Review Article

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Biomarkers Journal
ISSN 2472-1646

2016
Vol. 2 No. 1: 1

DOI: 10.21767/2472-1646.100009

# Biomarkers: An Essential Gizmo in Pesticide Toxicity

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**Citation:** Kori RK, Jain AK, Yadav RS. Biomarkers: An Essential Gizmo in Pesticide Toxicity. Biomark J. 2016, 2:1.

## Abstract

In the recent years the uses and applications of pesticides has been tremendously increased and therefore the risk of exposure to human also increased with adverse health effects including neurotoxicological alterations. Pesticide residues and their metabolites have been detected in dietary constituents, food materials, tissues, maternal blood and breast milk, which are further linked to the developer and neurological disorders. Biomarkers are considered as an important determinant for the examination of organ function, investigation of diseased conditions and therefore could be useful for the analysis procedure. In view of the increasing risk of human health through pesticide exposure, the present review has been focused on the use of biomarkers in pesticide induced biochemical and neurochemical alterations which could help in biomonitoring studies of populations exposed to pesticides along with the main routes of uptake and mechanism of action, which can be used to monitor risk assessment in occupational settings.

**Keywords:** Pesticides; Biomarkers; Human exposure; Neurological disorder

**Received:** December 11, 2015; **Accepted:** December 24, 2015; **Published:** January 03, 2016

## Introduction

In India, most of the population is dependent on traditional agricultural methods and therefore it becomes the largest producer of pesticides in Asia [1]. The risk of exposure to human has been increased and associated with various health hazards due to its high production and use pattern. The exposure of pesticides to human could be accidental or occupational during manufacturing, applying, handling of crops and public health issues [2]. Also, its exposure is quite imminent due to its indiscriminate and injudicious use in households, agriculture, veterinary practices, occupational and non-occupational settings [3, 4]. The contamination of food by means of crops through routinely sprayed with pesticides is an important source of exposure due to its accumulation in animal's tissue and food products [5, 6]. At the same time high levels of residues of organophosphate, pyrethroids and their metabolites detected in the dietary products and biological tissues of exposed individuals associated with adverse health effects are again a matter of concern (7-9]. Cases of pesticide poisoning from India and many other countries have been frequently reported [10-12]. The organophosphate pesticide such as monocrotophos and others are expected to involve the highest incidences of suicidal poisoning different regions and States of India [11, 12].

Several epidemiological studies have identified pesticide exposure as a significant risk factor for the various health problems, neurological disorders, including Parkinson's disease, Alzheimer's disease and multiple sclerosis [13-15]. The other negative outcome of pesticide exposure includes birth defects, fetal death, still, preterm birth, adverse pregnancy outcomes and neurodevelopmental disorder [16, 17]. Association of pesticide exposure with the incidence of chronic diseases, multiple myeloma lung sarcoma and cancer of the pancreas, stomach, liver, bladder and gallbladder, mitochondrial dysfunction and oxidative stress have been frequently reported [15, 18, 19].

## Biomarkers of Exposure

Biomonitoring can be defined as the standardization of analytical methods for diagnostic examination of biological materials to recognize a subject's health, whether it is suffering from exposure of pesticide, hazardous substance or intoxication [20]. Further, these biomarkers could be categorized as pesticides, their

metabolites or reaction products in blood or blood components, urine, exhaled air, hair or nails and tissues [21, 22]. Biomarkers are measurable indicators of diseased or toxic conditions, pathogenic processes or pharmacological responses to a xenobiotic agent [23]. These are used to measure and evaluate the normal biological and pathogenic processes, or pharmacologic responses to monitor and predict health status in the populations so that appropriate therapeutic measures intervention can be adopted. A single or multiple biomarkers together can be used to assess the health or disease condition of an individual which are specific for each biological system. Most of these biomarkers are safe and easy to measure, cost efficient and consistent across gender and ethnic group which form the part of routine medical examinations. These are used to predict serious illnesses such as diabetes, cardiovascular disease, neurological disorders, etc. Biomarker indicates the detailed picture about the health of a person and let know whether or not a diagnosis needs to be made. Also, a biomarker can be a substance used to trace its pathway to examine organ function or other aspects of health. It refers to a broad spectrum of the medical signs and symptoms, including from in vitro assays to molecular imaging and genetic mutations which could be precisely measured with reproducibly. These measurable indicators include blood, body fluids or tissue that represents an abnormal process or diseased condition. Biomarkers can be classified into two types including biomarkers of exposure which could be predictive of risk and associated with the measurement techniques and the toxicokinetics of the substance and biomarkers of effect which cover a range of measurements such as assays on blood and liver, tissues, depending upon the nature of the effect under investigation and it provide information about the mechanism of action. The development of various biomarkers related with the functional organ or system is represented in **(Figure-1)**.

## Blood

The residues of pesticides in blood or other blood products including serum, plasma have of great importance to monitor their exposure. The parent compound of pesticides could be directly analyzed in blood while their metabolites are usually detected in urine. The measurement of the pesticide in blood is the most complex due to the instability of the pesticide in blood [21, 24]. At the same time the blood collection by invasive techniques such as venipuncture puts some ethical issues to obtain samples from children and pregnant women [25]. In these cases, the amount of blood collected is often limited to perform the analysis, hence; very ultrasensitive analytic techniques are required. Further, the concentration of residues in a blood sample is very low therefore the analysis procedure becomes complicated [26, 27]. The blood obtained from umbilical cord could overcome some of these concerns as we could get a large quantity of blood sample (>30 mL) without veinpuncture. The measurement of pesticide residues in the blood provides information about the dose available for the target organ or site which could be helpful for the determination of the dose – response relationship. Also, blood can be a valuable biomarker for the determination of adducts to DNA, hemoglobin or albumin, which is useful as early biomarkers of effect, providing more relevant information related to a selected health effects [21]. Blood plasma can be used for the detection of alterations in neurotransmitters in pesticide exposed population. Platelet in a blood sample depicts dopamine and serotonin receptors, which could be a useful tool for the neurotoxic alterations in pesticide exposure. At the same time, biomarkers also could be useful in the diagnosis of cardiovascular diseases. The identification of such biomarkers able to detect the early stages of such diseases which may be helpful to reduce the worsening of clinical condition. Soluble ST2 (suppression of tumorigenicity 2) is a blood protein involved in pathophysiology of myocardial dysfunction. The measurement of soluble ST2 protein in blood samples could be a clinical prognostic biomarker of cardiovascular diseases, myocardial infarction, heart failure and dyspnea [28].

## Urine

As compared to blood, urine is the most common biomarker used for the monitoring of pesticide exposure and toxicity. It is the ease of sample collection having the large amount of concentration of metabolites and also present in abundance in the analysis. In some cases, including infants and small children the collection of urine sample needs special consideration. There are various factors which affect the daily urinary outputs includes water intake, urea, salts, specific gravity and osmolarity. Also, the concentration of toxicants and their metabolites may vary with varying amount of urinary outputs [29, 30]. Urinary excretion rate calculations can be used to eliminate the variations in metabolite levels due to water contents [31]. The metabolite present in the urine is a very specific indicator of pesticide exposure than the AChE monitoring which have been demonstrated in several studies in children [21, 32, 33].

## Saliva

Saliva can be used as a matrix for the evaluation of pesticides as it has also been used to assess a variety of biomarkers, drugs, and environmental contaminants. It represents a simple and readily obtainable fluid which could be utilized as biomarker but it is based on the pharmacokinetics of the chemical [34]. Studies have been reported to use saliva as a biomarker but the findings indicate that the levels of pesticide in the saliva are very less than those present in blood and urine. Therefore the presence of concentration of pesticides in saliva may indicate its availability in the organ or tissue and will helpful for the biomonitoring process [35]. Studies are also available to find out the levels of AChE in saliva but due to the very low concentration it could not be used as a replacement for blood for the assay of AChE levels [34, 36]. At the same time the variation in AChE levels also depends on the inter-individual variations. Further, the use of saliva as a biomarkers needs very sensitive and specific analytical techniques for qualitative and quantitative analysis [34].

# Enzymatic Biomarkers

Acetylcholinesterase (AChE), an enzyme involve in the degradation of acetylcholine, is one of the most important biomarker in case of pesticide toxicity especially in organophosphate toxicity. Alterations in the erythrocyte AChE and serum butyrylcholinesterase (BChE) have been reported in organophosphate induced toxicity [36, 37]. Organophosphate compounds are largely associated with the

inhibition of the activity of AChE through phosphorylation [38]. AChE is generally present in the brain, but it is also present in red blood cell membrane while BChE is synthesized in the liver and is available in serum. The activity of both AChE and BChE could be measured in blood samples as a substitute for neuronal AChE activity. These enzymes are considered as convincing biomarkers in organophosphate induced health effects as they give early warning of exposure prior to adverse clinical health effects occur in individuals. Inhibition of AChE at nerve terminals causes over accumulation of acetylcholine, neurotransmitter involve in the process of synaptic transmission, leading to paralysis and finally cell death through the apoptosis.

Altered levels of neurotransmitters, including dopamine and serotonin in pesticide induced toxicity have been reported which are further found to be associated with the Parkinson'd disease, depression and anxiety disorder [39-41]. Experimental studies are available that exposure to environmental chemicals, including pesticides may affect the integrity of the serotonergic system and hence decreased the brain serotonin levels [42-44]. Exposure of pesticides to the individuals have also been reported to enhance the oxidative stress through the production of reactive oxygen and nitrogen species which in turn further increase lipid peroxidation, protein carbonyl contents, DNA damage [45-47] and decrease the levels of reduced glutathione, superoxide dismutase, catalase and glutathione peroxide, enzymes involve in the antioxidant defense mechanisms. The analysis of these oxidative stress biomarkers could establish a link between the exposure pattern and diseased condition.

## Conclusion

The uses of biomarkers in the diagnosis of clinical conditions, drug development process and biomedical research have been increasing in the recent scenario. There is an urgent need for the development of early and sensitive biomarkers that will enable to diagnose the pesticide induce clinical damages and through which we could administer therapeutics and safety assessment studies for the development of some defensive mechanism. In preclinical studies, the identification of specific and reliable biomarkers for carrying out the right assays in toxic effects of experimental compound is very important. With this aspect of analysis these biomarkers can be used to confirm the targets, reveal the mechanism of action, predict the therapeutic usefulness and help to select the right patients for the alert of toxicity.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgement

The authors are thankful to Dr. Harisingh Gour Central University, Sagar (MP), India for providing the opportunity to work and their support and interest. Authors are also thankful to the University Grants Commission (UGC), New Delhi, India for providing the UGC-BSR startup research grants and research fellowship.

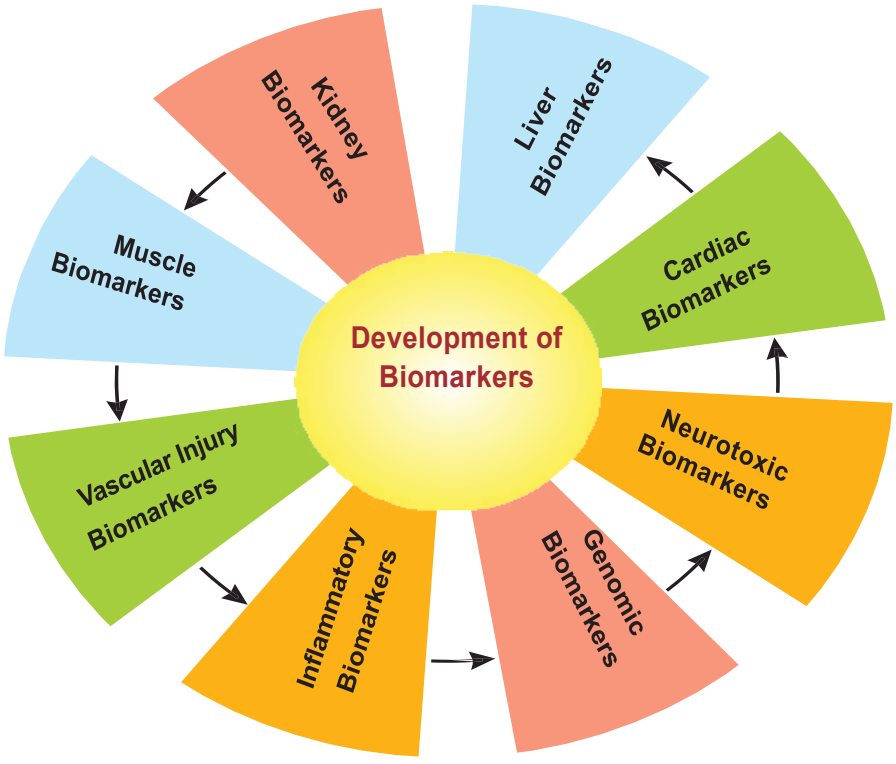


**Figure 1** Development of various biomarkers related with the functional organs or system.

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