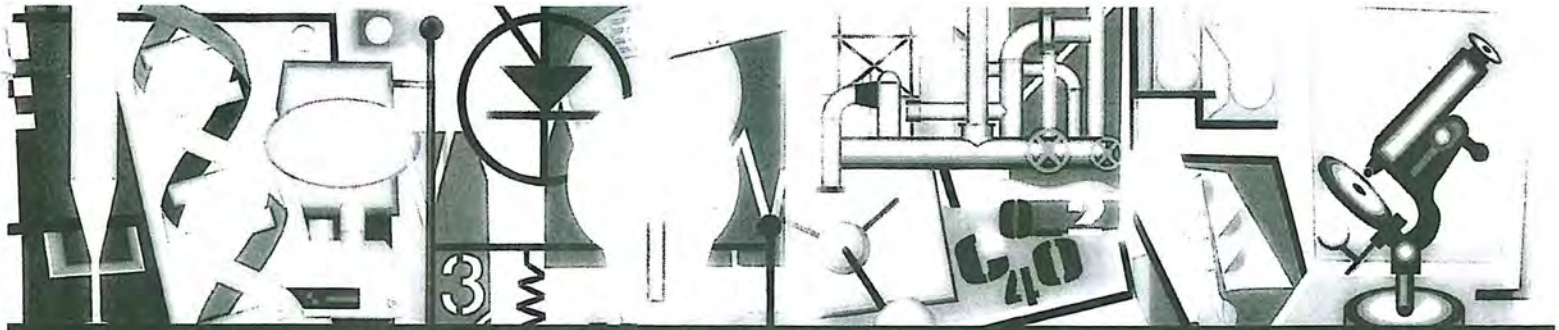


Biological Monitoring and Government Agencies: Past, Present and Future

By Shane Que Hee, Gayle DeBord, John Cocker and Peter Flessel

More than 100 people attended the AIHce 2005 roundtable on government agency efforts in biological monitoring. The roundtable was organized to present information on the state of government human biological monitoring programs in the past, present and future.

Biomonitoring is the general term to describe using biomarkers (chemical or physical markers) in all living things to estimate exposure, effect of exposure or the susceptibility to exposure, or the biomarkers left in the environment through contact between living things and their environments. Human biomonitoring focuses on the measurement of these biomarkers in people who are exposed at their worksites and during their everyday activities. Biological monitoring of workers is defined as the measurement of chemical markers of exposure to physical, chemical and biological agents. Biological monitoring reflects exposure from all possible routes, and is especially useful when dermal and oral exposures are present rather than, and in addition to, inhalation exposure, and when personal protective equipment is worn.

Biomarkers, therefore, can range from measuring a chemical, its metabolite(s) or participating enzymes in body fluids (chemical markers) to identifying specific genes that may affect the outcome of an exposure (genetic markers). Benefits from biomonitoring include assessing current exposure, linking exposure and disease, identifying unknown or unsuspected exposures like dermal or oral exposures, following trends of exposure over time and evaluating the mechanism of action. However, drawbacks exist as well. Taking a biological sample may be invasive; biological monitoring may not be as useful if the toxic reaction is at the point of contact; little new information may be gleaned depending on the route of exposure and there may be low cost benefit. Biological measurements tend to have greater variability than other tools used in exposure assessment due to confounding variables like non-workplace exposures, diet, genetic makeup, previous exposures at work and lifestyle factors. Some workers fear that markers for drugs of abuse also may be measured in their samples in addition to the specific markers produced after exposure to specific agents. Employers may not favor biological monitoring because of the added expense relative to air monitoring. Sufficient information on the biomarkers, their relationships to the exposing agent and the other potential interferences in the specific environment involved must be available to allow biological monitoring data to be interpreted correctly; hence, the necessity to have documentation (for example, for the Biological Exposure Indices or for Biological Tolerance Values) to allow a thorough understanding of the science involved.

Biomonitoring is only as good as the biomarker selected. Many factors affect the selection of the biomarker(s) for use in occupational health research or practice. The timing of the collection of the sample, the route of exposure, other exposures, the chemical properties of the agent and toxicity of the agent all affect what type of biomarker would provide the most useful information.

Biomonitoring and Health Assessment Branch Activities

D. Gayle DeBord, chief of the Biomonitoring and Health Assessment Branch at NIOSH in Cincinnati, spoke first on NIOSH programs. NIOSH uses biomarkers to complement traditional tools of exposure assessment such as surface and air monitoring and medical and work history questionnaires.

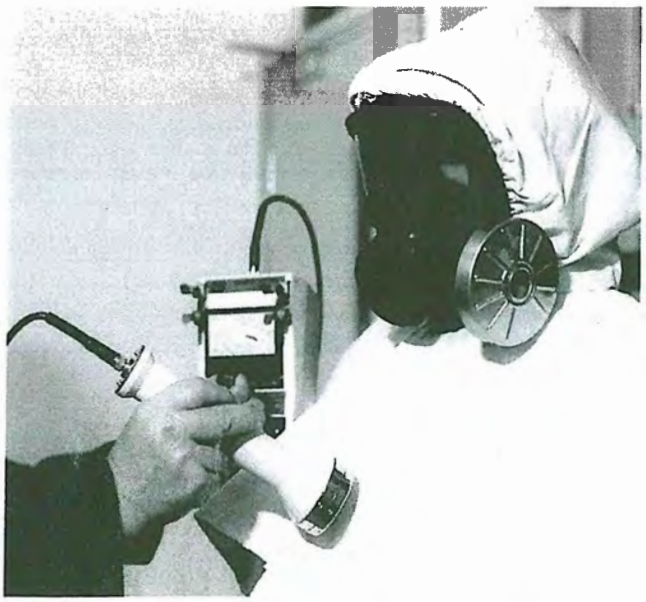
Research is conducted to identify and validate biomarkers, to develop new methods or improve existing ones and to develop direct reading devices. NIOSH also uses biomarkers to assess intervention effectiveness. Some examples of how the Biomonitoring and Health Assessment Branch utilizes biomarkers in occupational health research follow.

As far as identifying new markers or validating existing ones, examples can be found in the research conducted with 1-hydroxypyrene as an indicator of polycyclic aromatic hydrocarbons found in roofing asphalt and with 1- and 2-bromopropane. A new study is looking at a comparison of acrylamide metabolites vs. the acrylamide hemoglobin adduct to determine if there are advantages to one biomarker over another. Many of these studies compare biomarkers in the low-, medium- and high-exposure classifications.

Much of the research in BHAB is involved in developing new methods or improving existing ones. Traditional chemical analysis can be time-consuming and labor-intensive. One strategy that BHAB has employed is the use of immunochemical methods to measure parent compound or metabolites in urine. Immunochemical assays are generally faster, cheaper and have similar sensitivity to traditional chemical analysis. BHAB has taken this a step further and is using fluorescent covalent microbead immunosorbent assay. The microbead immunoassay is amenable to multiplexing

so that more than one chemical or agent can be measured at the same time. Nearly 300 samples can be analyzed in a 2-hour time period using only 200 µL of urine or serum. Multiplexing methods have been developed for several pesticides, CDC-selected bioterrorism agents and toxins produced by mold (for example, endotoxin of *Stachybotrys*) that are thought to be involved in indoor air quality issues. Take-home contamination also has been detected by these techniques.

One area of research that BHAB has fostered is that of direct-reading devices or field portable instruments or methods. These devices or methods allow either the field researcher or the worker to find the level of exposure in the field. The devices can be used to determine the effectiveness of a new intervention or to see if PPE is working properly. Such a direct-reading device for anthrax exposure was developed by BHAB for use by decontamination workers to check their immunization status and also to check whether PPE used during cleanup operations were effective.



Markers of effect that have been studied include DNA strand breaks, oxidative DNA damage, micronuclei frequencies, sperm morphology, sperm motility and the comet assay. The tests for DNA strand breaks and micronuclei collectively are called the GeneTox test. Such markers are useful to gauge the effects of pesticides and antineoplastic drugs.

Before biomonitoring is used or implemented, NIOSH requires consideration of some issues. First is that for most NIOSH research studies, the research protocol needs to be reviewed by an institutional review board. This is to ensure that informed consent is properly given, the rights of the participant are not affected detrimentally and the study design is appropriate, including sufficient sample size. Non-exposed participants are used for comparison. Medical and exposure questionnaires are an important part of biomonitoring, and NIOSH uses them to discern other conditions or exposures that might impact the biomarker that is being measured. In addition to these concerns, other issues that need to be considered are protection and privacy, notification of the workers of the results and the process for addressing results and data outliers.

In the future, NIOSH would like to compile a worker biomarker database.

Audience questions concerned chemical warfare agents, the CDC anthrax test and why markers of effect were investigated, since they appeared to be more like clinical markers.

Health and Safety Laboratory of the United Kingdom

John Cocker, together with Kate Jones, Jackie Morton and Howard Mason of the Health and Safety Laboratory, explained the location and function of the HSL in the United Kingdom in support of the U.K. Health and Safety Executive (part of the Department for Work and Pensions) relative to policy development, and investigations by its factory and medical inspectors. The physical plant is in Buxton, Derbyshire, and a new laboratory has been completed recently. A database has been storing worker biological monitoring data since 1996. HSL utilizes mostly urine, breath and blood samples. Cocker immediately stated that HSL was concerned only with biological monitoring markers of dose, and not effect or susceptibility. He called out the U.K. top 10 relative to number of analyses for 2004:

1. lead
2. p,p'-methylene dianiline
3. arsenic
4. mercury
5. nickel
6. 4,4'-methylene bis(2-chloroaniline)
7. cholinesterase (a marker of effect)
8. dialkyl phosphates
9. cobalt
10. methyl hippuric acid

Most of their clients are small firms; 90 percent of the samples come from businesses with fewer than 10 workers and 75 percent come from those with fewer than five workers.

There are two types of guidelines used; Health Guidance Values or occupational exposure limits based on No Observed Adverse Effect Limits and the Benchmark Guideline Values based on the biomarker threshold for 90 percent of the observations (a parameter associated with good occupational hygiene practice used as a trigger to control exposures, similar to an OSHA action level). Cocker then discussed four case studies.

More than 200 businesses sent samples to be analyzed for MOCA [end of shift urinary guidelines: BGV, 15 µg/mol

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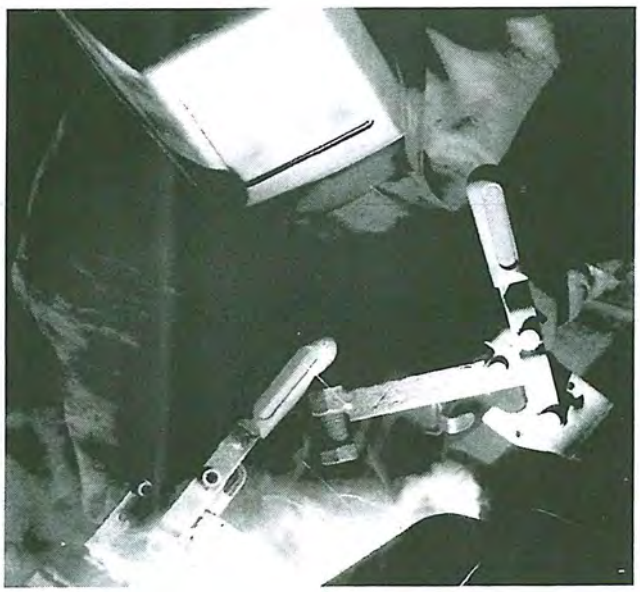
creatinine (1996); HGV, 30 µg/mol creatinine]. Air sampling and biological monitoring demonstrated that 100 percent of the exposure was via dermal exposure for nitroglycerin in pharmaceutical and explosives manufacturing industries (proposed urinary end of shift BGV, 15 µg/mol creatinine). The air monitoring data for nitroglycerin were too poor to set a HGV.



Cr(VI) exposure to workers who weld stainless steel is measured after the last shift of an end-of-week urinary sample with the guidance values of BGV at 10 µg/mol creatinine or 5 µg/L, based on eight years of data collection. The BEI is 54 µg/mol creatinine.

Exposure to polyaromatic hydrocarbons is through urinary measurement of 1-hydroxypyrene (BGV, 4 µg/mol creatinine). These results were given in another roundtable on biological monitoring of PAHs.

Isocyanates are important as the largest cause of environmental asthma and the marker is a protein adduct that requires gas chromatography-mass spectrometry analysis of the released corresponding diamine. The method works for diisocyanates. Biological monitoring was able to detect overexposed office workers who were exposed unknowingly to a ventilation leak in a spray booth with consequent urine levels higher than those of the exposed workers. Once the leak was repaired, the universe returned to what it should be; paint spray workers were more exposed than office workers, even if they wore PPE. About 40 percent of the sprayers admitted raising their visors (even though 96 percent knew they shouldn't) to examine their work at the end of spraying and, therefore, inhaled high levels of diisocyanate. The HSL detected increased biomarkers. Biological monitoring allowed unexpected exposures and behavior to be detected. A proposed BGV is 0.5 µg/mol creatinine.

The HSL will focus on isocyanate exposures for the short term, and then will concentrate on other respiratory sensitizers and carcinogens for the long term. An example of biological monitoring used for post-approval surveillance and exposure and also to check regulatory models was a study of Cr(VI) in the copper chrome arsenic wood preservative industry. This involved 163 companies and was conducted by mail. Biological monitoring to oversee the effectiveness and behavioral aspects of wearing PPE will continue. It is likely that any future biological monitoring guidance values will be based on good occupational practice (that is, BGVs) rather than being HGV based. PBPK modeling and assessment of nonoccupational exposures also will increase.

The HSL has found that biological monitoring can help to assess exposure at the level of the individual, the workplace and industry. It is a useful tool for employers and regulators to show reductions in exposure and the risk of ill-health. It is an indispensable tool to detect unexpected exposures, dermal and oral exposures, to confirm the results of air monitoring, the protectiveness of PPE and whether PPE are being used correctly.

Audience questions predominantly concerned the Cr(VI) guidance values and the validity of the BGVs.

California Department of Health Services: Public Health Biomonitoring

Peter Flessel, chief of the Environmental Health Laboratory branch in Richmond, Calif., immediately supported Cocker's interest primarily in markers of dose.

Flessel traced the history of the California Biomonitoring Program through CDC financial support of the California Biomonitoring Planning Project to identify chemicals and health conditions of greatest concern to the California public, and through California legislation introduced in the current session, titled "The Healthy Californian's Biomonitoring Program" (SB 600) to set up public health biomonitoring in the California Department of Health Services. State Health Officer Richard Jackson also established a CADHS work group to promote biomonitoring in California similar to the CDC's National Health and Nutrition Examination Survey, using representative urinary and blood samples.

Jackson stated that public health officials and the public are concerned that certain individuals and groups may have biomarker concentrations different from a population reference range (formerly called "normal range") or some kind of benchmark. He discussed the need for public education on biomonitoring in a public health setting. CDC's National Center of Environmental Health (now combined with ATSDR under CDC, as is NIOSH) operates a stellar national program in biomonitoring for chemicals in people. He then discussed some specific case studies associated with workplace and child exposure to lead, environmental and mainstream tobacco smoke and community exposures to pesticides and chemical weapons.

One of the triumphs of environmental health biomonitoring is the decline of blood lead concentrations in the general public after the phase-out of lead in gasoline initiated by the California Air Resources Board and the U.S. EPA in the mid-1970s. Blood lead levels still continue to decrease in the general population, as recorded by the CDC. Its "National Report on Human Exposure to Environmental Chemicals" also reports the reference ranges of more than 100 chemicals measured in blood and urine. These include cadmium and other metals, cotinine (a major metabolite of nicotine), phthalates (from plastics), chlorinated dioxins/dibenzofurans (combustion products of chlorinated materials), polyaromatic hydrocarbons (combustion products of gasoline and other carbonaceous materials), pesticides, phytoestrogens and polychlorinated biphenyls.

With regard to blood lead levels in children, about 14 percent of 1,200 Los Angeles children exceeded 30 µg/dL in 1975, with levels statewide now generally below 10 µg/dL. Now with more than 500,000 tests done every year, less than 1 percent are elevated above 15 µg/dL. Lead still exists in traditional sources (old paint, soil and dust), but also crops up in surprising materials like pottery, candy wrappers and grasshopper snacks! Childhood lead poisoning prevention activities are funded by fees from oil, gasoline and paint companies, and they are coordinated by CADHS. Control of occupational lead exposure continues to be important, too. The CADHS Occupational Lead Program supports case management, and has achieved notable consultative success in conjunction with CAL/OSHA, even with take-home contamination.

A lower level in urinary cotinine is the direct result of anti-smoking media campaigns and new regulations banning smoking in workplaces and in many public venues.

Biomonitoring for pesticides is carried out by the California Department of Food and Agriculture's Center for Analytical Chemistry in support of the Department of Pesticides Regulation. For example, the center measures urinary metabolites of organophosphates and captan to estimate pesticide worker exposures.

Since 1999, CADHS has participated in a CDC-sponsored program to measure metabolites of chemical weapons and toxic industrial chemicals in blood and urine. Chemical detection is a dual-use activity relative to spills, industrial accidents and potential chemical terrorism. Laboratory capability has been achieved for metabolites of nerve agents, nitrogen and sulfur mustards, ricinine (a ricin marker), cyanide, heavy metals and certain toxic industrial chemicals.

The future of public health biomonitoring is largely dependent on state funding, especially since CDC funds after the California Biomonitoring Project have become very scarce. Nevertheless, a recent unfunded laboratory pilot study measured persistent organic pollutants in serum samples obtained from pregnant women. In addition to funds for laboratory sample testing, the program needs funds for specimen collection and banking, eliciting community input about wise use of biomonitoring and for more public health educational materials.

Audience questions focused on the feasibility of public health officials giving talks about biomonitoring, public outreach methods and content and the need for science writers to convey complex ideas to the public.

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