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Rapid Diagnosis in Populations at Risk from Radiation and Chemicals

Edited by
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Rapid Diagnosis in Populations at Risk from Radiation and Chemicals

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RAPID DIAGNOSIS IN POPULATIONS AT RISK FROM RADIATION AND CHEMICALS

Rapid Diagnosis in Populations at Risk from Radiation and Chemicals
A. Cebulska-Wasilewska et al. (Eds.)
IOS Press, 2010

Preface

Populations can potentially be exposed to varying doses of ionising radiation or to hazardous chemicals as a result of an accident, act of terrorism, or war. This exposure could cause direct clinical effects within days or weeks or bring about late effects on human health in such as an increased cancer rate. A determination of the magnitude of the exposure to individuals is crucial so that those persons with a significant health risk can have appropriate procedures initiated immediately. It is extremely unlikely that the potential victims will wear adequate exposure indicators. Therefore, there is a critical need for a method to measure the dose from molecular and cellular effects that occur within the individual and that are associated with levels of chemical, biological, radiological and nuclear (CBRN) agents, and their possible short and long term effects on potentially exposed members of a population at risk. Many methods are now available for biological monitoring both of the environment and of humans, and measuring genetic damage and other changes in macromolecules and body tissues. Damage to DNA and other molecules, tissues, and organs after acute or chronic exposures are referred to as biomarkers. For the best kind of study, human monitoring needs close contact with many other disciplines like epidemiology, medical physics and others. As an experimental science, it also has to keep pace with the rapidly growing understanding of the language of the genome and mechanisms of deterministic and stochastic effects, particularly risk of cancer. An individual's genetic constitution, lifestyle, age, diet and levels of physical activity, can affect the body's response to exogenous agents. Gene and pathway complexity have to be considered when investigating gene–environment interaction and "phenotypic" response of individuals at risk. The efforts of research and applied science should ultimately contribute to an approval of regulated biodosimetry and diagnostic tests integrated into the national and international radioprotection and human monitoring programs. The main aim of the RADIPER NATO Advanced Training Course was to cover scientific aspects in this field by taking in advance the best action to protect the public against consequences of terrorism and other threats on the basis of state-of-the-art knowledge. On the 95th anniversary of the First World Scientific and Scientists Service for Protection Against War Injury, and on the 60th anniversary of NATO, we have welcomed to Poland scientists and researchers from 22 countries, with the support of the NATO Science for Peace and Security Programme. We have welcomed them to the country of Madame Curie[1] (awarded twice with the Nobel Prize). Maria Skłodowska-Curie was the first, in 1914, to organize radiological and therapeutic services for the frontline of the First World War and to start training courses for medical doctors and nurses from two continents.

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[1] *Nobel Award 1903* - 'In recognition of the extraordinary services they have rendered by their joint research on the radiation phenomena discovered by Professor Henri Becquerel'. *Nobel Award 1911* - 'In recognition of Maria Skłodowska-Curie services to the advancement of the chemistry and many other fields of radiation research, by the discovery of the elements radium and polonium, by the isolation of radium and the study of the nature and compounds of this remarkable element'.

We hope that participants of the RADIPER course have gained knowledge of the deterministic and stochastic effects and biomarkers associated with humans' early and late health risk, after exposure to physical and chemical agents. We hope they have also gained expanded practical skills in detecting biomarkers of exposure to genotoxicants using different well established biological assays, such as dicentrics, micronuclei, translocations, premature chromosome condensations, comet and more.

Finally, we hope that the participants of the RADIPER course will cherish and preserve the created network for use in the future, in order to protect the public from a pointless health risk.

The Editors

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Monitoring Exposed Populations for Health Risk Assessment Using Biomarkers[1]

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Abstract. Exposure to environmental toxic substances is a significant cause of human health problems. However, the critical question to ask is, at what concentrations and exposure conditions are these substances hazardous to human health. One approach to address the question is to conduct population monitoring studies using reliable biomarkers that can be used to indicate excessive exposure, identify biological damage and functional deficit, and predict increased risk for health problems. In this review, the application of traditional and functional biomarkers in population monitoring studies will be presented. A major emphasis in the review is to show how to design rigorous study protocols so that results from these studies will be appropriate for use in disease prevention programs.

Keywords. population monitoring, biomarkers, chromosome aberrations, challenge assay, DNA repair, health risk assessment

Introduction

Traditional epidemiological studies are instrumental to our understanding of health hazards from exposure to environmental toxic substances. On the other hand, these studies, in general, do not provide information on dose response, mechanisms for disease induction and inter-individual differences in response to the exposure. To address these shortcomings, scientists began to incorporate analytical procedures into epidemiological investigations. The revised protocols became known as molecular epidemiological studies [1]. Subsequently, the analytical procedures were expanded to include a variety of biomarkers that assess chemical metabolites, cellular response to exposure and biological consequences. In this brief review, the use of biomarkers in population monitoring studies is presented.

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[1] Presented in the NATO (North Atlantic Treaty Organization) Advanced Training Course, Oct 19-23, Krakow, Poland

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1. Strategies for Designing Population Monitoring Studies

The underlying reason for conducting population monitoring studies is to investigate whether exposure to certain environmental hazardous substances at some particular level poses a health risk to the population. In these investigations, scientists often use biomarkers to make the linkage between exposure, induction of abnormal biological effects and functional deficits, and risk for development of disease.

The initiation of a population study is often caused by the recognition of a serious pollution problem and the concerns for health problems in an exposed population. After gathering some exposure information and the composition of the exposed population, it is then necessary to conduct a careful literature research to validate the levels of health concerns. With the well-organized information, it is possible to formulate a good study hypothesis. The hypothesis should be testable with a well-designed investigation. It is essential that the design includes a vigorous protocol in the selection of individuals and appropriate biomarkers for the study. The overall goal of the investigation is to confirm or refute the health concerns and to test assumptions.

A vigorous protocol for the selection of exposed and control populations should include a list of predetermined criteria for inclusion or exclusion of volunteers. The selection process should be open to all qualified individuals so that there will not be a selection bias and/or any under-representation of certain subgroups of individuals.

It is well known that previous or concurrent exposure to other hazardous substances will have an undesirable effect on the outcome of investigations. These other environmental factors may include occupational exposure to other toxic substances, use of toxic medications, smoking of cigarettes and living near hazardous waste sites. In addition, it is important to select healthy individuals because certain medical conditions will influence individual responses to the exposure. Since the cigarette smoking habit is so prevalent in the population, it is, sometimes, impractical to exclude them from the exposed population but to match them with unexposed controls.

It should be emphasized that having appropriate controls is an essential component of the study. Ideally, the controls are identical to the cases in all aspects except the exposure conditions. In practice, the controls are selected based on the same criteria that are used for the exposed, except for the exposure. Then, the two qualified populations are matched based on certain essential characteristics such as age, gender and ethnicity. A general approach for matching for age is +/- 5 years. For studies using small populations, e.g. around 50 cases and 50 controls, the matching can be done on a one-to-one basis. When the study populations are larger, frequency matching is more practical. In the latter approach, the matching is done based on the group characteristics rather than on individuals, (e.g. matching the mean age and pack-years of smoking for the two groups).

2. Selection of Biomarkers

Several review papers have addressed the use of different biomarkers in population monitoring studies [2, 3]. A summary of representative biomarkers is shown in Table 1. The available biomarkers are grouped into several categories: biomarkers of exposure, biomarkers for early biological effects and biomarkers for health risk. Biomarkers that are listed on the top of the table are of higher value because of their sensitivity and/or

specificity of measurements. It should be emphasized that a combination of biomarkers needs to be selected for the study in order to demonstrate the linkage from exposure to biological effects and to health risk.

Table 1. Traditional biomarkers for population monitoring studies[a]

Biomarkers that are useful for indication of		
Exposure	**Early biological effects**	**Health risk**
Chemical metabolites	Chromosome aberrations	Chromosome aberrations
DNA adducts	Micronuclei	Specific gene expression
Protein adducts	DNA strand breaks & repair	
	HPRT gene mutation	
	Glycophorin A mutation	

[a]The biomarkers under each category are listed in the order of usefulness, the highest on top.

3. Functional Biomarker

Recently, several new interests have been focused on developing biomarkers to provide information on genome-based responses and on functional deficit to exposure. The former is based on genome-wide analysis and bio-informatic interpretation of the vast amount of data. Development of a functional biomarker, the cytogenetic challenge assay, is based on the assumption that the extensive and complex DNA machinery can be damaged by exposure to environmental toxic substances [4, 5]. Furthermore, damage to any component of a repair pathway will interfere with the pathway-specific repair activities.

In the challenge assay protocol, lymphocytes from exposed individuals and matched-controls are irradiated in vitro with 100 cGy X- or γ-rays (or 6 Joules/m UV-light) at the G_1 phase of the cell cycle and the expression of chromosome aberrations (CA) is determined at the metaphase stage of the cell cycle [6]. The X- or γ-ray-induced DNA damage would be subjected to the vast DNA repair machinery throughout the G_1, S, and G_2 phases of the cell cycle. Increased level of observed CAs in the exposed individuals compared with that in the controls is therefore indicative of in vivo exposure-induced DNA repair deficiency, e.g. chromosome deletions indicate the lack of (or incomplete) repair and translocations indicate mistakes in repair activities. Using the protocol, cigarette smokers, and workers exposed to butadiene, lead, pesticides and styrene, and residents exposed to uranium mining and milling waste and those exposed to heavy air pollution were found to have significantly higher CAs than the respective matched-controls [5]. On the other hand, mothers who were exposed to low level of air pollutants and workers who were exposed to very low levels of benzene did not show the defective repair capacity [5]. These studies show that prolonged exposure to environmental toxic substances, at high enough concentrations, causes damage to cellular repair mechanisms. In addition, the prediction of cancer risk among the uranium-exposed population [7] was confirmed by independent cancer epidemiological studies [8, 9].These studies show that such exposure was significantly associated with the development of lung and kidney cancers.