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BIOMARKERS: THEORETICAL ASPECTS AND APPLICATIVE PECULIARITIES NOTE I. GENERAL CHARACTERISTICS OF BIOMARKERS

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Abstract

By analytical investigation of tissues and body fluids as well as of metabolites it is possible to evaluate an integrated response at the action of diverse xenobiotics of food interest or of pharmacologic interest on the exposed organism. There are certain substances that are considered "bioindicators". With a generic term these substances have been denominated "biomarkers" (biological markers). By the interactions between xenobiotics and the organism, modifications take place that affect metabolism and determine the appearance of some bioincompatible substances resulted by the biotransformation of xenobiotics. Thus, modifications of homeostasis are produced that can be revealed by investigations. Human health is affected by all the activities of an individual, who is subject to a continuum of chemical exposures in the external environment, including air, water, soil and food. The important considerations for assessment of risk are the dose, route, duration and frequency of exposure.

***Keywords**: biomarkers, environment and food safety*

Concept of Biomarker

Biomonitoring studies are based on the evaluation of the levels of residual xenobioderivatives with specific of "bioindicator", of the response of an organism, a population or a community to chemical stressors in the environment. The responses, defined as biomarkers

constitute a signal on the level of contamination and, in the main time, on the level of toxicological risk (McCarthy and Shugart, 1990, Fossi, 1991).

In the acceptation given by Hulka et al. (1990) the *biological markers* can be defined as "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells or fluids". The term "*biomarker*" is used in a broad sense to include almost any measurement reflecting an interaction between a biological system and a chemical, physical or biological environmental agent.

In accordance with the National Research Council - USA (1989) it was defined as "a change induced by a contaminant in the biochemical or cellular components of a process, structure or function that can be measured in a biological system". A main concept of this approach is based on the intercorrelability of the effects of a contaminant at different levels of structural organization (enzyme activity, cells, tissues, organism a.o.). The homeostatic responses to the chemical injury are potential biomarkers (McCarthy and Shugart, 1990).

In practice biomarkers include tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression or outcome of treatment of disease (Mayeux, 2004).

Typological Characterization of Biomarkers

The reaction to exposure to a chemical depends on inherited and acquired characteristics and the life-style of the biological system, the properties and form of the chemical, and the circumstances of the contact. The outcome may be no effect, some adverse effect with recovery, or toxicity with morbidity.

Perera and Weinstein (2000) have been classified biomarkers by based on the sequence of events from exposure to disease. The use of biomarkers improves the sensitivity and specificity of the measurement of exposure to risk factors.

Interactive types

A general classification of biomarkers is of interest in order to understand the way of approaching their role in the evaluation of the morphofunctional status of the organism. Generally, biomarkers can be

included in three classes having in view exposure, susceptibility, and effect:

Biomarkers of exposure - exogenous substances or their metabolites or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism.

Biomarkers of susceptibility - indicators of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance.

Biomarkers of effect - measurable biochemical, physiological, behavioral or other alterations within an organism that, depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease.

Functional characteristics

Approaching the problem of functional characteristics of biomarkers can reveal interesting aspects. These can be successively discussed.

Biomarkers of exposure can be used to confirm and assess the exposure of individuals or populations to a particular substance, providing a link between external exposures and internal dosimetry. These biomarkers are important in toxicology because they indicate the amount of chemical exposure that has been absorbed into the body. An adequate understanding of the chemistry and toxicology of the considered substance permits an accurate measurement. Analytical methods can detect and/or quantify the presence of natural or synthetic xenobiotics or their metabolites in a biological matrix.

Biomarkers of susceptibility help elucidate the degree of the response to exposure elicited in individuals.

Biomarkers of effect can be used to document either preclinical alterations or adverse health effects elicited by external exposure and absorption of a chemical. Thus the linkage of biomarkers between exposure and effect contributes to the definition of dose-response relationships.

Generally, biomarkers may be used for three goals:

a) To assess the exposure (absorbed amount or internal dose) and effect(s) of chemicals and susceptibility of individuals, and

they may be applied whether exposure has been from dietary, environmental or occupational sources;

b) To elucidate cause-effect relationship and dose-effect relationships in health risk assessment, in clinical diagnosis;
c) To supplement environmental or ambient workplace measurements of chemicals with recognized potential adverse health effects that may be subject to regulatory controls for monitoring purposes (Schulte, 1989; Schugart et al., 1992; Naylor, 2003).

In the case of biomarkers of exposure and of effect it may be used to evaluate compliance with advice for minimizing exposure or for remedial measures in a public health context, e.g., to confirm reduced exposure to lead from environmental sources in a population group.

Several exposure characteristics need also to be considered, such as the concentration of the chemical and the duration, frequency and magnitude of exposure. Exposure of the host can be through various routes including the respiratory tract (inhalation exposure), the gastrointestinal tract (oral exposure) and the skin (dermal exposure). Finally, there are a number of host characteristics that can influence response to chemical exposure, including age, race, gender, health status, genetic susceptibility, and previous exposure to the same or other chemicals.

Recent developments in molecular biology, information technology and instrumentation have provided new tools for use in environmental health research and biologically based risk assessment.

Markers of Nutritional Exposure

Biomarkers of exposure will reflect the distribution of the chemical or its metabolite throughout the organism. Theoretically, this distribution can be tracked through various biological levels (e.g., tissue, cell, etc.) to the final target. A part will be distributed to internal macromolecules, and a smaller amount will reach the critical site on the macromolecule, with only a fraction of the latter amount acting as the biologically effective dose (Margetts and Nelson, 1987).

Methods for assessing exposure to a chemical are as follows:

a) Measurement of levels of chemical agents and their biotransformation products and/or derivatives in cells, tissue, body fluids or excreta;
b) Measurement of biological responses such as cytogenetic and reversible physiological changes in the exposed individuals.

Measurements could be made for chemical concentrations in food, water and air, selecting environmental concentrations (e.g., occupational or residential settings) as well as measures of the actual exposures experienced by the individual or population.

The problem of evaluating by biomarkers can present interest also for the action of chemical xenobiotics of food interest of organic nature (polycyclic aromatic hydrocarbons, mycotoxins, steroid hormons etc.) and of inorganic nature (nitrates, nitrites, bioelements with toxycogen potential).

In evaluating exposure, one will make distinction between the external dose - the amount of a chemical agent in environmental contact with the organism, and the internal dose - the total amount of a chemical agent absorbed by the organism over a period of time.

Regarding the markers of nutritional exposure, the author discuss problems referring to markers in their relationship with the environment, i.e. air, water, plants and animals up to the distribution in foods. In this way the problem integrates the markers in the trophic chain: soil-plant-animal-man.

Knowledge of the kinetics of formation and removal from the body of these types of biomarkers provides a link between exposure and internal dose. Specific measures of internal dose are the active chemical species (either parent compound or metabolite) delivered to target tissues or cells, the reactive chemical species delivered to target organelles or macromolecules, or the reactive chemical species that participates in biochemical reactions. For example, quantification of the generalized covalent binding of reactive species to macromolecules will provide a measure of absorbed dose delivered to target tissues or cells, while measurement of total DNA adducts is indicative of the dose delivered to target organelles or macromolecules (Anderson et al., 1994; Gârban, 2001). Finally, specific DNA adducts could be the biologically effective species that initiate the carcinogenic process (D'Erricco et al., 1996; Avacovici et al., 2003).

A strategy to help relate biomarkers to prior exposures is to obtain quantitative information about the kinetics of formation and breakdown of the biomarker

Biomarkers for chemicals that are cleared rapidly, such as vapours in exhaled breath or urinary metabolites, may be present in large amounts soon, during or immediately following an exposure, but are not detectable at later times. Other biomarkers, such as adducts formed with blood proteins, may represent only a small fraction of the total internal dose but, because they have a long half-life in the body (relative to exposure frequency), may accumulate to detectable levels with continued exposure (Schulte, 1989; Gârban, 2004).

Absorbed chemicals are distributed between various compartments in the body, with the distribution being dependent on the nature of the compartment and the lipophilicity of the chemical.

More recently, physiologically based toxicokinetic models have been developed that make use of the physico-chemical properties of a chemical, the kinetics of metabolism of the chemical and physiological parameters of the exposed individual (such as tissue blood flow, respiratory minute volume, cardiac output) to predict the actual concentrations of biomarkers that will occur after specific exposure regimens.

Another use of models is in defining the quantitative relationship between biomarkers in readily available biological samples (e.g., blood cells) and in those less readily available which might be more pertinent biomarkers for the health effect of concern (e.g., tissue DNA). Based on such information a model can be developed to show the quantitative relationships between the markers under different exposure conditions or at different times after exposure (Ehrenberg et al., 1996).

Biomarkers are used extensively in the surveillance of workers occupationally exposed to metals such as lead, cadmium, mercury, nickel, chromium and arsenic, and to organic chemicals such as aniline, benzene, carbon disulfide, styrene, chlorobenzene and chlorinated aliphatic hydrocarbon solvents

Considerable efforts are being made to develop biomarkers associated with exposure to chemical carcinogens and to establish the relationship between a marker and the future health risk. DNA fidelity replication assays were used to show one type of adduct that had both a long half-life and was capable of inducing mutations.

Conclusions

Distribution of xenobiotics (pollutants) in environment is not uniform. The relation between exposure, concentration of xenobiotics in organisms and induced effects is a complex one. Effects vary for individuals of the same species or of different ones;

Having in view the relation chemical structure – biological activity the effects induced by xenobiotics of food interest lead to the biochemical injury at molecular level that has its specificity revealed by adequate investigations;

The rapid development of molecular biology and laboratory techniques will contribute at understanding the large spectrum of diseases with applications in epidemiology, clinical trials, disease prevention, diagnosis and disease management.

References

Anderson S., Sadinski W., Shugart L., Brussard P., Depledge M., Ford T., Hose J., Stegemen J., Suk W., Wirgn I., Wogan G. (1994). Genetic and molecular ecotoxicology: a research framework, *Environ. Health Perspect.*, 102 (12), 3-8

Avacovici A.–E., Martău A.–B., Gârban Z. (2003). *Biologie moleculară: metode specifice şi aplicaţii*, Editura Eurobit Timişoara

D'Erricco A., Taioli E., Chen X., Vineis P. (1996). Genetic metabolic polymorphism and the risk of cancer: a review of the literature, *Biomarkers*, 1, 149-173

Ehrenberg L., Granath F., Törnqvist L. (1996). Macromolecular adducts as biomarkers of exposure to environmental mutagens in human populations, *Environ. Health Perspect.*, 104 (3), 423-428

Fossi M. C. (1991). L'utilizzo dei "Biomarkers" nella valutazione del rischio ambientale: metodologie ed applicazione, *Inquinamento*, 12, 44-50

Gârban Z. (2001). *Biologie moleculară: Probleme fundamentale şi aplicative*, ediția 4-a, Editura Eurobit Timişoara

Gârban Z. (2004). *Xenobiotice chimice de interes alimentar,* Editura Eurobit Timişoara

Hulka B.S., Griffith J.D., Wilcosky T.C. (eds.). (1990). *Biological markers in epidemiology*, New York: Oxford University Press

Margetts B.M., Nelson M. (eds.). (1987). *Design concepts in nutritional epidemiology*, New York, Oxford University Press

Mayeux R. (2004). Biomarkers: Potential use and limitations, *J. Am. Soc. Experim. Neuro Therap*., 1 (2), 182-188

McCarthy F., Shugart L.R. (1990). *Biomarkers of environmental contamination*, Lewis Pub., Chelsea, USA

Naylor S. (2003). Biomarkers: current perspectives and future prospects, *Expert Rev. Mol. Diagn*., 3, 525-529

Perera F.P., Weinstein I.B. (2000). Molecular epidemiology: recent advances and future directions, *Carcinogenesis*, 21, 517-524

Schugart L.R., McCarthy J.F., Halbrook R.S. (1992). Biological markers of environmental and ecological contamination: An overview, *Risk Analysis*, 12, 353-360

Schulte P.A. (1989). A conceptual framework for the validation and use of biomarkers, *Environ. Res.*, 48, 129-144

Schulte P.A., Perera F.P. (Eds.). (1993). *Molecular epidemiology: principles and practices*, San Diego Academic Press

*** National Research Council. (1989). *Biologic markers in reproductive toxicology*, National Academy Press., Washington, DC.