F. APPLICATION OF BIOLOGICAL MONITORING METHODS

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1. INTRODUCTION

Biological monitoring is the assessment of worker exposure to a hazardous agent through the measurement of a biomarker which results from contact with the agent. The biomarker typically is the agent or its metabolite in a biological specimen derived from the worker; examples are styrene in expired air, styrene in blood, and mandelic and phenylglyoxylic acids (metabolites of styrene) in urine. The biomarker also can be an effect of the agent, such as elevated levels of zinc protoporphyrin in blood, caused by exposure to lead. Industrial hygiene professionals use biological monitoring to assess the risk to workers from exposure hazards and to demonstrate the adequacy of control technologies and intervention strategies.

This chapter provides an overview of the effective and appropriate application of the biological monitoring analytical methods published herein. The analytical results should be interpreted in light of what is known about the uptake, metabolism, and excretion of the agent and the effect of the agent on the body. This chapter introduces these areas, provides other considerations, and gives references to sources of more comprehensive information on specific agents and situations. Additional resources on biological monitoring include reviews [1-10], books [11-17], and methods and quality assurance manuals [18-22].

2. GENERAL CONSIDERATIONS

A worker exposed to a chemical receives a dose of that chemical only if it is absorbed into the body. Absorption can occur after dermal contact, inhalation, ingestion, or from a combination of those routes. The extent of absorption from an exposure and the rate of absorption depend on the properties of the chemical (especially its solubility in lipids and water) and the route of exposure. Once absorbed, a chemical is distributed and partitions into various tissues due to tissue variations in pH, permeability, etc. Highly water-soluble chemicals may be distributed throughout the total body water, while more lipophilic substances may concentrate in the body fat or other lipid-rich tissues, such as the brain. The loss of chemical from the body can loosely be defined as elimination, which depends on metabolism and excretion. Chemicals may be eliminated by numerous routes, including fecal, urinary, exhalation, perspiration, and lactation. A chemical can be excreted from the body without metabolism, in which case the parent compounds may be detectable in the urine, breath, or fecal material. In other cases, the chemical may be metabolized through oxidation, reduction, hydrolysis, or a combination of these processes, often followed by conjugation with an endogenous substrate. Conjugation of a chemical or metabolite is a pathway for excretion. The more important conjugation reactions include glucuronidation, amino acid conjugation, acetylation, sulfate conjugation, and methylation. Metabolism and excretion and the rates of metabolism and excretion can be affected by age, diet, general health status, race, and other factors. In general, the metabolic products will be more water soluble than the parent chemical. Where metabolism yields more than one product, the relative amounts of each and the parent-metabolite ratios are affected by an individual's general health status, diet, genetic makeup, degree of hydration, time after exposure, and other factors. The kidney is the major organ of excretion and is the primary route for water-soluble substances. These substances enter the urine by either glomerular filtration, tubular secretion, or sometimes both mechanisms.

Biological monitoring has the potential to assess worker exposure to industrial chemicals by all routes, including inhalation, skin absorption, and ingestion. Selection of an appropriate biomarker for an exposure requires knowledge of the distribution, metabolism, and excretion of the toxicant sufficient for selection of the proper compound to be determined, biological medium to be sampled, and time for obtaining a specimen. Often, most of the toxicological and pharmacological information available is from experimental animals and, thus, not always directly applicable to humans.

Monitoring Goals. Air monitoring (or workplace environmental monitoring) and biological monitoring have complementary goals and frequently are applied simultaneously in industrial hygiene investigations.

1. *Air monitoring*. Air monitoring provides an estimate of the potential for exposure to an agent. The presence of a health hazard is estimated by reference to environmental exposure limits, such as the NIOSH recommended exposure levels, the Occupational Safety and Health Administration (OSHA) permissible exposure levels, or the threshold limit values (TLVs^{TM}) of the American Conference of Governmental Industrial Hygienists (ACGIH). Compared with biological monitoring, air monitoring offers advantages in certain situations. If the agent has acute toxic effects on the respiratory tract or the eyes, air monitoring is the logical tool for controlling the exposure. Air monitoring can be conducted continuously and, thus, can detect peak exposures to dangerous chemicals.

2. *Biological monitoring of exposure*. A biomarker of exposure represents uptake of the agent through all routes of exposure. Thus, compared to air monitoring, biological monitoring offers a better estimate of the health risk in situations where routes of exposure other than inhalation are significant.

    a. The rate of disappearance of a biomarker determines the period of time after exposure during which the level of the biomarker is still affected by the exposure [7]. The levels of rapidly disappearing biomarkers primarily reflect exposures during the previous several hours. On the other hand, biomarkers which disappear over the course of several weeks reflect one, several, or numerous exposure incidents occurring anytime during a period of several weeks previous to the measurement.

    b. Some toxicants accumulate in one or several parts of the body and are in dynamic equilibrium with the sites of toxicity. In the case of polychlorinated biphenyl (PCB), which accumulates in fatty tissue, the blood level of PCB reflects the amount stored in the body.

    c. When the site of critical action for a toxicant is known, the concentration of the biomarker at that site can be used as a measure of the biologically effective dose. Carboxyhemoglobin is such a biomarker for carbon monoxide poisoning. In this case, the biomarker level is correlated with the health effect.

3. *Biological monitoring of effect*. This term is defined as monitoring reversible biochemical changes resulting from exposures. The degree of change is less than that which leads to injury and is not associated with a known irreversible pathological effect [23]. Biological monitoring of effect is not health surveillance through which individuals with early signs of adverse health effects are identified. Some examples of biomarkers of effect are:

    a. Zinc protoporphyrin in blood, levels of which increase with lead exposure, because lead inhibits the biosynthesis of heme [24].

    b. Protein and DNA adducts of aromatic amines in blood. These adducts can both reflect the intensity of exposure and be correlated with the biologically effective dose.

    c. Antibodies produced against low-molecular-weight molecules [25]. Some chemicals, while not immunogenic in their own right because of small size and other limitations, may bind to constitutive polymers (such as host proteins) and become immunogenic, causing the production of specific antibodies. Alternatively, such exposures may lead to production of new antigenic determinants, through nonadduct-forming reactions of the agent with selected protein-carrier molecules. Antibodies can be made to these modified proteins or to the parent hapten-conjugate [26]. In both cases, the antibodies

may remain in the human system much longer than the toxicant which initiated their development.

Biological Matrices. The most common matrices used for biological monitoring are exhaled air, blood, and urine.

1. Monitoring exhaled air is limited to volatile chemicals. Exhaled air monitoring is not suitable for chemicals inhaled as aerosols or for gases and vapors, which decompose upon contact with body fluids or tissues, or which are highly soluble in water, such as ketones and alcohols [3].

2. Blood is the medium which transports chemicals and their metabolites in the body. Therefore, most biomarkers present in the body can be found in the blood during some period of time after exposure [4].

    a. A chemical in the blood is in dynamic equilibrium with various parts of the body: the site of entry, tissues in which the chemical is stored, and organs in which it is metabolized or from which it is excreted. Thus, the concentration of a biomarker in the blood may differ between regions of the circulatory system. This would be the case during pulmonary uptake or elimination of a solvent, which would cause differences in concentration between capillary blood (mainly arterial blood) and venous blood.

    b. Two advantages of blood monitoring are: (1) The gross composition of blood is relatively constant between individuals. This eliminates the need to correct measured biomarker levels for individual differences. (2) Obtaining specimens is straightforward and with proper care can be accomplished with relatively little risk of contamination.

    c. An important consideration in blood monitoring is that obtaining blood specimens requires an invasive procedure and should be performed only by trained persons.

3. Urine is more suitable for monitoring hydrophilic chemicals, metals, and metabolites than for monitoring chemicals poorly soluble in water. The concentration of the biomarker in urine usually is correlated to its mean plasma level during the period the urine dwells in the bladder [5].

    a. In some instances the urine concentration is affected by the amount of the biomarker stored in the kidneys. Examples are cadmium and chromium.

    b. The accuracy of the exposure estimate, using urine monitoring, depends upon the sampling strategy. The most influential factors are time of collection and urine output.

    c. Measurements from 24-hour specimens are more representative than from spot samples and usually correlate better with intensity of exposure. However, collection, stabilization, and transportation of 24-hour specimens in the field are difficult and often not feasible.

3. PRACTICAL CONSIDERATIONS

Selection of Methods. The occupational health professional and the laboratory scientist should decide on appropriate methods so that the test results are interpretable to the exposure situation. The following issues should be addressed:

1. The goal of the biological monitoring method should be consistent with the goal of the industrial hygiene investigation. Is the goal to measure exposure or a health effect related to the exposure?

2. The method needs to be evaluated for the required specificity and possible interferences. If interferences from diet, drugs, alcohol, disease states, or other workplace chemicals or agents exist, they must be accounted for.

3. The method should have a sufficiently low limit of detection to differentiate exposed from nonexposed workers. A method developed when biological monitoring reference levels were higher may be inadequate for measuring exposures at and below the current guidelines.

4. Limitations of the sample matrix and its affect on the analysis need to be assessed. In general, blood serum and urine specimens require different sample preparations and may require separate methodologies to eliminate matrix effects.

5. Because of sample instability, some methods may be impractical or not feasible.

6. The method should have guidelines for interpretation of collected data. Such guidelines are discussed in **Interpretation of Results** below.

7. To minimize the risk of harm to workers, when two biological monitoring methods will provide the same information, the less invasive method should be used. Thus, methods monitoring urine or exhaled breath are preferred over those monitoring blood.

Sampling Strategy. Strict attention to specimen handling and collection is essential for quality data. The analytical laboratory should be consulted for sampling instructions. Analytical methods should provide specific directions on the collection, storage, and transportation of specimens to the laboratory. Adherence to these directions is of the utmost importance to ensure sample integrity.

1. Timing of specimen collection should be appropriate. The method should include instructions for the timing of specimen collection, that is, whether specimens should be obtained during the work shift, at the end of the shift, or at some other time during the work week. The longer the half-life of the xenobiotic, the less critical is the timing of the collection [11].

2. The baseline of a biomarker should be evaluated when the toxicant accumulates in the body, as do cadmium, lead, and polychlorinated biphenyl [11]. The baseline should also be assessed, if there is large intersubject variability in the population, such as when pseudocholinesterase in plasma is measured.

3. Care should be taken not to contaminate the specimen with either chemicals or bacteria.

4. The proper preservative (for urine or blood samples) or anticoagulant (blood) should be used, if appropriate.

5. Stability of the biomarker is assured through proper storage and shipment of the specimen to the laboratory and proper storage by the laboratory.

Correction of Urinalysis Data for Dilution. Determination of biomarkers in individual urine samples is confounded by urine dilution, which can vary substantially with fluid intake and physical work load. In practice, this effect of urine dilution is reduced by adjusting the measured concentration of the biomarker to a normal value [5,27], such as:

1. Specific gravity. This adjustment is made by multiplying the measured concentration of the biomarker by the ratio of [(1.024 - 1)/(sp.g. - 1)], where sp.g. is the specific gravity of the urine sample and 1.024 is the assumed normal specific gravity value.

2. Urine output. The measured concentration of the biomarker is multiplied by the ratio R/0.05, where R is the output for the sample in liters per hour. The urine output for the sample is

computed from the volume (liters) of the sample and the time (hours) elapsed since the last voiding. The adjustment is to a mean output of 0.05 L/h.

3. Creatinine concentration. This is the most frequently used adjustment. Creatinine is excreted by glomerular filtration at a relatively constant rate of 1.0-1.6 g/day. Urinary creatinine concentration can be determined by spectrometric or kinetic methods based on the Jaffé alkaline picrate reaction, enzymatic methods, and methods based on mass spectrometry and liquid chromatography [28]. The adjusted value is the quantity of the biomarker per unit quantity of creatinine.

There are other considerations to be taken into account when adjusting urinalysis data for dilution:

1. Adjustment to the creatinine level is not appropriate for compounds, such as methanol, that are excreted in the kidney primarily by tubular secretion.

2. Since the mechanism of excretion of a biomarker can be altered if the urine is very concentrated or very dilute, measurements on samples, having creatinine concentrations outside the range 0.5 to 3 g/L or having specific gravities outside the range 1.010 to 1.030, are unreliable [5].

3. Adjustment for creatinine concentration, while correcting for dilution, introduces additional variation, which must be considered when the data are evaluated. Among the factors affecting the rate of creatinine excretion are the muscularity of the subject, physical activity, urine flow, time of day, diet, pregnancy, and disease [27].

Quality Assurance. Good data require the utilization of an effective quality assurance program. In 1992, regulations implementing the Clinical Laboratory Improvement Amendments (CLIA) of 1988 were published by the Health Care Finance Administration and the Public Health Service to ensure that analysis of human specimens was done accurately and under good quality control procedures [29]. Any analysis of human specimens that can be used by a health care practitioner to assess the health of the individual or used in the diagnosis, prevention, or treatment of disease or impairment falls under the CLIA guidelines. Since, as a minimum, biological monitoring data are used to prevent occupational disease or impairment, CLIA guidelines apply. Key components of the CLIA quality assurance program include:

1. Strict management of specimen collection, handling, storage, and transportation, thus ensuring sample integrity

2. Thorough verification of a method by the laboratory before use on field specimens

3. High level of analytical quality control

4. Participation in proficiency testing programs, if available

5. Documented instrument evaluation and maintenance programs

6. Investigation of communication failures and complaints

7. Documentation of performance and corrective actions

Ethical Considerations. There are several ethical issues that must be considered before initiating a biological monitoring procedure [30, 31]:

1. Method should be appropriate for the requirements of the investigation.

2. Procedures should not threaten the health of the participant.

3. Risk of using invasive methods must be justified by the benefits.

4. Informed consent from the participant is required. This consent must be given when the participant feels no fear of reprisals, if consent is withheld.

5. Results should be kept confidential and shared only with the occupational health professional and the participant.

Laboratory Safety. When dealing with human specimens, a biosafety program is essential. Pathogens such as hepatitis B and human immunodeficiency virus (HIV) may be present in blood, saliva, semen, and other body fluids. Transmission can be by an accidental nick with a sharp object; exposure through open cuts, skin abrasions, and even dermatitis or acne; and indirectly through contact with a contaminated environmental surface. There are five major ways to reduce the potential for exposure to biological pathogens [32, 33]:

1. Engineering controls, which include mechanical or physical systems used to eliminate biological hazards, must be available. These are items such as biosafety cabinets or self-sheathing needles.

2. Employee work practices are essential to minimize exposure to pathogens. Good personal hygiene procedures and avoidance of needle recapping can lessen exposure to pathogens.

3. Personal protective equipment, such as gloves and masks, should be used when necessary.

4. Good housekeeping procedures, which involve cleanup of the work area, are essential to avoid contamination of the laboratory.

5. Employees, who have been identified as potential exposure candidates, should be vaccinated for hepatitis B.

Universal precautions that take into account the above five measures should be practiced with every biological sample received. It is not possible to know if a particular sample may contain pathogens; therefore, each sample should be treated as if contaminated.

4. INTERPRETATION OF RESULTS

A biological monitoring analytical result is a determination of the level of the biomarker in the biological matrix from which the sample was taken, at the time it was taken. Extrapolation from that datum to insight on the exposure of the worker requires knowledge of how the human body responds to the agent.

1. Exposure can be estimated when a quantitative relationship between environmental level and biomarker level has been demonstrated.

2. Health risk can be estimated when a quantitative relationship between a health effect and biomarker level has been demonstrated.

3. Where knowledge of a biomarker is limited, one can only infer from its presence above the background level that exposure has occurred.

Reference Levels. For a number of agents there exist published reference levels, termed "biological action levels" by the World Health Organization [18], which serve as guidelines for interpreting biological monitoring data. In the absence of published biomonitoring action levels, biomarker levels

indicating occupational exposure have been inferred by comparison with the normal background levels of the biomarker.

1. Biomonitoring action levels vary in their derivation, some being from correlations with exposure, others with health effects. These reference levels should be used only when one has full understanding of their derivation. Sources of biomonitoring action levels include:

    a. Biological Exposure Indices (BEI) adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) [34];

    b. Biological Tolerance Values for Working Materials (BAT) published by the Deutsche Forschungsgemeinschaft's (DFG) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area [35];

    c. Lauwerys' and Hoet's "Summary of Recommendations" in *Industrial Chemical Exposure. Guidelines for Biological Monitoring* [11];

    d. Occupational Safety and Health Administration (OSHA) standards [36, 37].

2. When biomarker data are available for exposed and nonexposed populations that are otherwise similar, the upper limit of the range for the nonexposed population may serve as a reference level. Levels of biomarker significantly above that limit suggest occupational exposure to the agent. For those biomarkers for which there is no measurable background level in nonexposed humans, this reference level is effectively the detection limit of the analytical method. In any case, levels of the biomarker above the reference level suggest there was occupational exposure, but give no information on the potential health effect.

Variability. Biological monitoring data are subject to a number of sources of variability [2], including:

1. Rates at which an agent is taken up by the body, metabolized, and excreted. These vary from person to person and are affected by the person's age, sex, and physical workload.

2. Route of exposure. For example, absorption through the lungs is much faster than adsorption through the skin. Thus, the appearance and elimination of a biomarker will be slower if the agent entered through the skin. If the biomarker is rapidly excreted, the optimum timing for collection of biological samples will be different for the two routes of entry.

3. Fluctuation in environmental exposure. Such fluctuations will be tracked by the levels of rapidly eliminated biomarkers, those reflecting exposure of the immediately previous several hours.

4. Personal protective equipment worn and a person's work practices.

5. Existence of a biomarker in both a free and a conjugated form, the relative proportions of which can vary substantially from person to person. For example, aniline is present in urine as both the free amine and as acetanilide, its acetyl derivative. Some persons are genetically predisposed to excrete primarily free aniline; while others, primarily, acetanilide.

6. Concurrent exposure to several agents that compete for the same biotransformation sites in the body. This may lead to altered metabolism and excretion, which would change the relationship between exposure or health effect and the level of the biomarker [8].

7. Concurrent exposure to several agents, which are metabolized to the same biomarker. This frustrates the interpretation of the biological monitoring data. For example, trichloroacetic acid is a biomarker for trichloroethylene, 1,1,1-trichloroethane, and perchloroethylene.

8. Consumption of alcoholic beverages [9], since ethanol is metabolized by three pathways used for metabolism of other organic agents. After consumption of one drink, the ethanol concentration in the blood is about 1000 times higher than from a normal occupational exposure and may affect significantly the metabolism of industrial chemicals.

9. Medications [10], health, and diet.

Because of the variability of biomarkers, judgments on the exposure or health risk of workers frequently cannot be made based on a single determination. It may be necessary

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