortify the QC material should be from a different source than the solutions used to generate calibration standards.
- Due to the possibility of endogenous species, the QC material should be characterized after it has been fortified. QC characterization is accomplished with a minimum of 20 analytical runs to produce an average target concentration and a standard deviation from which to derive the acceptance limits. Ideally, the 20 samples should be analyzed by multiple analysts over multiple days.

The laboratory must establish the system by which the QC results are evaluated and accepted or rejected. A good QC resource is the Westgard Rules.[1]

External verification of internally-prepared QC materials is strongly encouraged. Refer to the NBN member profiles to identify a member laboratory that may be able to assist.

Blank Matrix for Calibration and/or Quality Control Samples

Blank matrix is used to determine if the analytical system is free from contamination and also to prepare calibration samples and QC materials. The materials may be purchased or derived from a clean source or from pooled human urine and/or blood. Synthetic matrices are available if analyte free natural matrix cannot be obtained. If an analyte free matrix is not available, it may be necessary to use the method of standard addition.

For other biological matrices, the laboratory may be able to use a surrogate or substitute if available.

Correction for Urine Dilution

Some clinical measurements, such as analytes measured in urine, more accurately reflect an individual's internal dose when normalized. However, analyte measurements (trace metals, parent compounds and metabolites) in urine can vary significantly depending on the hydration status of the donor (i.e., how diluted or concentrated the urine sample is).

A common way to account for variability is to correct the analyte concentration for the amount of creatinine measured in the same sample. (Creatinine correction can also partially adjust for differences in lean body mass or renal function among persons.) Creatinine is a normal breakdown product of muscle creatinine, which is filtered from blood by the kidneys and excreted in urine. It serves as a good indicator of kidney function and urine concentration. Final test

EQUATION FOR CORRECTION

ug analyte/L x dL/mg creatinine x 100 = ug analyte / g creatinine

1 Westgard Rules. www.westgard.com/westgard-rules.htm

results are typically reported as micrograms (ug) analyte/gram (g) creatinine.

Creatinine correction is particularly important when collecting the "spot" urine samples frequently used for biomonitoring, as these specimens have greater variability in concentration as compared to a 24-hour urine collection. Generating the correction factors requires separate analytical procedures (in compliance with all respective laboratory QA standards) run on each of the participant specimens. This is, in effect, an additional biomonitoring analyte. In the absence of in-house capability, the methods can be contracted to clinical laboratory services.

Besides creatinine, other methods used for adjusting urinary dilution are specific gravity and osmolality. Specific gravity can be easily measured using a refractometer, which is calibrated with deionized water prior to each measurement.

An NHANES Environmental Data Tutorial provides more information on creatinine correction and lipid adjustment.[1]

Lipid Adjustment

Certain analytes are concentrated in the lipid fraction of serum, so lipid adjustment of results is recommended (reported per gram of total lipid). Lipid adjustment of the results better reflects the amount stored in body fat. Examples of serum analytes that are often lipid adjusted include poly-brominated diphenyl ethers (PBDEs), organochlorine pesticides, polychlorinated biphenyls (PCBs) and dioxins. Of note, however, serum results also may be reported per whole weight of serum to allow comparison with studies that report levels using these units.

Proficiency Testing

Proficiency testing (PT) establishes the capability of a laboratory to accurately perform testing under a given set of circumstances. It is an important comparison and objective assessment of staff competencies, specimen handling, equipment functionality and results reporting. Enrollment in an external PT program is the preferred method for confirming the quality of laboratory measurements as well as pre-analytical and post-analytical laboratory procedures. Note: no one PT program is comprehensive.

PT samples must be treated in the same manner as study samples in order to be an effective measurement tool. Many PT programs operate semi-annually to quarterly. Proficiency testing programs are operated by the Wisconsin State Health Department, State of New York through the Wadsworth Center, the CDC-BQASP, OSEQAS and CAP among others. Internationally, PT programs are operated by the Centre de Toxicologie du Québec External Quality Assessment Schemes[2] and the University Erlangen-Nuremberg German External Quality Assessment Scheme.[3]

Since all potential study analytes are not covered by PT programs, PT requirements can be satisfied through testing of blinded samples within the laboratory or exchange of samples with other labs. If enough labs are performing similar testing, a round-robin style of program can be established where each lab measures the same QC material and the results are compared.

Questionnaire Data

Questionnaires can be used to collect data to supplement biomonitoring data. Questionnaire data can include, for example, sources of exposure, exposure contact frequency and duration, and potential routes of exposure. Questionnaires can also collect specific information on factors (e.g., dietary information, culture behaviors, and exercise habits) that can affect exposure and thus biological levels of target contaminants. Demographic information is also often collected through questionnaires so that the information can be used to examine the exposure distribution and identification of subpopulations that may suffer high exposures to environmental contaminates.

1 NHANES. Environmental Data Tutorial. wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx

2 Centre de Toxicologie du Québec. External Quality Assessment Schemes. www.inspq.qc.ca/en/ctq/eqas

3 University Erlangen-Nuremberg. German External Quality Assessment Scheme. app.g-equas.de/web/

10. PREPARING & COMMUNICATING RESULTS

IN THIS SECTION

- Generating Laboratory Results Data
- Interpreting Results
- Reporting Results

The laboratory has an essential role in providing sufficient information in reports to support the needs of the many end users. The communications plan developed in the study design phase must address how laboratory results data are translated into meaningful results that are provided to participants. The plan also must include strategies for communicating with key stakeholders and the general public.

APHL's Biomonitoring Module video training module[1] provides an in-depth view of the stages and considerations involved in reporting aggregate and individual biomonitoring data. The links to the video and other resources are included at the end of this section.

1 APHL. Biomonitoring Module. vimeo.com/showcase/4767908?video=258108654

GENERATING LABORATORY RESULTS

Following is a summary of the systems used to compiled data, provisions to take to protect the integrity and confidentiality of data, interpretation standards and components of a report.

Data Elements

Typically, laboratory data are collected on computer-controlled analytical instruments and uploaded to the LIMS. Data elements used by each analytical instrument need to be mapped to the appropriate data elements in the LIMS. Further, elements of laboratory QA (e.g., QC samples) need to be matched with subject sample testing results. The final report, including both testing results and other necessary information, are usually reported to study participants by the health department.

CLIA Requirements

Under CLIA, CMS requires all clinical laboratory reports to contain certain mandatory elements when issued to the agency that requested diagnostic testing. Laboratories reporting confidential medical information must ensure adherence to all relevant data privacy regulations and policies and validate periodically that electronic transmissions are consistent with hardcopy results produced. A full description of the CLIA requirements for laboratory reporting is available online.[1]

The National Biomonitoring Network urges all member laboratories to seek certification for their biomonitoring laboratories and perform CLIA compliant methods.

CLIA EXEMPTION

CMS has guidance (42 CFR §493.3(b)(2))[1] on whether biomonitoring laboratories require a CLIA certificate or may qualify to be exempted. The description of "research laboratories" allows exemption for facilities performing research testing on human specimens not used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."

1 CMS. Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations. Accessed June 2019. www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/Research-Testing-and-CLIA.pdf

Integrity of Data Elements

Whether or not the biomonitoring tests fall under CLIA, the laboratory should adhere to the rigor and consistency of its reporting requirements. These include:

- Name, address and telephone number of the laboratory
- Two unique sample identifiers (any combination of subject name, date of birth, study participant identification, medical record number, or similar may be used)
- Specimen type or source (e.g., urine, blood, serum)
- Date of specimen collection
- Date of sample receipt
- Date of sample analysis
- Tests performed
- Results including units

1 CDC. CLIA Law and Regulation. www.cdc.gov/clia/php/about/

- Reference ranges
- Additional testing used to normalize contaminant levels (e.g., creatinine, lipids)
- name of the outside laboratory, if one was used
- Date report was printed

In addition to CLIA-required information, there are elements that are needed for epidemiologic and other interpretation, such as the method detection limits and information on the analytical methodology. Analyte levels of various groups and specimen types (e.g., non-persistent chemicals in urine, persistent lipophilic chemicals in serum) are generally presented in specific units, based on experience or recommendations, presented in **Table 1**.

Table 1. Recommended units to present chemical analyte levels

ANALYTE TYPE	RECOMEMENDED UNITS
Non-persistent chemicals measured in urine (e.g, phthalates, PAHs)	• Mass per volume of urine (**µg / L**) • Mass per gram of urinary creatinine (**µg / g Creatinine**) • Mass per volume of urine adjusted by its specific gravity (**µg / L x 24/(SG-1)**) Creatinine partially adjusts for urine dilution in spot urine samples, differences in lean body mass or renal functions. Specific gravity is less affected by age, gender, body size and meat intake and may be more appropriate when comparing individuals or populations with large differences in those parameters.
Persistent lipophilic chemicals measured in serum (e.g., dioxins, PCBs, PBDEs, organochlorine pesticides)	• Mass per whole weight of serum (**µg / g**) • Mass of chemical per kilogram of total lipids (**µg / kg total lipid**) Serum levels reported per kilogram of total lipid reflect the amount of these compounds that are stored in body fat.
Non-lipophilic chemicals measured in serum (e.g., cotinine)	Mass per liter of serum (**µg / L**)
Chemicals bound to hemoglobin (e.g., acrylamide, glycidamide)	Mass per mass blood hemoglobin (**µg / g HGB**)
Chemicals measured in whole blood (e.g., lead and other metals)	Mass per volume of whole blood (**µg / L**)

Individual biomonitoring results should be reviewed by project staff and compared to appropriate reference values or ranges. Individual participant results should be triaged based on the measured analyte levels to ensure that any levels that exceed health-based reference levels are rapidly communicated based on established laboratory procedures.

INTERPRETING RESULTS

Advances in biomonitoring techniques allow laboratories to detect very low levels of environmental chemicals. However, information on the health impacts of low levels of exposure is not as advanced, and it is often unknown whether certain levels are dangerous. Measurement of a chemical in the body is not necessarily associated with diseases or health effects.[1] Below are various methods for presentation of results: reference ranges, critical values and action levels. (When preparing the study design and selecting biomarker and sample media, also consider the availability of reference ranges that would allow for this type of interpretation.)

Reference Ranges

Reference ranges indicate the concentrations of analytes expected to be found in the general population. Biomonitoring measurements from study participants can make comparison within to the study population as well as to outside reference groups, for example the US population exposures as reported in the CDC's *National Report on Human Exposure to Environmental Chemicals*.[1] For some chemicals, health guidelines exist, allowing for biomonitoring results to be presented in reference to these guidelines or reference ranges for known adverse health effects.

Reference ranges may not always be available for all analytes of interest. The *National Report on Human Exposure to Environmental Chemicals* is a reference for select compounds and elements. Alternatively, *Toxicological Profiles,*[2] prepared by the Agency for Toxic Substances and Disease Registry, or the primary literature may have data regarding specific human levels. In the absence of established reference ranges, the laboratory must indicate that there are none on the laboratory reports. Occasionally, the laboratory will also report concentrations found in all study individuals as an aggregate report so that participants can see where they fall within the study population.

Critical Values

Critical values are those which may indicate higher than average levels. They typically trigger additional activities such as priority review of survey data to identify either potential exposure sources or confounders. Actions may include confirmatory or reflex testing by the laboratory.

Action Levels

Action levels are those which greatly exceed the expected clinical concentration warranting immediate notification of findings by the laboratory, so that not only additional sampling, testing and review be initiated, but also medical treatment begun if available.

1 CDC. Updated Tables: National Report on Human Exposure to Environmental Chemicals. CDC. 2019. www.cdc.gov/exposurereport/

2 ATSDR. Toxicological Profiles. 2019. www.atsdr.cdc.gov/toxicological-profiles/about/

REPORTING RESULTS

Reporting of results may involve returning individual data to specific participants or the reporting of aggregate data more broadly. The following section discusses key considerations in communicating results to various audiences.

Reporting Individual Results

Laboratories typically report results to the health department or medical provider rather than the individual study participant. CLIA regulations include a detailed listing of what is required.

Biomonitoring study participants should be provided their individual test results as soon as practical and prior to the conclusion of the study. This requires careful coordination with the community, medical providers and public health officials to ensure that there are clinical support and risk communication teams are in place to provide appropriate answers that may result from the release of information.

The notable exception to this procedure is for participants with significantly elevated results (at identified action levels) who should be notified immediately during the course of the investigation to obtain additional information that may be relevant to the exposure, to collect a confirmatory sample or to initiate suitable medical treatment (see Rapid Results Reporting Procedure below).

REPORTING RESULTS: KEY CONSIDERATIONS

Explain that the measurement of an environmental chemical in a person's body tissues or fluid provides an estimate of how much of a chemical is present in a person but does not necessarily predict what health effects, if any, may result from that exposure.

When relevant for certain chemicals, explain that presence in the body alone does not indicate if the exposure was high or low, acute or chronic. Also explain that chemical levels in blood, serum and urine are affected by how much of the chemical has entered the body through all routes of exposure, including ingestion, inhalation and dermal absorption, and how the chemical is distributed in body tissues, transformed into metabolites, and eliminated from the body. Finally, state that biomonitoring data alone do not pinpoint the exposure source, the route of exposure nor linkages between the chemical and adverse health effects.

For biomarkers that are not specific to a particular chemical, offer possible interpretation of findings. For chemicals that are also formed as a result of a normal metabolic process (such as formaldehyde and acetone), explain that their presence cannot be attributed solely to an external exposure.

Public health agencies involved in biomonitoring should employ or contract with medical toxicologists, occupational health physicians and/or relevant medical specialists (e.g., pediatricians) to assist in crafting messages to participants. They may also directly advise participants (and their medical providers) regarding the significance of their individual results and any appropriate exposure reduction actions or medical interventions they might suggest.

Reporting Aggregate Results

Some studies report aggregate data in addition to or instead of individual participant results. Although the focus on presenting aggregate results is not the individual, highly exposed individual(s) or groups can be identified by comparing individual results to: the overall study population; comparable groups; or particular occupational groups.

Various reports may be necessary depending upon the intended use and audience. For example, a detailed report documenting all methods, protocols, analyses and findings may be needed for collaborating agencies. These may also be necessary to meet CLIA requirements. For other audiences, such as the public and policymakers, an executive summary may be more appropriate for the public and policy makers.

Report Formats

Study results are typically prepared in varied formats, such as a formal report, a summary sheet, a slide presentation for use in public forums and other techniques. Below is an example of a format for presentation of results in a formal study report.

Study Purpose

List objectives, methods, procedures, and if applicable, the study hypotheses.

Population Studied. If the sample was intended to be representative of the target population of interest, comparisons can be made to show whether the sample is truly representative of the target population for defined variables of interest (e.g., age, sex, geographic location, ethnicity).

Findings

Results for each research question should be presented individually in the same order proposed in the study objectives. For each research question, present the data, using tables and/or graphs, as appropriate. Information on the type of statistical test(s) performed and results of such tests, such as p-values, should be included.

- Summarize highlights of findings by using tables showing the analytes to which people are exposed and at what concentrations.
- Report the prevalence of people with levels above known specified toxicity levels, (e.g., a blood lead level greater than or equal to 10 micrograms per deciliter).
- Report whether exposure levels are higher among certain groups, especially potentially vulnerable groups such as the elderly, pregnant women and children.
- Report trends in levels of exposure of the population over time or geographical area if such data is available.

Interpret Findings

Provide a narrative description of what the results mean with respect to a potential health risk. When possible, the results should be put in context by comparison with other appropriate biomonitoring data (e.g., other studies of comparable populations). If applicable, describe how these data differ from the general population as reported by CDC. Investigators will need to determine if the aggregate results will include an interpretation of "normal" vs. "high." If clinical

PROVIDING INDIVIDUAL RESULTS: SPECIAL PROCEDURES AND PROTOCOLS

Rapid Results Reporting Procedure

The study design should consider rapid results communication in instances where the measured concentrations exceed an actionable level (e.g., one that meets or exceeds a Critical Call Value or Panic Level established in the laboratory SOP). In such instances, study staff with expertise in health sciences should consult with medical specialists to determine appropriate follow-up with the participant's medical provider. Study design considerations should include plans to de-identify participant results (to preserve participant confidentiality) when discussing participant results with a medical specialist or executing a new medical consent form to communicate results directly with a physician, on behalf of the participant.

Notification of Routine Test Results Protocol

If the study design includes a consideration of reporting results back to all participants, there should be an established communications protocol that addresses the interpretation and communication of results to participants. These protocols should consider the reporting of technical results to individuals at various levels of health literacy, and English language proficiency using established standards, such as HHS' *National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care* (The National CLAS Standards).[1] The protocols should also consider individuals that are vision or hearing impaired.

Results should be compared to reference populations or health-based reference values, and the interpretation should consider the differences of each type of reference value. A protocol for referral for clinical intervention should be established for any analytes with established health-based thresholds (e.g., lead, mercury, cadmium). For these analytes, the study should have established timely reporting protocols to meet clinical guidelines. It is important to include the appropriate contact information for staff that will be communicating directly with the participants.

1 HHS. National CLAS Standards. Accessed June 2019. thinkculturalhealth.hhs.gov/clas

reference values or health-based reference values are not available, determine whether other standards exist that are applicable (e.g., RfD, NIOSH RELS, other occupational standards).

Acknowledge if health-based reference values are not available but try to provide comparisons with other available data. To the extent possible it will be important to provide an explanation whether observed differences in analyte levels by age, gender, or race/ethnicity are because of the differences in exposure, pharmacokinetics (absorption, distribution, metabolism, and excretion), or the relationship of dose per body weight.

Conclusions

Recommendations may be possible at two different levels. First, the findings may be useful in setting priorities both for public health efforts to reduce exposure to specific analytes and for research on human health effects. Second, they can be used to provide recommendations for reference or comparison values that can be used by physicians and scientists to determine whether a person or group has an unusually high exposure.

Communicating Results to the Community

In communicating results to the community, explain the study methods including how study participants were chosen and how data were collected, analyzed, etc. The benefits and limitations of the study should also be clearly articulated.

Communicating with the public and policymakers requires special thoughts and skills. Effective communications provide a complete picture of potential risks while avoiding the use of technical jargon. They also acknowledge the limitations of the available information and identify areas where additional data would be beneficial to understanding the risks and uncertainties. This is especially important in communities that are affected by a known source of chemical contamination. Ongoing communication efforts and integration of audience feedback are needed to ensure clarity of key messages and about the extent to which biomonitoring can inform and/or influence government remediation actions or legal actions against a responsible party.

Typically, the dissemination of aggregated data and individual results are synchronized so that individuals have not only their specific levels but understand them within the context of their community.

COMMUNICATING TECHNICAL INFORMATION TO THE COMMUNITY

A contaminated former factory site in Colonie, New York led to concerns about possible exposure to depleted uranium (DU) among retired factory workers and local residents. In order to characterize exposure among workers and residents to DU dust over a period of many years, the New York State Department of Health's Wadsworth Center worked collaboratively with a number of groups and professions. They included the department's Center for Environmental Health epidemiologists and public health professionals, along with other stakeholders like a community organization that was involved in the design and implementation of the study. DU was measured in "spot" urine samples as a ratio of two naturally occurring isotopes (235U/238U), with measurements of 236U, which is an additional biomarker of DU.

Translating isotope ratio data into information that is meaningful to lay persons is a major challenge. The laboratory worked with the community organization and other study team partners to craft a results letter for participants so that they could understand the extent of their exposure. The letter also specified that laboratory staff were available to answer questions, which some participants took advantage of after the data were released.

For more information:

Arnason JG, Pellegri CN, Moore JL, Lewis-Michl EL, Parsons PJ. Depleted and enriched uranium exposure quantified in former factory works and local residents of NLI industries, Colonie NY USA. Environmental Research. 2016;150:629-638.

RESOURCES

APHL Biomonitoring Module (APHL)
vimeo.com/showcase/4767908?video=258108654

CLIA Law and Regulations (CDC)
www.cdc.gov/clia/php/about/

National Report on Human Exposure to Environmental Chemicals (CDC)
www.cdc.gov/exposurereport/index.html

National CLAS Standards (HHS)
thinkculturalhealth.hhs.gov/clas

Toxicological Profiles (ATSDR)
www.atsdr.cdc.gov/toxicological-profiles/about/

11. APPENDICES

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APPENDIX 1: GLOSSARY

Absorption

Process of active or passive transport of a substance into an organism: in the case of a mammal, such as a human being, this is usually through the lungs, gastrointestinal tract, or skin.

Action values (see also critical values)

Action values are those which greatly exceed the expected clinical concentration warranting immediate notification of findings by the laboratory, so that not only can additional sampling, testing, review be initiated, but also medical treatment begun, if available.

Acute exposure

Short-term (in relation to exposure or effect) single contact with a substance or repeated contact over a 24-hour period of time.

Adverse effect (or adverse health effect)

A change in biologic function or structure that leads to dysfunction or disease.

Analyte

A substance, such as a chemical, measured by a laboratory method.

Analytical chemistry[1]

Analytical chemistry is the science of obtaining, processing, and communicating information about the composition and structure of matter. In other words, it is the art and science of determining what matter is and how much of it exists.

Bioaccumulation

Progressive increase in the amount of a substance in an organism or part of an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body.

Bioavailability

Extent to which a substance to which the body is exposed (by ingestion, inhalation, injection, or skin contact) reaches the systemic circulation, and the rate at which this occurs.

Bioconcentration

Process leading to a higher concentration of a substance in an organism than in the environmental media to which the organization is exposed.

Biomarker

1. Indicator signaling an event or condition in a biological system or sample and giving a measure of exposure, effect, or susceptibility. As related to biomonitoring, a biomarker is the presence of any substance, or a change in any biological structure or process that can be measured as a result of exposure to a substance. Many biomonitoring studies focus on chemical substances or their metabolites as biomarkers.
2. Parameter that can be used to identify an effect in an individual organism and which can be used in extrapolation between species for risk assessment.

Biomonitoring

The assessment of human exposure to environmental chemicals by measuring the chemicals or their metabolites in human specimens such as blood or urine.

Biosafety engineering controls

Laboratory protective equipment that acts as the primary barrier to hazards in the lab and includes biosafety cabinets and chemical hoods.

Body burden/chemical body burden

The total amount of a substance in the body.

Case control study (see also study design)

A study that compares exposures of people who have a disease or condition (cases) with people who do not have the disease or condition (controls).

Chronic exposure/long-term exposure

Contact with a substance that occurs over a long time (usually months to years).

1 American Chemical Society. Analytical Chemistry. Accessed June 2019. www.acs.org/content/acs/en/greenchemistry/research-innovation/analytical-chemistry.html

Clean room

A confined area in which the humidity, temperature, particulate matter, and contamination are precisely controlled within specified parameters. The class of the clean room defines the maximum number of particles of 0.5-micrometer size or larger that may exist in one cubic foot of air in the designated area. For example, a class 1 clean room allows one such particle of any kind to exist in one cubic foot of space; a class 10 area may contain no more than 10 such particles in one cubic foot of space.[1]

CLIA

Clinical Laboratory Improvement Amendments

CMS

US Centers for Medicare and Medicaid Services

Cohort study (see also study design)

Looks at multiple health effects of an exposure; subjects are defined according to their exposure levels and followed for disease occurrence.

Collection blank

An empty specimen container from the same lot as the specimen containers used to collect participant specimens.

Compound

Substances composed of two or more stable chemicals.

Contaminant

A substance that is either present in an environment where it does not belong or is present at levels that might cause harmful (adverse) health effects.

Convenience sample

Participants are selected at the convenience of the scientist, not randomly.

Critical values (see also action values)

Values which may indicate higher than average exposure and typically trigger additional activities such as priority review of survey data to identify potential exposure sources or confounders as well as confirmatory or reflex testing by the laboratory.

Cross-sectional study design (see also study design)

Looks at relationship between exposure and disease prevalence in a defined population at a single point in time.

CRM (Certified reference material)

Controls or standards used to check quality.

Ecologic study (see also study design)

Looks at the relationship between exposure and outcome at population-level.

Epidemiology

Study of the distribution and the determinants of health-related states or events in populations as well as the application of the results to control health problems.

Exposure (see also acute and chronic exposure)

Contact with a substance by swallowing, breathing, or touching the skin or eyes.

Exposure assessment

The process of finding out how people come into contact with a hazardous substance, how often and for how long they are in contact with the substance, and how much of the substance they are in contact with.

Field blank

An empty container (or a container filled with high-purity solvent) the laboratory transfers to the sampling site for the purpose of determining ambient contamination levels both in the field and in the laboratory.

GC-MS/MS (see also mass spectrometry)

Gas chromatography tandem mass spectrometry; a method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a test sample.

Half-life

The time it takes for 50 percent of the original amount of a substance to disappear.

1 Chemicool Dictionary. Definition of Cleanroom. Accessed June 2019. www.chemicool.com/definition/cleanroom.html

ICP-MS (see also mass spectrometry)

Inductively-Coupled Plasma (ICP) Mass Spectrometry (MS); a method that combines a high-temperature ICP source with a mass spectrometer. The ICP source converts the atoms of the elements in the sample to ions. These ions are then separated and detected by the mass spectrometer.

IRB

Institutional Review Board.

Isotopes

Atoms that contain the same number of protons but a different number of neutrons.

Laboratory Information Management Systems (LIMS)

A class of software that receives, processes, and stores information generated by laboratory processes and often interacts with laboratory instrumentation.

LC-MS/MS (see also mass spectrometry)

Liquid chromatography tandem mass spectrometry; an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry.

Limit of Detection (LOD)

The level at which the measurement has a 95% probability of being greater than zero.

Longitudinal study (see also study design)

A correlational research study that involves repeated observations of the same items over long periods of time—often many decades; a study that evaluates changes over time.

Mass spectrometry

Mass spectrometry is a powerful analytical technique that is used to identify unknown compounds, to quantify known compounds, and to elucidate the structure and chemical properties of molecules. Detection of compounds can be accomplished with very minute quantities (as little as 10-12 g). This means that compounds can be identified at very low concentrations (one part in 1012) in chemically complex mixtures.[1]

Matrix

Specific sample types such as blood, urine or hair which in analytical chemistry are tested for the presence or absence of a compound or mixture (analyte).

Metabolism

The conversion or breakdown of a substance from one form to another by a living organism.

Metabolites

Any intermediate or product resulting from metabolism.

NHANES

National Health and Nutrition Examination Survey; ongoing survey designed to assess the health and nutritional status of adults and children in the United States.

Parent compound

A chemical compound that is the basis for one or more derivatives.

Persistence

Length of time a chemical remains in the environment or the body.

Pharmacokinetics

The study of what the body does to a drug (absorption, distribution, metabolism and excretion).

Prospective study (see also study design)

A study in which the subjects are identified and then followed forward in time.

Randomized sample

Group of items or individuals from a larger population selected in such a way that all individuals from the population have an equal chance of being selected.

Reference values

Value (or range of values) that serves as a comparator, often used as to describe what is common or normal in a population.

Risk

The probability that something will cause injury or harm.

1 American Society for Mass Spectrometry. About mass spec. Accessed June 2019. www.asms.org/about-mass-spectrometry

Samples/Specimens

Human (clinical) sample such as blood, urine, other bodily fluid or tissue taken for biomonitoring testing.

Serum

The liquid portion of blood that remains after the removal of clotting proteins and blood cells.

Statistics

A branch of mathematics that deals with collecting, reviewing, summarizing, and interpreting data or information. Statistics are used to determine whether differences between study groups are meaningful.

Study design

Broadly describes public health investigations involving human biomonitoring for surveillance, emergency response and research purposes.

Toxicant

Toxic or poisonous substance.

Toxicity

The degree to which a substance or mixture can harm humans or animals.

Toxicology

The study of the harmful effects of substances on humans or animals

UPS System

An uninterrupted power supply system is used for emergency power in the event of a power outage. This ensures computers and instrumentation do not loose information or data.

COMPILED FROM:

US Agency for Toxic Substances Disease Registry. Glossary of Terms. Accessed June 2019.
www.atsdr.cdc.gov/pha-guidance/glossary/index.html

US Centers for Medicare and Medicaid Services. Clinical Laboratory Improvement Amendments. Accessed June 2019.
www.cms.gov/clia/

APPENDIX 2: STATISTICAL ANALYSIS

Data preparation is the process of cleaning and organizing data for analysis. Data usually are gathered from many different sources, such as questionnaires, medical records and laboratory results.

Checking the data analysis results against the primary sources or original forms used for data collection is often a necessary step. In order to be able to successfully track back records, there should be protocols established before data collection is initiated. Protocols should address checking for data completeness and accuracy, recording and keeping track of data, data entry, etc.

A data element dictionary should be created. The data element dictionary should include at minimum, the variable name, description, formats, codes, null value acceptance, access privileges, collection method, location in the database for each variable.

For data that will be manually entered into a database, such as hard copy questionnaires, measures should be defined to identify entry errors. It is also good idea to develop a log for documenting all QA/QC activities—recording who, when, how and why for any updates—so that changes can be understood or undone.

Descriptive analysis is used to describe the basic features of the data in a study. This type of analysis may be sufficient by itself when the aim is to provide a reference range. When defining a reference range, consider sampled population and factors affecting pharmacokinetics of specific chemicals, such as age, body mass index, genetics, disease, medication, alcohol, and diet.

Descriptive analysis should include findings related to each analyte measured in specific biomatrix (e.g., blood, serum and/or urine) by sample size (n), percentage or results that fall below the limit of detection (LOD), arithmetic mean, geometric means and percentiles (e.g., 10th, 25th, 50th, 75th and 90th), with associated 95th percentile confidence intervals.

Geometric means or medians (50th percentile) generally are better estimates of central tendency than arithmetic means, because biomonitoring data usually have a distribution with a long tail at the upper end of the distribution. However, it is not recommended to calculate geometric means if more than 40% of data is below the LOD.[1, 2] Percentiles will provide information about the shape of the distribution. The 90th or 95th percentile can be helpful for determining whether levels are unusually high.

For each chemical, results should be presented for the total population sampled, as well as stratified by age group, gender, and race/ethnicity. Other demographic variables such as education or income may also be of interest if available.

Temporal trends can be estimated by comparing data collected over defined time periods. The non-parametric Kendall test can be used for trend detection; it is less affected by outliers, and it does not require fulfilling assumptions required for linear regression.

Inferential analysis is used to make inferences from the sampled data to more general conditions, and to look at relationships between chemical (biomarker) levels and variables relevant to the sample characteristics. For representative or population-based samples, sample weights will likely need to be applied to adjust for unequal probability of selection and also non-representativeness. Given that statistical models vary in their inferential utility, statistical consultation is recommended to determine which statistical models should be applied to the data set. Biomonitoring data are usually not normally distributed, and the data may need to be transformed or nonparametric methods may need to be employed.

1 EPA. Report on Environment, "Reporting Data Below the Limit of Detection." 2018. Accessed June 2019. cfpub.epa.gov/roe/technical-documentation.cfm?i=63&pvw=

2 CDC. About the National Health and Nutrition Examination Survey. Accessed June 2019. www.cdc.gov/nchs/nhanes/about/index.html

Statistical methods used for inferential analysis depend on data type for outcome and explanatory variables (predictors) as well as the study objective.

Depending on study design, strength of relationship between an exposure and outcome is quantified using cumulative incidence or incidence rates in a cohort study, and odds ratio in case-control study. **Table 1** below summarizes appropriate statistical analysis methods by data type.

Table 1. Guide for statistical analysis method

OBJECTIVE	DATA TYPE		
	CONTINUOUS WITH NORMAL DISTRIBUTION	RANK / SCORE	BINOMIAL / CATEGORICAL
Compare Two Groups	T-test	Mann-Whitney rank test	• Chi-square • Fisher's exact test
Compare Three or More Groups	ANOVA (Analysis of Variance)	Kruskall-Wallis	Chi-square test
Describe Direction and Strength of Relationship Between Two Variables	Pearson correlation if the distribution is normal*	Spearman correlation to quantify relationship if distribution is not normal	Contingency coefficients
Model Outcome Using Predictors	Simple or multiple linear regression		• Simple or multiple logistic regression • Factorial logistic regression • Discriminant analysis

* Biomonitoring data are usually not normally distributed. First check the data for normality and transform the data, if necessary, before applying parametric tests based on normality assumption.

Conclusion Validity

Whenever a study concludes that there is a relationship, conclusion validity should be discussed. Conclusion validity is whether a relationship is a reasonable one or not, given the data. The two possible error scenarios are: 1) to conclude that there is a relationship when in fact, there is not one (this is called Type I error or false positive or alpha (a) error); and 2) to conclude that there is no relationship when in fact, there is one (this is called Type II error or false negative or beta ß error).

In order to improve conclusion validity, researchers can choose a high statistical power, such as 0.9 or higher. This means the chances of finding a relationship when there is one (true positive) will be at least 90 chances out of 100 or more. One strategy to increase power is having a large sample size. Additionally, researchers can increase reliability by having good quality control and assurance measures as discussed above in the data quality section as well as in the sampling method section.

Caveats in Statistical Analysis of Data

Instrumentation and analytical science improvements have made comparison of studies with significant time between the studies difficult. Four common problems faced with biomonitoring health data are analytical LODs, missing data, small sample size and outliers.

Analytical LODs

LOD is the level at which the measurement has a 95% probability of being greater than zero.[1] As laboratory methods evolve, LOD values change over time. The LODs for each analyte and the proportion of samples that fall below the LOD (%<LOD) should be provided in each data table and collectively in an appendix. Methods used to assign a value to analytical results <LOD in data analysis should be described and referenced. If LOD values change during the study period, the most conservative approach is to use the highest LOD value.[2]

For most chemicals, the LOD is constant for each individual specimen analyzed. For dioxins, furans, PCBs, organochlorine pesticides, and a few other pesticides, each individual sample has its own LOD. These analyses have an individual LOD for each sample, mostly because the sample volume used for analysis differs for each sample. A higher sample volume results in a better ability to detect low levels, and a lower LOD. It is not uncommon to get results below the LOD especially when the exposure to a certain chemical is low. Various statistical methods have been developed to address this issue.[3,4,5] Therefore it is important to partner with a statistician to determine how best to interpret results and to resolve issues related to LOD.

Missing Data

The three common reasons for missing data are true missing data, refusal to answer, and "don't know." Methods for dealing with missing data must be clearly defined. First, determine if there is a pattern for missing data and if it is necessary to make adjustments to avoid non-response bias. The lower the response rate, the higher the non-response bias possibility.

Small Sample Size

Small sample size might lead to unreliable data. Combining several years of data based on sample size and power calculations might help dealing. A minimum sample size of 30 is recommended for reporting any descriptive statistics.[6]

Outliers

Methods are needed for defining, identifying, and dealing with data outliers in the data analysis. It is important to review all values defined as outliers to make sure coding errors were not made. Data can be analyzed both with and without the outlying cases to see how results differ. Justification is necessary for including or excluding outliers – including why the outlier does not really fall into the population of interest or why the outlier values differ so much from the rest. Transforming data, using square roots and logarithms, softens the impact of outliers. As a last resort, consider deleting outliers, but note how doing so changes the summary statistics.

1 US Department of Commerce. Quality Assurance of Chemical Measurements—Principals of Measurement. 1985. Accessed June 2019. nvlpubs.nist.gov/nistpubs/Legacy/IR/nbsir85-3105.pdf

2 CDC. NHANES Key Concepts About the Limit of Detection of Environmental Chemicals. Accessed June 2019. medbox.iiab.me/modules/en-cdc/www.cdc.gov/nchs/tutorials/environmental/

3 Finkelstein MM, Verma DK. Exposure Estimation in the Presence of Nondetectable Values: Another Look. AIHAJ 2001;62:195–198.

4 Lubin JH, Colt JS, Camann D, et al. Epidemiologic Evaluation of Measurement Data in the Presence of Detection Limits. Environ Health Perspect 2004;112:1691–1696.

5 Helsel D. Nondetects and data analysis: Statistics for censored environmental data. Hoboken, New Jersey: John Wiley & Sons, Inc. 2005.

6 CDC. NHANES Survey Methods and Analytic Guidelines. Accessed June 2019. wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx

APPENDIX 3:
SUMMARY OF INFORMATICS ISSUES RELEVANT TO BIOMONITORING

Once thought of as a support function, the delivery of laboratory IT services has now evolved to the point where electronic record keeping and automated data management are mission-critical components of public laboratory operations. And while laboratories may once have had complete control over essential informatics activities, more often than not, this is not the case today.

The Laboratory Information Management Systems (LIMS) and the infrastructure that supports the LIMS are among the most important technologies in a public health laboratory. LIMS are typically directly connected to analytical instrumentation. The interfacing of these analytical devices to the LIMS has become an integral part of the analytical process. LIMS implementation has become highly collaborative through efforts such as APHL and new federal data-sharing requirements which include a comprehensive set of 500 or more LIMS requirements that span across 16 specific business processes.

The LIMS themselves are highly specialized IT installations tailored to the kinds of laboratory work being performed. The long-term success of LIMS implementations requires PHL leaders to thoroughly plan and appropriately budget for the design, acquisition, installation, and maintenance phases of the LIMS project cycle.

The LIMS familiar to virtually all governmental laboratory directors is only the most visible component of the laboratory's IT infrastructure; the proverbial "tip of the iceberg." To be sure, technologies such as the LIMS and associated hardware and software are critical as-sets. However, the larger IT infrastructure also includes:

- Governance functions, such as contract oversight, budgeting for IT products and services, policymaking and other management activities.
- Technical support, including software customization, staff training, trouble-shooting and other activities to implement commercial technologies and otherwise assist end-users.

The management of IT may lie outside of the laboratory and IT services may be shared or consolidated within a larger organization structure. Like state laboratories, shared IT services arrangements can take many forms however there are some common approaches that laboratory leaders can use to negotiate with IT leaders. A recommendation is to first focus on the totality of the laboratory IT infrastructure (which is more than just the laboratory information management system). Additionally, memoranda of understanding (MOUs) and service level agreements (SLAs) are the two major tools recommended for IT services negotiations and ongoing management; these document the IT activities that are necessary for successful laboratory operations.

IT and laboratory leaders can use these tools to communicate and document the costs, risks and metrics of laboratory IT services. The documents must convey the importance and functions of laboratory services and be written in the language of the IT professional with clear business case models.

The ability to perform the following IT/informatics capabilities should be included in any MOU or SLA:

- Meet complex customer data requirements of multiple state and federal public health agencies.
- Meet rapid response times associated with emergency response and surge capacity, requires scalability and high availability 24/7.
- Store and retrieve large amounts of analytical data; fully redundant and configured for no data loss to ensure continuity of operations.
- Maintain high levels of security for infectious and toxic agencies tracked by the LIMS-Laboratory personnel with access to this data must maintain security clearance such as FBI secret security level clearance.
- Standardize laboratory data collection and reporting of measurement quality objectives to assure interoperability with other national laboratory partners.

- Better manage laboratory fiscal and business needs.
- Manage the increased complexity associated with laboratory deliverables including complex reporting and security requirements such as CDC's select agent rule, CLIA, HIPAA and MITA.
- Integrate complex analytical instrumentation and automation into data collection and reporting.
- Integrate data and interoperability connect with other laboratories and federal agencies.
- Serve within a national implementation as much as an individual state implementation, with PHLs acting as a group.
- Provide the necessary bandwidth for data communication.

While there are many perceived differences in laboratories, on closer examination and exploration— the laboratories are organized differently but had many informatics commonalities. These commonalities lead to the ability to collaborate and share common data sets. Both nationally and internationally, public health networks depend on the ability of LIMS to share data interoperably.[1]

Interoperability can be looked at as an approach to extend data collection and exchange beyond the individual laboratory and jurisdiction. As laboratories automate many current services, the future for laboratory informatics may include implementing solutions that are multi-directional that promote the goals of nation-wide laboratory data exchange.

APHL's Public Health Laboratory Interoperability Project (PHLIP)[2] is a successful interoperability model to consider for multi-laboratory biomonitoring collaborations. The goal of PHLIP is collaboration. PHLIP's vision is for improved data quality and accessibility with increased distribution of pertinent health data for faster decision making for the patient and the greater community. Learn more about the APHL Informatics Program website at aphl.org/informatics.

Table 2. IT and informatics components or services necessary for successful LIMS operation and automated data handling

IT SERVICES	COMPONENTS REQUIRED
Operational Services	• Provide system backups and other support functions • Schedule job and performance monitoring
Service/Help desk	Have systems and processes in place to efficiently and completely handle large volume (10's to 100's) of support, service and project requests daily
IT Training	Topics should include (among others as needed): • Basic network and desktop software use • Security • Regulatory requirements • Data messaging
Development Services	• Build custom reports • Implement components of the LIMS • Support other operational systems
Other	• Security enhancement tools • Legacy application modernization • Records management

1 The term "Interoperable" describes the technical requirements for bringing two systems together to work in concert with each other to serve a common purpose. Interoperability allows for discreet informatics systems to be unique in what they do and how they deal with data but, when they exchange data it is understood on a similar context.

2 APHL. Infectious Disease Messaging. aphl.org/focus-areas/informatics/initiatives/ID-messaging

APPENDIX 4: ELECTRONIC MESSAGING OF ANALYTICAL RESULTS—THE ELECTRONIC DATA DELIVERABLE

In this age of increased electronic communication, it is common for data users to request laboratory data in a standardized electronic format also known as an Electronic Data Deliverable (EDD). Reporting EDDs saves laboratory scientists time by sending data directly from a Laboratory Information Management System (LIMS), minimizing and possibly eliminating manual data entry. Additionally, EDDs reduce transcription errors and speed up data delivery in a secure manner. For the data user, EDDs save time by standardizing the data collected from multiple laboratories using multiple analyses. It also allows the use of automated data review software to approve and share data. Overall, EDDs minimize the need to harmonize and cleanse data.

Laboratories reporting confidential medical information electronically must ensure and validate periodically that electronic transmissions are consistent with hardcopy results produced and adhere to all relevant data privacy regulations and policies.

Given the extreme diversity in laboratory information management systems and the various formats and reporting requirements of response agencies, the creation of a standard to address analytical reporting of environmental health and environmental results is critical. APHL's Environmental Health Committee, Environmental Laboratory Subcommittee and Informatics Committee created a white paper, *Environmental Laboratory Electronic Data Management,*[1] as a reference document for standardized electronic data exchange. APHL also has a draft EDD, based on EPA's Environmental Response Laboratory Network data deliverable. It is matrix-independent, method-independent and program-independent in an effort to increase standardization across programs. Please contact EH@aphl.org for a copy.

Reporting the Electronic Data Deliverable

EDDs have different formats depending upon the data consumer. Sometimes the results can be provided as a spreadsheet, where every column represents a data element such as sample number, specimen type or source (e.g., urine, blood, serum), date of specimen collection, date of sample receipt, tests performed, results and result units. Results can also be provided in languages intended for machine readability such as eXtensible markup language (XML) or Health Level 7 (HL7).

An XML file is a structured file that contains data. It is a type of database. It uses author-created tags to surround and organize content, like an outline. The design goals of XML emphasize simplicity, generality, and usability over the Internet. It is a textual data format with strong support via Unicode for the languages of the world. Although the design of XML focuses on documents, it is widely used for the representation of arbitrary data structures, for example in web services. XML allows data elements to be related to each other. These relationships facilitate data review and interpretation.

Typically, clinical data is reported using HL7, which is an all-volunteer, non-profit organization involved in development of international healthcare informatics interoperability standards. "HL7" is also used to refer to some of the specific standards created by the organization (e.g., HL7 v2.x, v3.0, HL7 RIM). CDC has a version of HL7 tailored for biomonitoring and clinical chemical data exchange that can exchange associated quality control data along with the specimen results.

HL7 and its members provide a framework (and related standards) for the exchange, integration, sharing, and retrieval of electronic HL7 v2.x of the standards, which support clinical practice and the management, delivery, and evaluation of health services, are the most commonly used.

1 APHL. Environmental Laboratory Electronic Data Management. 2010. www.aphl.org/aboutAPHL/publications/Documents/EH_2010Dec_Environmental-Laboratory-Electronic-Data-Management.pdf

Including Quality Control Data within the Electronic Data Deliverable

Increasingly, data users are requesting electronic data deliverables (EDDs) that include the raw measurement quality control data that can meet unique measurement quality objectives (MQOs). APHL supports this trend: sharing quality control data, adds to certification or accreditation by providing specific accountability to each result data result set.

Data may include laboratory-generated (positive and negative control) samples, target and non-target substances, some batching information, instrument performance and calibration information. To provide this quality control data, each quality control sample is reported just like patient specimens, each with a unique specimen laboratory number and all result associated data elements like analytic name, results, analysis time, method and units.

Policies, Brokering and Nomenclature

Policies, brokering, and nomenclature details are critical technical issues for electronic data exchange. Policies are necessary to address security issues. Record content and messaging protocols are necessary to provide significant security constraints on EDDs. Data standards that include, for example, nomenclature, content, and analyte valid values need to be understood before mapping between multiple formats if possible.

Any LIMS implementation must address valid values for each data element. These constraints on the value sets define the allowable values for an EDD. For older laboratories with a legacy of method names and allowable values, these valid values may require complex translators to migrate data. Newer implementations between agencies may resolve brokerage by allowing a direct LIMS-to-LIMS data exchange where the valid values are part of the interface. More typically, data is exchanged from separate systems and requires an intermediate stage using translators to broker data exchange. These translators can be on the data generator or the data consuming end: internal facing or external facing.

Automated Data Reporting Tools

Lastly, there is a desire for data review software that can serve as a data checker to assure that data meets formatting and nomenclature requirements. Data review software is also useful for data users that seek to rapidly review reported results against client requests and method quality objectives. By providing this information, data generators and consumers can review a data submission and know that all the data measurements submitted match what the results generated.

Secure Transport of Electronic Data Deliverables

EDDs can be transported in different ways. Two issues need to be addressed: 1) the transport mechanism and 2) the security of the data. Sharing of patient information is regulated under HIPAA and requires strict security measures.

The most basic approach (and least recommended) to transport data is to attach a spreadsheet EDD to an email and send the email. This option is considered easy for the data generator to send and the data consumer to receive, but this approach limits program data review and automated usage and provides limited data security.

Clinical data transport in the realm of healthcare is highly secure and employs machine readable messages. The current approach for data transport of public health infectious disease information is to place the data into an HL7 message. To use a metaphor: HL7 is the letter, and PHIN MS is the postal carrier (requires envelopes to look just so in order to deliver them). PHIN MS is one such messaging option. Others include NHIN Direct, Active encryption, Certificates (state and other authorities), VPN, SSL, sFTP.

APPENDIX 5: EXAMPLES OF INFORMED CONSENT DOCUMENTS

[INTRODUCTORY LANGUAGE]
Thank you for your interest in the NH TrACE Study (Tracking and Assessment of Chemical Exposures), which is being conducted by Biomonitoring*NewHampshire*. If you have already agreed to participate and taken this survey, please do not take it again. To modify one of your answers, please call a representative of the BiomonitoringNH program at 603-271-4611 or BiomonitoringNH@dhhs.nh.gov.

This survey should take 20 to 30 minutes. You must complete the entire survey in one sitting, otherwise your responses will be lost.

NH Public Health Laboratories
Information and Informed Consent Form

Title: 2019 NH TrACE Study
Principal Investigator: Dr. Christine Bean
Institution: NH Public Health Laboratories
Address: 29 Hazen Dr., Concord, NH 03301
Phone: (603) 271-4611
Email: BiomonitoringNH@dhhs.nh.gov

This consent form explains the study. Before you decide to be part of this study, you need to know why the study is being done, what it will involve, and the risks and benefits. Ask study staff to explain anything in this form or if you want more information (see above for contact information). Please take time to read this form carefully. Feel free to discuss it with your relatives, friends, and your primary care provider. If you agree to take part in this study, you must sign this consent form. Children aged 7-12 will have the ability to read a shortened form written to their age level.

KEY INFORMATION ABOUT THIS STUDY

The following information is an overview of the study to help you decide whether you want to participate. More detailed information is presented on the following pages.

Purpose:
The New Hampshire Department of Health and Human Services (NH DHHS) is coordinating this project to evaluate whether NH residents age 6 and older are coming into contact with certain chemicals from the environment. Your blood, urine, and household water will be tested for many chemicals. A list of these chemicals can be found on the study webpage: https://www.dhhs.nh.gov/programs-services/population-health/public-health-laboratories/biomonitoring/tracking-and

Voluntary Participation:
Your decision to be in this study is voluntary.

Withdrawal:
If you decide to be in this study and then change your mind, you can leave the study at any time without penalty.

Length of Participation:
Your participation will take place over the next few weeks, however the time you spend on this study will only be a few hours. You will receive a $25 Walmart gift card and free household water testing to thank you for your commitment to this study.

Main Study Procedures:

- Complete the exposure survey
- Have your blood and urine collected
- Have your household water collected
- You will **NOT** receive any experimental drugs or procedures as part of this study

Risks:
There is no anticipated risk to you for completing the survey. Besides the usual risks of having your blood drawn, some people may find knowing the levels of chemicals in their body distressing because it is not known whether those chemicals will affect your long-term health.

Benefits:
You will get many benefits from this study. Your home will receive free water testing for many chemicals, which may help you decide whether you need to make changes to your home water system. If you choose to receive your results, you will also learn whether your body contains chemicals from the environment. With that knowledge, you will be better informed to make lifestyle changes so you can live a healthier life.

Costs:
There is no cost to you to participate. Study staff will pay for your blood and urine collection and testing and your water testing.

Confidentiality:
There are procedures in place to help protect the privacy and confidentiality of your personal health information and study information.

This overview does not include all of the information you need to know before deciding whether or not participate. Much additional detail is given in the full consent document, which can be found on the pages that follow.

NH Public Health Laboratories
Informed Consent Form

Purpose
The New Hampshire Department of Health and Human Services (NH DHHS) is coordinating this project to evaluate whether NH residents age 6 and older are coming into contact with certain chemicals from the environment. There are many ways you may come into contact with these chemicals:

- From your job
- From the foods and beverages you consume
- From the air you breathe
- From the products you use in your home or
- From the things you like to do for fun, to name a few.

The following survey asks questions to determine how you may come into contact with these chemicals. Please answer the questions to the best of your ability. These answers, along with your blood, urine, and water results, will give us insight into how you have come into contact with these chemicals and how much of them get into your body. This information will not tell you whether you will get sick or develop a health effect or disease from these chemicals. This is because many factors play into whether you experience a health effect, like your age, nutrition, general health status, and genetics, among many others. You will **NOT** receive any experimental drugs or procedures as part of this study. You will have the option to choose whether you want to receive printed copies of your blood/urine and/or water results.

Study staff use data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Survey (NHANES) to identify average levels of chemicals in the U.S. population. You will be contacted by study staff if your blood or urine results indicate a high level of exposure when compared to national averages. You will also be contacted if the chemicals in your water exceed the maximum contaminant levels set by the Environmental Protection Agency and the State of New Hampshire. You may be offered additional blood, urine, and/or water testing depending on your results; you can choose to decline this testing. You will still receive your incentive gift card.

How to qualify, who can participate, and what you can expect if you participate:
Your decision to participate in this study is voluntary. To be able to participate in the NH TrACE Study, you must be:

1) At least six (6) years of age (with parent/guardian consent if you are younger than 18 years old),
2) A New Hampshire resident who lives in NH full-time for at least six (6) months of the year,
3) Non-institutionalized (this means you do not live in a hospital, treatment center, or prison; it is okay if you live at a school or in a nursing home), and
4) Mentally capable of understanding the purpose and potential consequences of the study.

Enrollment is on a first-come, first-served basis. As the study gets closer to the end of enrollment, participants may be selected based on geographic area and other demographics (such as age and ethnicity) in order to ensure that the people in this study are a representative sample of New Hampshire. The study will be closed after 400 participants have been selected or by September 30, 2019, whichever comes first. **Click on the following link to see whether enrollment has ended in your area or for your demographic (age, sex, household water source, etc.):**

https://www.dhhs.nh.gov/programs-services/population-health/public-health-laboratories/biomonitoring/tracking-and. **Please exit this survey if enrollment has ended for your area or demographic.**

Everyone in your household who meets the above qualifications is eligible to participate. Each interested person must complete this survey. **A parent or guardian must assist any child under 13 with completing this survey.**

Once your completed survey has been submitted, you will be mailed a collection kit with instructions on how to get your blood drawn and urine collected at a local medical facility. There is no fee associated and you do not need medical insurance for this because BiomonitoringNH will pay for the cost of the collection. Your blood/urine collection kit will be mailed to you within one (1) week after you complete the following survey. You will have three (3) weeks from the day you complete your survey to have your blood and urine collected or until September 30, 2019 (whichever comes first). The kit will provide instructions on where you can go to have your blood and urine collected.

After this step, one person from your home will be contacted by the NH Department of Environmental Services (NHDES) regarding the collection of your household water sample. Only one set of samples is needed per household. NHDES staff will schedule this collection during business hours: Monday through Thursday, 8am-4pm and Friday, 8am-noon. Travel time of staff (from Concord, NH) will also be within these hours. You will have three (3) weeks from the day you have your blood and urine collected to have your water samples collected or until October 31, 2019 (whichever comes first). You will need to provide NHDES access to any water filtration system, water treatment system, or water storage tank (if you have one). One person from your home will also need to collect a "first draw" water sample from your kitchen sink on the morning of the day that NHDES will go to your home to collect the rest of your water samples. You will be provided the instructions and materials needed for this collection. These materials will be included in the collection kit that will be mailed to your home once you have completed this survey. Only one person in your home will receive the collection materials and instructions for this "first draw" sample collection.

Once your blood, urine, and household water are collected, you will be mailed a gift card to thank you for your time and commitment to this project. Each person who completes the study process (survey, blood/urine collection, and water collection for their home) will receive a $25 gift card to Walmart. Your household will receive free water testing for many chemicals and some bacteria. You will be given the option to receive all of your blood, urine, and water results. If you choose to receive these results, it is recommended that you share them with your health care provider. Your participation is expected to last up to six weeks depending upon how quickly you have your blood/urine and water samples collected. The total amount of time you will need to devote to this study though is only a few hours. More information about this study (including a list of chemicals that your urine, blood and water will be tested for) can be found on the study webpage: https://www.dhhs.nh.gov/programs-services/population-health/public-health-laboratories/biomonitoring/tracking-and

This authorization does not have an expiration date. In other words, if you decide to be in this study and then change your mind, you can leave the study at any time without penalty. Email the Biomonitoring*NewHampshire* Program at BiomonitoringNH@dhhs.nh.gov if you would like to leave the study. Please note: if you leave the study without completing all study processes (survey, blood/urine collection, and water collection), then you are not eligible to receive the $25 Walmart gift card. If you leave after your blood, urine, or water has been collected, then you will still have the option to receive

those test results. Information that has already been gathered may still be used if it were necessary for the study data to be reliable.

Procedure

You will be asked survey questions on ways you may have come into contact with these chemicals. Your blood, urine, and household water will be tested to see if they contain these chemicals. A list of these chemicals can be found on the study webpage: https://www.dhhs.nh.gov/programs-services/population-health/public-health-laboratories/biomonitoring/tracking-and. Your household water samples will be collected by NHDES. These samples will be analyzed for a variety of water quality factors and that information will be shared with NHDES for scientific purposes or to help you design a water treatment system, should the need exist. The New Hampshire Public Health Laboratories and NHDES contracted water laboratories will perform this testing at no cost to you ($0). If you choose to receive your results, your water results and the majority of your blood and urine results will be returned to you as soon as they are completed, which will take eight to sixteen (8-16) weeks. The rest of your blood and urine results will be returned at the end of the study so you can compare your levels to other people in the study. The results of others in the study will be aggregated (combined); no one will be individually identified. You will receive a $25 gift card to Walmart when you complete the study process, which includes the survey, blood and urine collection, and household water collection.

You may be contacted earlier if a second sample of your blood, urine, and/or water is necessary or if it is important for you to share your test results with your primary care provider (PCP) right away. You can contact study staff to discuss your test results or you can speak with a medical consultant at the Northern New England Poison Center.

You may qualify for additional water testing based on the results of your blood and urine testing. If you qualify, you will be informed to contact NHDES for additional free water testing. You are NOT required to have this additional water testing as part of your participation in this study; this additional testing is purely for your benefit to ensure that your drinking water is safe.

Financial and technical assistance for this study is being provided through cooperative agreement with the Centers for Disease Control and Prevention (CDC) Division of Laboratory Sciences at the National Center for Environmental Health RFA EH14140202. The contents of these pages do not necessary represent the official views of the CDC.

Risks of Participation

There is no anticipated risk to you for completing the survey. Besides the usual risks of having your blood drawn, some people may find knowing the levels of chemicals in their body distressing because it is not known whether those chemicals will affect your long-term health.

Benefits of Participation

You will get many benefits from this study. Your home will receive free water testing for many chemicals, which may help you decide whether you need to make changes to your home water system. If you choose to receive your results, you will also learn whether your body contains chemicals from the environment. With that knowledge, you will be better informed to make lifestyle changes so you can live a healthier life.

CONFIDENTIALITY AND AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

All personal information, including blood and urine test results and survey responses, will be kept confidential according to New Hampshire and federal laws. NH DHHS and NHDES project staff as well as other public health authorities such as the Centers for Disease Control and Prevention (CDC) may be given access to your information to assist with addressing individual and community health concerns to the extent that it is required to do so by law. **Your urine and blood samples will not be screened for drugs or alcohol and your individual responses to questions about tobacco and alcohol use (legal or otherwise) will not be shared with anyone. Individual results of cotinine (a breakdown product of nicotine) testing will not be shared with anyone.** All of your confidential information will be kept in a secure database or file at all times. You will be given the option to receive a copy of your blood and urine results. If you choose to receive these results, it is encouraged that you share them with your health care provider. You will also be given the option to receive a copy of your water results. NHDES will not release names or identifying information related to your water results except to the extent that it is required to do so by law. If you have any questions about the water testing process, please contact NHDES at (603) 271-7174. For questions about the survey or blood and urine testing, please contact the BiomonitoringNH Program at (603) 271-4611 or (603) 271-5113 during normal business hours.

The study institution will use your medical information collected or created as part of the study, such as test results and demographics. Some of this information may identify you by name or in another way. The purposes for using and sharing your medical information include: to carry out the research study and evaluate its results and to meet government reporting requirements. Results of this research may be presented at meetings or in publications. Your name will not be used in any study reports or presentations. You have the right to review and copy your health information, but you may not be allowed to do so until after the research is completed.

Questions, Complaints, or Concerns

Please contact the Biomonitoring*NewHampshire* Program at (603) 271-4611 or (603) 271-5113 during normal business hours. You may also email the program at BiomonitoringNH@dhhs.nh.gov.

If you have any questions about your rights as a participant, complaints regarding this study, or you are unable to reach the Biomonitoring*NewHampshire* staff, you may contact a person independent of the study team at the Biomedical Research Alliance of New York Institutional Review Board (BRANY IRB) at (516) 318-6877. Questions, concerns, or complaints about the study can also be registered with the BRANY IRB at www.branyirb.com/concerns-about-research.

Statement of Consent

I have read this consent form and have been informed of the risks involved. I understand that NH DHHS will not be able to tell me whether or not chemicals found in my blood or urine will impact my health. I have had the opportunity to ask questions and I know that the study staff will answer any future questions I may have. I understand that my water quality results will be shared with NHDES. I acknowledge that I will be receiving a $25 Walmart gift card from the NH Division of Public Health Services, Bureau of Public Health Laboratories for participation in a public health study. I agree to use the gift card for my personal use and understand the gift card may not be used for the purchase of alcohol or tobacco products. I voluntarily agree to participate in this study.

I understand that I am only eligible to receive a $25 gift card if I fulfill ALL of the following requirements:

- My blood and urine samples must be collected within 3 weeks of when I complete this survey (by *[auto-populate the date 3 weeks out]*) or by September 30, 2019 (whichever comes first). *If you know that you cannot collect your blood and urine samples by* [auto-populate 3-week date] *or by September 30, 2019 (whichever comes first), please exit the survey now.*
- My household water samples must be collected within 6 weeks of when the first person in my home completes this survey (by *[auto-populate the date 6 weeks out]*) or by October 31, 2019 (whichever comes first). My household water samples must be collected AFTER urine and blood samples have been collected from all study participants in my home. *If you know that you cannot collect your water samples in this timeframe, please exit the survey now.*
- The study will be closed after 400 participants have been selected or by September 30, 2019 (whichever comes first). I must have completed my blood and urine sample collection no later than this date. (More information about your sample collection will be provided at the end of this survey.)
- If others in my household are participating, then in order for each of us to receive a $25 gift card: 1) we must all complete our survey, 2) we must all have our blood and urine samples collected, AND 3) our household water samples must be collected.
- Participants with a private well: If I disinfect my private well between today and the day that I schedule with NHDES to collect my water samples, then water samples will not be collected from my home and I will not be eligible to receive a $25 gift card. *If you must disinfect your private well, please exit the survey now and complete the survey no sooner than the day after you disinfect you private well.*

Release and Waiver of Liability:
By submitting the consent form and participating in the study, you agree to indemnify and hold harmless the State of New Hampshire, its agents, officers and employees from any and all legal liability or claims for any injuries or damages of any kind which may arise or are claimed to arise during or subsequent to participation in this testing program. *In other words, you cannot hold the State of New Hampshire, its agents, officers and employees responsible for any harm or injury you may experience from knowing what chemicals (and how much) are in your body and your drinking water. This is also true for having your blood drawn and urine collected because your samples will be collected at a local medical facility and not by the State of New Hampshire.*

Please select one. Parent/guardian consent is required for anyone under 18 years old.
☐ I am a parent or guardian of a participant who is 6 years old. *[Reflexes to Option 1, see page 8]*
☐ I am 7-12 years old and my parent or guardian is helping me participate in this study. *[Reflexes to the assent form, see pages 10-11]*
☐ I am 13-17 years old. My parent or guardian may help me participate in this study. *[Reflexes to Option 3, see page 8]*
☐ I am over 18 years old. *[Reflexes to Option 4, see page 8]*
☐ I will not be participating in this study. *[Reflexes to end of survey "CLOSING LANGUAGE (NOT QUALIFIED)"]*

Consent for participation. I have read and understand all the information presented.

[Option 1]
Please type the name of the participating 6-year-old child (first and last):_____
Please type your legal name (first and last) as the consenting parent/guardian and today's date. You must also provide a phone number to complete the consent process.
Type your legal name (first and last):_____
Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____
Parent/guardian phone number:_____

[Option 3]
You and your parent/guardian must type your legal names (first and last) and today's date. Your parent/guardian must also provide their phone number to complete the consent process.
Child 13-17:
Type your legal name (first and last):_____
Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____
Consenting parent/guardian:
Type your legal name (first and last):_____
Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____
Parent/guardian phone number:_____

[Option 4]
Please type your legal name (first and last) and today's date to complete the consent process.
Type your legal name (first and last):_____
Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____

As previously stated, you **will** be contacted if the results of your urine or blood (clinical) testing should be shared with your primary care provider (PCP) right away or if the results of your water testing show that additional water testing is needed. However, you have the option to receive the printed results of your clinical and water testing in the mail. Please indicate your preference below. When your results are ready, you will be reminded of your selection (via email) at which time you can choose to change your mind.

Please indicate your reporting preference:
☐ I would like to receive the results of my urine, blood, and water testing.
☐ I would like to receive the results of only my urine and blood testing. This means I will NOT receive the results of my water testing.
☐ I would like to receive the results of only my water testing. This means I will NOT receive the results of my urine or blood testing.
☐ I do NOT wish to receive any results. This means I will NOT receive the results of my urine, blood, or water testing.

May we keep your samples?
☐ YES: I agree to have my blood and urine samples de-identified and tested for other contaminants or health indicators in the future. De-identified means my name and other identifying information will be removed. I will not receive any test results from additional testing that occurs outside of this study because my sample will have been de-identified; however my sample will help further the knowledge of chemical contamination in New Hampshire and the United States. This means my sample could be used for future research studies without additional informed consent from myself or my parent or guardian.
☐ NO: My sample will be destroyed when the study has been completed.

Please print your signed consent form for your future reference.

Thank you. You may now begin the survey.

(This is only made available if the participant selected "I am 7-12 years old" on page 7)
Please have the child aged 7 to 12 read this information before consenting to participate in the study.

NH Public Health Laboratories
Information and Assent Form - Children Ages 7-12

Title: 2019 NH TrACE Study
Principal Investigator: Dr. Christine Bean
Institution: NH Public Health Laboratories
Address: 29 Hazen Dr., Concord, NH 03301
Phone: (603) 271-4611
Email: BiomonitoringNH@dhhs.nh.gov

- I was randomly invited to be in this study.
- I can say "Yes" or "No" to being in this study.
- I can ask as many questions as I like before I decide to be in this study. You or your parents can contact us at the phone number or email above.

Why is this study being done?
This study may help scientists learn more about chemicals from the environment and whether they are getting into your body. The scientists are testing blood, urine, and water to learn more about these chemicals and your health.

About 400 other children and adults around New Hampshire will be in this study.

What will happen if I am in this study?
- I will be in this study for about 6 weeks, but it will really only take a couple hours of my time.
- I will need to have my blood and urine collected.
- About 3.5 teaspoons of blood will be collected from me using a needle.
- I will be asked to pee in a cup for tests on my urine.
- My home water will be collected and tested.
- I will get a $25.00 gift card to Walmart as a thank you for participating if my blood, urine, and water are collected.

Can I get hurt in the study?
The needle will hurt like a pinch and I might get a bruise or feel dizzy. The hurt will go away after a little while.

Will this study help me?
Being in this study might not help me, but the scientists hope to learn more about the chemicals in me so that it might help other children in the future.

Do I have to be in this study?
- I do not have to be in this study, even if my parent or guardian wants me to be.
- I can say "No". No one will be mad at me.
- If I say "Yes" now, I can change my mind at any time. I just have to tell my parent or guardian or the study staff that I want to stop. I don't have to say why. Just email the study staff (or ask

your parents to email the study staff) at BiomonitoringNH@dhhs.nh.gov if you want to stop participating.

Consent for participation. I have read and understand all the information presented.
You and your parent/guardian must type your legal names (first and last) and today's date. Your parent/guardian must also provide their phone number to complete the consent process.
Child 7-12:

Type your legal name (first and last):_____

Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____

Parent/guardian: Type your name (first and last): _____

Enter today's date (*Auto-populated date, mm/dd/yyyy*):_____

Parent/guardian phone number:_____

(After signing, reflexes to top of page 9)

[END OF 2019 TrACE Study CONSENT]

NH DIVISION OF Public Health Services
Improving health, preventing disease, reducing costs for all

New Hampshire Public Health Laboratories
Arsenic and Uranium Public Health Study
Informed Consent Form
(18+ or parent/guardian of child 5-11)

The purpose of this study is to determine whether there is arsenic and uranium in your well water and if those minerals are present in your body. Approximately 550 subjects will be enrolled into this study.

Summary
You will be asked survey questions on ways you may have come into contact with arsenic or uranium. Your water and your urine will be tested to see if they contain these minerals. If your urine contains arsenic above a certain level, then your urine will be tested for different forms of arsenic. This will help tell you how the arsenic is getting into your body. The New Hampshire Public Health Laboratories will perform this testing for free.

Your water will also be tested for other chemicals at no cost to you ($0). This is our way to thank you for your time and participation. Your water results will be returned to you as soon as they are completed. Your urine results will be returned at the end of the study. You may be contacted earlier if a second urine specimen is necessary or if it is important for you to share your test results with your doctor. You can ask study staff for help interpreting your test results or you can speak with a medical consultant.

Your participation in the survey and this study is voluntary; you can refuse to participate or stop participating at any time without any penalty or loss of benefits to which you are otherwise entitled.

You may contact the Study Coordinator, Amanda Cosser, at (603) 271-4611 or the Principal Investigator, Dr. Christine Bean, at (603) 271-4657 if you have any questions or concerns about the study. If you have questions about your rights as a research subject or you want to voice a complaint or concern, you may contact the BRANY IRB at (516) 318-6877 or at www.branyirb.com/concerns-about-research.

_____ Initial here if you would like to be contacted for future studies.

Risks of Participation
There is no anticipated risk to you for completing the survey or lab testing, and all of your information will be kept confidential. Records identifying you as participant will be kept confidential and any published results will not reveal your identity.

Benefits of Participation
You will get many benefits from this study. You will receive a free water test for many chemicals which will help you decide whether you need to make changes to your home water system. You will also learn whether your body contains an unhealthy amount of arsenic and/or uranium. With that knowledge, you can make lifestyle changes so you can live a healthy life.

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BRANY IRB approved 12/08/2017 through 12/07/2018.

CONFIDENTIALITY AND AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

To the extent allowed by law, every effort will be made to keep your personal and medical information confidential. However, total confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

The study institution and study doctor will use your medical information collected or created as part of the study, such as medical records, test results, research records, and billing information. Some of this information may identify you by name or in another way. The study institution and study doctor may obtain your medical information that they request for study purposes from your physicians and your other health care providers and may also inspect and copy this information.

The study doctor and staff may use and share information about you and your health with other professionals involved in the study, such as the FDA, Biomedical Research Alliance of New York Institutional Review Board, accrediting and regulatory agencies, and health insurers/payers. These groups may then also share your personal health information, in which case it may no longer be covered by federal privacy laws.

The purposes for using and sharing your medical information include: to carry out the research study and evaluate its results, to seek marketing approval for new products resulting from this research, and to meet government reporting requirements. Results of this research may be presented at meetings or in publications. Your name will not be used in any study reports or presentations. You have the right to review and copy your health information, but you may not be allowed to do so until after the research is completed.

This authorization does not have an expiration date. You have the right to cancel your consent at any time by giving written notice to the study doctor. If you withdraw your permission, you will not be able to continue in this study, but you will not lose access to treatment or other benefits to which you are entitled. When you withdraw your permission, no new health information about you will be gathered after that date. Information that has already been collected may still be used and given to others.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Notice Concerning HIV-Related Information: HIV-related information that either is collected as part of the research or that may already exist in your medical record might be accessed for the research by the research staff and the study sponsor, but will not be shared with others without your authorization, unless federal or state law requires the disclosure. You have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at 212-480-2493 or the New York City Commission on Human Rights at 212-306-7450. These agencies are responsible for protecting your rights.

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Statement of Consent

I have read this consent form and have been informed of the risks involved. I have had the opportunity to ask questions and I know that the study staff will answer any future questions I may have. I will be given a copy of this signed consent form to keep. I voluntarily agree to participate in this study.

_____	_____	_____
(Print your name here)	(Sign your name here)	(Date)

_____
(Child's name, if applicable)

_____	_____
(Printed name of person obtaining this consent)	(Date)

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NH DIVISION OF Public Health Services
Improving health, preventing disease, reducing costs for all

New Hampshire Public Health Laboratories
Arsenic and Uranium Public Health Study
Informed Assent Form
(Ages 12-17)

You are being asked to be in a public health study. A public health study is a special way to learn about something. We are trying to find out whether the water you use at home contains arsenic and uranium and if those minerals are getting into your body.

Summary
You will be asked survey questions on ways you may have come into contact with arsenic or uranium. Your urine will be tested at the New Hampshire Public Health Laboratories to see if it contains these minerals. If your urine contains arsenic above a certain level, then your urine will be tested for different forms of arsenic. This will help tell you how the arsenic is getting into your body. This testing is free and your test results will be returned at the end of the study. You may be contacted earlier if study staff need a second urine specimen or if it is important to share your test results with your doctor. You can ask study staff for help interpreting your test results or you can speak with a medical consultant.

Your parents (or guardians) must say it is okay for you to be in this study. This study will not cost you or them any money. You can ask the study staff questions at any time. Answering the survey questions and being in this study is voluntary; that means you can stop participating at any time. You can call us at (603) 271-4611 or (603) 271-4657 if you have any questions and/or concerns.

_____ Initial here if you would like to be contacted for future studies.

Risks of Participation
There is no anticipated risk to you for completing the survey or lab testing and all of your information will be kept confidential. That means we won't share your answers with anyone.

Benefits of Participation
You will benefit from this study because you will learn whether your body contains an unhealthy amount of arsenic and/or uranium. With that knowledge, you can make lifestyle changes so you can live a healthy life.

Statement of Consent
I have read this form and been told the risks and benefits involved with being in this study. I have had the chance to ask questions and know I can ask more questions in the future. I will be given a copy of this signed assent form to keep. I voluntarily agree to participate in this study.

_____	_____	_____
(Print your name here)	(Sign your name here)	(Date)
_____	_____	_____
(Printed name of parent/guardian)	(Parent/guardian signature)	(Date)
_____	_____	
(Printed name of person obtaining this assent)	(Date)	

BRANY

Version A

BRANY IRB approved 12/08/2017 through 12/07/2018.

APPENDIX 6: CHAIN OF CUSTODY

Maintaining and processing Chain of Custody (COC) is an important aspect to any study involving human samples. Sample tracking is a vital part of biomonitoring. Some states maintain a strict chain of custody. Programs should consider whether a strict chain of custody is necessary. This appendix includes a comprehensive example based on one laboratory's process and documents.

Initiating and Maintaining a Chain of Custody Document

Once a sample has been determined to require a COC, the Sample Collector must initiate the COC.[1] The COC is initiated and maintained by all who transport and/or receive the sample within an organization/hospital. This legal document helps to ensure that the integrity of the sample is preserved. Do not transport chain-of-custody forms with specimens. Once the specimens leave the facility, the chain-of-custody stays behind. Each entity or organization handling the specimens is responsible for the specimens only during the time that it has control of the specimens. Each entity or organization receiving the specimens must sign-off on the chain-of-custody form of the entity or organization relinquishing the specimens to close that chain. Electronic procedures such as electronic chain-of-custody and barcode readers will expedite this process. When receiving specimens, each new entity or organization must begin its own chain of custody. The entity or organization relinquishing the specimens must sign its chain of custody to close the chain and indicate that they have transferred the specimens.

> **Note:** When the person relinquishing the specimens (relinquisher) and the person receiving the specimens (receiver) are not together at the time of specimen transfer, the relinquisher must document on its chain-of-custody form that the receiver is the express courier (e.g., FedEx, Delta Dash, DHL, UPS) and must document the shipment tracking number or have the person transporting the specimens sign the chain-of-custody to indicate that he or she has taken control of the specimens. Likewise, when receivers get the specimens, they will document on their chain-of-custody form that the relinquisher is the express courier (and provide the tracking number) or have the person transporting the specimens sign the chain-of-custody form.

Instructions

- Ensure that the Clinical specimen ID numbers (or a range of ID numbers for multiple specimens) is provided in the designated space.
- The Sample Collector first prints and then signs their name.
- The "Date" and "Time" must reflect the actual time of collection.
- The "Organization" line must include the **full name** of the organization/hospital (no acronyms).
- Include the full mailing address and telephone number of the organization/hospital.
- Any person subsequently receiving or transporting the specimen must fill out the next "Received by" section of the COC.
- Continue these steps for all subsequent Sample Couriers/Operators or Sample Custodians until the sample leaves the organization.
- Once sample has left the organization, keep the COC internally for your records.

> **Note:** The "Date" and "Time" must reflect the **precise** time and date at which custody was transferred from the previous person to the new person. Because this information relieves the previous person from custody, it is essential that the new Sample Custodian notes this date and time as precisely as possible. Also, include the new Sample Custodian's name (printed), signature, and telephone number in the spaces provided Under "Organization," include without acronyms the organization represented by the new Sample Custodian.

1 The Sample Collector may either use his/her organization's own COC or the one provided by your laboratory. All fields must be filled in completely with ink.

In general, a sample requiring a COC will follow a path as follows:

Sample Collector > Sample Courier/Operator > Sample Custodian

However, it is important to note that anyone who receives or transports a suspect Select Agent must complete the appropriate section(s) of the COC.

Acronyms and Definitions

Chain of Custody (COC)

A written legal document used to track the transfer of a sample(s) from person to person.

Sample Collector

For clinical samples sent from hospitals, this would be the person forwarding the sample to the CTRL.

Sample Courier/Operator

The person responsible for transporting the sample from the Sample Collector to the CTRL.

Sample Custodian

The person who receives the sample (e.g., CTRL personnel), and has demonstrated competency in handling of samples and maintaining a COC.

Sample: External Chain of Custody Document

External Chain of Custody Report

Agency Name: _____

Laboratory Name: _____

City, State ZIP: _____

Instructions

This form must be completed for any specimen that might be used in enforcement proceedings or litigation.

Transportation

During transportation of the specimen from collection site to the laboratory, the chain of custody must be unbroken. If the integrity of the specimen is questionable, describe the problem on the reverse side of this form.

Table 3. Example chain of custody document

IDENTIFYING #	COLLECTION DATE	SPECIMEN TYPE	NUMBER OF SPECIMENS	COMMENT
		☐ Blood	#	
		☐ Urine	#	
		☐ Blood	#	
		☐ Urine	#	
		☐ Blood	#	
		☐ Urine	#	
		☐ Blood	#	
		☐ Urine	#	
		☐ Blood	#	
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		☐ Urine	#	
		☐ Blood	#	
		☐ Urine	#	
		☐ Blood	#	
		☐ Urine	#	

Sample Custody of Specimens Document

Name: _____

Affiliation: _____

Date: _____

Time: _____

Specimens Collected by / /

Specimens Shipped by / /

Specimens Received by / /

Specimens Received by / /

Specimens Received by / /

Specimens Received by / /

Specimens Received by / /

Specimens Received by / /

Specimens Received by / /

Received [Insert Laboratory Name] by / /

APPENDIX 7: CLINICAL METHOD VALIDATION EXAMPLE

Validation Plan for Analyte Detection In Human Urine by Liquid Chromatography / Inductively Coupled Plasma-Mass Spectrometry

This plan outlines the validation for measuring various analytes in urine by Liquid Chromatography/ Inductively Coupled Plasma Mass Spectrometry (LC/ICP-MS). This is simply provided an example; all biomonitoring work should follow all the data quality objectives practiced by the respective public health laboratory or sponsoring organization.

1. **Accuracy**
    a. Two controls (high and low) for each analyte will be run 20 times each.
    b. The percent recovery for each test value will be calculated.
    c. Percent recovery = [test value/actual value*100]
    Note: Percent recover must be between 80-120%
2. **Precision:** intra- and inter-run variability
    a. Two concentrations (high and low) of each analyte will be run.
    b. Twenty replicates of each concentration will be run over a minimum of two runs on different days.
    c. The following calculations will be performed:
        I. Mean
        II. Standard deviation
        III. % CV
        Note: The within-run % CV must be < 10% and the % CV for samples run on both days must be < 15%
3. **Specificity:** Run individual species standards (made from neat standards) to verify retention times of each species.
4. **Range Validation**
    a. **Linearity:** correlation coefficient (R2)
        I. A standard curve consisting of five levels (e.g. 1 ppb, 5 ppb, 10 ppb, 50 ppb, 100 ppb) will be run for each analyte to assess linearity of the standard curve.
        II. Each level of the standard curve will be run in triplicate.
        III. The mean of the three values will be determined.
        IV. The correlation coefficient of the standard curve using the mean values will be determined.
        Note: The correlation coefficient must > 0.990.
    b. **Analytical Sensitivity:**[1] the smallest amount of an analyte in the sample that can accurately be measured by the method.
        I. Limit of Detection: CLSI C-17-A2[2]
        II. For each analyte, a blank urine sample will be spiked to equal the concentration the lowest calibration standard.
        III. Seven replicates will be analyzed (n=7).
        IV. The standard deviation (SD) will be calculated.
        V. Using the equation [MDL = (SD) X (3.143)],MDL will be calculated.[3]

1 Taylor, JK. Quality Assurance of Chemical Measurements—Principals of Measurement. CRC Press LLC. Boca Raton, FL. P:79

2 CLSI. EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. 2012. clsi.org/media/1430/ep17a2_sample.pdf

3 3.143 is the student t value for n-1 Degrees of Freedom

5. **Reportable Range:** the numeric range of analyte concentration over which the method is able to produce certifiable accurate values.
   Linearity beyond upper boundary of curve will be demonstrated:
   a. A spiked sample 2x the concentration of the highest calibration standard (200 ppb) will be run as part of the standard curve.
   b. The curve must demonstrate linearity (R2 ≥ 0.990).
   c. The sample will then be diluted, run again, and the concentration calculated.
   d. The two values must be within the criteria established by the laboratory, typically +/- 10-20%.
6. **Reference Range:** Varies by analyte/matrix combination and/or age or occupational sub-populations.
7. **Westgard Rules**[1]
   a. The mean data will be plotted along with +/- 2SD and +/- 3SD.
   b. The data will automatically be evaluated by Westgard Rules, and any failing results will be flagged.
   c. If a run fails the Westgard rules, it will be rejected.
   d. When the data passes the Westgard rules, it will be accepted for validation statistics.

Table 4. Westgard Rules

RULE	REJECTION PARAMETERS	ERROR
1_{3S} Rule	Run result is outside a 3SD limit	Random Error
2_{2S} Rule	Two consecutive run results are outside the same 2SD limit	Systematic Error
10_{X} Rule	10 consecutive run results fall on same side of the characterization mean	Systematic Error
R_{4S} Rule	Two consecutive run results differ by more than 4SDs	Systematic Error

Laboratory Supervisor signature	Date
Laboratory Division Director signature	Date
QA Manager signature	Date
Laboratory Director	Date

1 Westgard QC. Accessed June 2019. www.westgard.com/westgard-rules.htm

Notes

Notes

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