BIOMARKERS OF ENVIRONMENTAL EXPOSURE AS A TOOL OF PREVENTION

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Abstract: The aim of this paper is to discuss the expectation towards the usage of environmental exposure biomarkers as a preventive tool and to emphasize the challenging fields of innovation from public health aspect. Basic definitions, properties of an ideal biomarker, current status, and future expectations about biomarkers will be overviewed.

The final decision is that biomarkers will be future’s most important tool of preventive medicine. Scientific research and technologic infrastructure will be the driving force of many innovations and inventions.

This article should not be considered as a review on biomarkers. The basic aim is to discuss the expectations towards the use of environmental exposure biomarkers as a preventive tool and to emphasize the challenging fields of innovation. Thus in this article I will be contented with the basic definitions and explanations.

John M. Last states that “Health is a resource for everyday life, not the object of living; it is a positive concept, emphasizing social and personal resources as well as physical capabilities” (1). Interaction between the genetic patterns and environment determines the human health.

Data on environment and health should be evaluated and analyzed to predict the effects of pollution on health and to determine the priorities of the actions to be taken. A wide range of waste in the form of solid, liquid and gas are disposed of into the environment and these wastes pollute air, water and soil. The pollutants which are accumulated and concentrated in the environment enter the body of the living creatures through respiratory, gastrointestinal and dermatological systems. An individual’s exposure begins before birth and includes those from environmental and occupational sources (2). John M. Last suggests a necessary sequence for the control of any public health problem (1).

- Awareness that the problem exists
- Understanding what causes the problem
- Capability to deal with the problem.
- A sense of values that the problem matters
- Political will to control problem.

Biomarkers and related innovations may become valuable tools for the first three sequences in the control of environmental health problems.

Definitions

Environmental monitoring is the measurement of a contaminant’s concentration in a medium (3). Exposure is the contact between a substance and surface of the human body through inhalation, ingestion and dermal communication. The conceptual model for exposure-related diseases offered by McClean and Webster depends on the reality that, health is a result of interaction between environment and genetic texture and facilitates to understand exposure-clinical disease period. (4). Personal exposure and the formation of clinical disease is expressed by the following stages; internal dose- biologically effective dose- early effect- altered structure or function- and all of these stages are effected by genetic susceptibility. (Fig.1, McClean and Webster).

![Conceptual model for exposure related disease](Fig.1, McClean and Webster, ref.4., pg 565).
Some of the scientists draw a parallel between these procedures and the matryoshka doll (5). For the pollutant after entering the target molecule there is no other border to be passed, and the difference between exposure and dose disappears. In some of the references life style is also added to the model (6).

Biological markers or biomarkers give information about the activity of a substance after its absorption. It means they bare indicators of events in a biological system (4). WHO defines the biomarker as “a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body” (7). In clinical practice biomarker can be taken as a measurable characteristic that reflect the presence or severity of any disease state (8). Interest of public health is the use and application of biomarkers to identify the nature and amounts of chemical exposures in occupational and environmental situations and using some of them in the community screenings as a tool of prevention.

Many researchers concentrated on studies to develop biomarkers of exposure to chemicals and applied these for human monitoring. Main goals are to develop biomarkers that reflect specific exposures and permit the prediction of the risk of disease in individuals and groups (8). In this case biomarkers become an important tool in clinical practice, scientific research, and public health and even in the determination of policies (4).

An ideal biomarker should have the following properties (9-13):

- Could be measured on a readily available and harmless biological sample.
- Should measure the extent of exposure or the harm given to the living organism.
- Should be related directly with action mechanism of the pollutants
- Should be an extremely sensitive technique which requires very small samples.
- Should be easy to conduct and cheap (Cost effective).
- Should be convenient for different species (If it is also being planned to be used for the determination of the natural life exposure)

As a result of environmental exposure which is multifactorial, lacking specificity, having susceptibility differences among individuals and latent period; different results may be observed. Except for using some certain indicators it will be impossible to determine a real causality relation. In this case new analytic methodologies should be developed, validation studies, big scale field studies in representative samples should be conducted (8). In this aspect the statement of WHO is very important:

“Biomarkers may be particularly useful when they provide linkage to important exposure, but must be measured in the correct matrix for exposure route/source of interest, and there must be analytic technology available, reliable, and reproducible. Without proper study design, bio-monitoring can be confusing at best and dangerous at worst.” (14, 15, 16). Matrix means the body fluid or tissue to be tested (4). These are blood, urine, breast milk, expelled air, hair, nails, saliva, teeth, meconium, amniotic fluid, adipose tissue and other tissues and fluids.

Biomarkers, although cause some difficulties, may generally be examined in three groups: markers of susceptibility, markers of exposure, and markers of effect.

Biomarkers of exposure indicate how much of a substance has contacted or been absorbed into the body. Biomarkers of susceptibility are used to identify individuals with unusually high (or low) susceptibility to a particular stressor or xenobiotic. Biomarkers of effect are directly related to the toxic endpoint of interest (17).

Biomarkers are most useful if we understood primary source of environmental contaminant, pathways and/or routes of exposure, exposure- dose relationship, if we know timing and duration of exposure and finally if we relate human exposure to animal toxicology studies (7,18).

Current Status of Biomarkers;
There are some advantages and disadvantages of biomarkers (7). McClean and Webster reported that one of the main advantages of biomarkers is the integration of the multifactorial and time depended personal exposure by different systems (respiratory, gastrointestinal and dermatologic) by the measuring internal dose and biologically effective dose. And stated that “instead of repeated personnel measurements, biological measurements will be enough” to determine average long term
exposure. In addition these measurements will also evaluate the person specific metabolism and biological metabolism procedure differences which may affect the dose.

Disadvantages of biomarkers
- Basically biomarkers are related with the determination of an agent and the indicator of an agent in different biological samples such as blood. Thus, effects the participation of the individuals in field studies if the method is interventional,
  - The biomarkers of many exposures is not known yet,
  - A biomarker may be transient and may not appear at the time of measurement,
  - Does not define sources, pathways or duration of exposure,
  - Cannot define toxic dose,
  - Susceptible to inferior or unscrupulous analytical laboratories,
  - Lack of meaningful reference levels,
  - Lack of toxicological and epidemiological information about the vast majority of environmental chemicals.

Advantages of biomarkers
- Confirms absorption into the human body,
- Measures integrated exposure,
- Very low level exposures detectable,
- Helps to follow exposure trends,
- Helps to evaluate public health interventions.

Future of environmental exposure biomarkers
Biomarkers will be such an approach that will create evaluation chance between relation of environmental impact and environmental exposure. Maybe in the future it will become more prominent basic methods of public screening (20, 21).
1. The pathology of the disease will be understood better,
2. Provide more certain exposure assessment,
3. Reveal dose – response relation,
4. Reveal risks especially in low dose exposures,
5. Give a chance to diagnose the disease at its earliest stage,
6. Give a chance to determine the individuals who may be more sensitive and affectable to some exposures,
7. Exposure assessments become more efficient and prevent incorrect classifications.
Such errors by causing incorrect exposure classification may result in erroneous outcomes,
8. Determination of changes in the earliest stage caused by toxic exposure may increase the clinicians’ participation in preventive practices. In assessment of diseases with long latency period biomarkers will be helpful in saving time for the public health practitioners and epidemiologists. Especially will facilitate the difficulties about long latency period in cancer epidemiology (23, 24),
9. Early stage biomarkers may also be promising for the subclinical occupational diseases as screening tools,
10. The biomarkers used for determination of individual differences to the chemical exposures, may be very important tools for such assessments (25).

Assessments which are regarded as “non-specific” currently may appear as specific biomarkers with determination of molecular differences in the future. For example cellular and humoral immunity response may have extremely specific sub components. Many biomarkers may be identified including specific enzyme and hormone concentrations and communities’ phenotype distribution. In the identification of “traces” which are proven to be related with exposure, specific and measurable is most important issue (26).

Contribution of biomarkers to the analytic epidemiology assessments provided the improvement of molecular epidemiology concept (20, 21). The construction and development of reliable databases that integrate information from genomic and proteomic research programs should offer a promising future for the application of these technologies in the prediction of risks and prevention of diseases related to chemical exposures (8). Molecular epidemiology studies are needed to determine associations between exposures and disease (2, 27).
Currently adducts of chemicals with macromolecules are important and useful biomarkers especially for certain occupational chemicals. For monitoring exposure to genotoxic compounds protein adducts, such as those formed with hemoglobin, are considered effective biomarkers for determining individual exposure doses of reactive chemicals (8).

Molecular Epidemiology studies to identify relationships between occupational exposures and health outcomes are critical and can provide needed information about disease pathways and processes. Laboratory and field validation of biomarkers are needed. It requires improving study designs or survey methods because of there are many confounders and multiple exposures (27). It means exposure to chemicals with short half-lives, multiple-media, and multiple-chemical mixtures. As a result there are synergistic, additive, antagonistic, interactions and potentiation (28).

Mapping the human genome has created concept of the "exposome". Describing exposome require accurately measuring of exposures and their effect. The exposome can be defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. The impact of environmental or occupational exposures can be different for each individual because of differences in genetic and other personal factors. Some people will develop a disease while another person with the same or greater exposure will not. The exposome may help to determine the underlying causes for this difference (2).

Exposomics is the study of the exposome and use exposure assessment methods and data mining techniques (2). We need researches to determine utility of metabonomics (measuring of small molecular weight compounds act as signals to regulate metabolic systems) and adductonomics (DNA and protein adduct measurement) (2).

Although biomarker researches are continuously increase in living creatures other than human beings, the exposure assessment regarding McClean and Webster’s model cannot be used in human centered studies; this should be indoctrinated.

For assigning how the confounding factors and multifactorial exposure, change the susceptibility related with biomarkers, all the data all of related studies should be collected in a common database; and a common data base should be constituted. And the data collection should also be standardized.

Rapidly changing technologies and methodologies may not allow the comparison of the data sets. Methods for analyzing such big data sets should be developed.

In the “Measuring Environmental Exposure Workshop Report, Canada” the following priorities are determined. These priorities will facilitate the determination of future biomarkers which will be basic for preventive practices (28):

- The studies that might find correlation between environmental exposure and acute & chronic diseases and mental health problems
- Vulnerable people and populations,
- Individual susceptibility,
- Determination and implementation of interventions and changing their results.
- The biomarkers related with the living organisms which collect and accumulate the pollutants,
- New molecules and emerging issues related to new substances,
- Exposure gradients,
- Biomarkers of long-term, cumulative exposures,
- Sources of contaminants and the mechanisms by which they enter the body,
- Factors that cause epigenetic imprints and how to diminish harmful effects,
- The effects of gene-environment interactions on population health exposure assessment studies

GAPs about biomarkers that should be solved (fulfilled), future innovations;

Instead of studies which prioritize concentration measurements, the exposure assessment studies have to be preferred. Time averaged evaluations versus instantaneous measurements should be preferred. Environmental measurements are necessary but behavioral properties should not be neglected. If neglected erroneous conclusions may be reported (28).
New instruments and technologies should be developed for measuring both internal and external exposures. For the validation of bio-monitoring techniques new methodologies are necessary.

The rapidly changing technologies should not prevent the evaluation and comparability of the results. Providing common assessment of the past and future data and also developing biomarkers to determine past exposures are very important. These biomarkers will be very helpful to determine the exposures of long duration and to take preventive measures for the community.

NIOSH assume DNA alkylating agents, antibody formation, metabolites, adducts, genetic mutations, epigenetic changes, toxicogenomic effects as biomarkers of past exposures. These and other new biomarkers will become important research areas (2).

Synthesis of the results of various studies from different communities from different parts of the world gains importance (28). The priorities both nationally and internationally should be determined and harmonized for enhancing collaboration. For international relations ethical issues should be considered.

New researches to setup connections between various dispersed study fields should be planned. Thus, the results of the studies could be assessed holistically.

Determination of requirement related with measurement methods and platform of discussions will speed up innovations. For the onsite measurements the cost and other technological problems such as the battery life of the portable instruments should be solved.

This is a very promising research and innovation area. Since only measurements will not be enough, new modelling techniques should also be developed (28).

The opportunities of assessment of biomarkers together with environmental exposure results will facilitate the real preventive approaches.

There is not an agreement on the reliability of the biomarkers between the researchers (28). Since this may change the priorities of the researchers this may cause difficulties in collaboration.

The interventions related with exposure period will become more important continuously. After assessment of intervention results new methodologies should be developed.

It can be concluded that biomarkers will be future’s important tool of preventive medicine. During this period scientific researches and technologic infrastructure will be the driving force of many innovations and inventions.

References