

Ecotoxicology and Biomarkers For Assessing Health Risks In Exposure To Agrochemicals

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ABSTRACT

Interindividual variation in response to agrochemicals and their potential toxic effects is mediated by intrinsic and extrinsic factors. The intrinsic variations stem from inherited predispositions exemplified in different blood groupings, immunoantigens, metabolic activation and detoxification, and DNA extrinsic factors include the geographical climatic variations, background of infectious diseases, health sanitation, socioenvironmental stresses and standard of living. Populations in developing countries have their own genetic trait characteristics where some genetic diseases are more dominant e.g. sickle cell anemia such as schistosomiasis and hepatitis viruses are more abundant in the poor sanitation conditions of the third world countries. These unfavorable genetic and ecological factors when interacting synergistically together will render the people in the developing countries at higher risk because of high susceptibility to exposure and health hazards of agrochemicals. Highly susceptible population groups in general and those in the third world in particular, require specific biomarkers to measure and assess the agrochemicals. In this review, attempts are made to address such specific biomarkers needed to detect and to evaluate the levels of susceptibility, exposure and adverse health effects of agrochemicals with special reference to pesticides in developing countries.

Hazards of Transported and Bioaccumulated Toxic Residues

1. Pollution Transported by the Atmosphere

Synthetic chemicals, e.g. DDT and PCB's are concentrated by high-lipid marine organisms. Such substances are sometimes found in the surface microlayers in association with films and microorganisms.,

They are readily available for transfer to the atmosphere by bubble bursting and wind spray. Besides, some of these persistent pollutants have an appreciable vapor pressure which constitutes a main source for atmospheric input and transportation to remote areas far away from the initial sites of application or release. The GESAMP report 13 (1980) discussed the interchange of pollutants between the atmosphere and the oceans. The report also mentioned that aluminium showed the higher crystal material of the global flux of metals to the atmosphere.

Bidleman *et al.*, (1987) emphasized the presence of organochloride pesticides and polychlorinated biphenyls in the atmosphere of Southern Sweden. Human milk samples from Sweden and Finland also showed traces of polychlorinated camphenes (PCC). Since these pesticides are not used in Sweden, air transport from distant application regions is a likely source.

2. Translocation From Soils

Movement of pesticides in a matrix is a dynamic process. Upward as downward movement can occur over a period of time. Volatilization of a pesticide from the soil from the soil surface will depend primarily on its inherent volatility (McMinn and Roberts, 1983). Experimental evidence proved the uptake of PCB,s and chlorinated hydrocarbon insecticides, e.g. DDT, BHC, and endrin via the soil and the food chain through the non target soil organisms such as the earth worms.

3. Across the Food Chain and Placenta to the New Born Babies

Octanol / water partition coefficients have correlated with the bioaccumulation of organic chemicals in biological systems. Once ingested, chemicals residues of highly lipophilic characters accumulate in the fatty portions of adipose tissues, heart, milk and blood (Travis *et al.*, 1988). Besides, Pyysalo and Antervo (1985) detected toxaphene in Finnish seals, fishes, human milk and adipose tissues. Kanja *et al.*, (1982) reported that organochlorine pesticides are transferred from the mother to fetus and new born babies through placenta and mother,s milk.

Similar data were reported by Albert (1983), Ansari *et al.*, (1986) and Matuo *et al.*, (1992). Patterson *et al.*, (1988) indicated the

high correlation between human adipose tissue dioxins content (2,3,7,8-TCDD) and the serum level. Dioxin is the main impurity of the 2,4,5-T herbicide released in the environment.

Health Risk of Long Term Exposure To The Pesticides and Related Toxicants

1. Hazards To Non-Target Organisms

According to Hansen (1993), the hazards associated with synthetic chemical pesticides are widely known. Extensive use of pesticides result in adverse effects on non-target organisms. Soil microorganisms, and earth worms are killed resulting in disturbing soil ecology. In rice areas, fish crab, and frogs which are used as food are killed. Host plants are affected by phytotoxicity. Birds and mammals are poisoned. Besides, pesticides frequently kill bees thus reducing pollination and crop yield, and also reducing honey production. Finally, heavy and indiscriminate use of pesticides is often counter productive and unsustainable in the long run due to the twin problems of wide-spread multiresistance, and resurgence of heavy infestations and also outbreaks of the secondary pests (FAO/UNEP,1992).

2. Pesticide Residues and Cancer Risk

Hileman (1993) reported that recent research pointed to organochlorines as one possible cause of cancer whose rates are rising in the general population. The occurrence of several of these cancers is also rising among farmers but at a faster rate. This increase in certain cancers in farmers points to a common cause, occurring in excess include non-Hodgkin,s Lymphoma, multiple myeloma, leukemia, and cancers of skin, prostate, brain, pancreas, and kidney. Children who used a lindane-containing shampoo to kill lice were found to have increased rates of brain cancer.

Fat tissue in woman with breast cancer has been found to have higher levels of DDE than that of healthy woman. It is believed that DDE from organochlorines can mimic estrogen and could bind to estrogen receptors and thereby increase the body,s effective estrogen level which is essential for the initiation of mammary gland tumors in animals and humans and also promotes these tumors. Atrazine and

other triazine herbicides may play a role in human breast, prostate, ovarian and endometrial cancer by inducing some hormones and inhibiting others, (Colborn et al., 1993).

3. Health Risk Assessment of Chemical Mixtures

Complex mixtures of related compounds used or produced as commercial products, e.g. PCB,s, gasoline, and pesticide formulations are eventually released to the environment. It is generally recognized that toxicant interactions may occur during any of the toxicology processes that take place with a single compound absorption, distribution, metabolism, excretion and activity at the receptor site(s). This is why EPA published in 1985 guidelines for the health risk assessment of chemical mixtures of pollutants.

4. Endocrine Disrupting Agents and Reproductive Adverse Effects

A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans. Among these are the persistent, bioaccumulative, organohalogen compounds that include some pesticides and industrial chemicals. (Colborn, 1995).

Chemicals known to disrupt the endocrine system include: DDT and its degradation products, DEHP (di-(2-ethylhexyl) phthalate), dicalof, HCB (hexachlorobenzene), kepone, lindane and other hexachlorocyclohexanes, methoxychlor, synthetic pyrethroids, triazine herbicides, EBDC (ethylene bis-dithiocarbamates), certain PCB,s, 2,3,7,8-TCDD and other dioxins.

It is during differentiation that construction of the vital physiological systems and programming of the pituitary/hypothalamic region of the brain take place, this time that endocrine disruption may be the most threatening leading to endocrine, immune, and nervous systems that are unsound, and hypothalamic that do not respond to normal hormonal and neurotransmitter messages. The endocrine system holds the key to fertility. For some sensitive populations the message is clear: avoidance and prevention are the only options for survival.

5. Genetic and Molecular Ecotoxicology

It can be defined as the induced changes in the genetic material of natural biota. Changes may be direct alteration in genes and give expression or selective effects of pollutants on gene

frequencies including direct DNA damage, epigenetic effects, and changes in gene pools attributable to toxicant exposure (Anderson et al., 1994).

6. Epidemiological Biomarker of Exposure Effect and Susceptibility to Pesticides and Agrochemicals

Measurement of activity of target enzymes, hormones receptors, and neurotransmitters are commonly used as a biomarker for acute and short term exposure to agrochemicals including pesticides as well as other toxic chemicals. However, few biomarkers have been validated as tools for environmental epidemiology. Validation of any epidemiological biomarker must involve the following four stages : association between the marker and a preceding exposure or subsequent effect; dosimetry of the exposure/marker relationship; the threshold of “ no observed effect level” if any; and the positive value of the biomarker for exposure or adverse effect. Besides, the biomarker must have the capacity to include and identify the genetically and occupationally highly susceptible individuals in the exposed group. The successful biomarker must finally be applicable under both laboratory and population conditions (Griffith , 1989). To determine whether the biomarker is measuring the degree of exposure, the adverse effect (disease) or the level of susceptibility in an exposed population depends on the available knowledge and the possibly quantified biological processors or phenomena under exposure. DNA and various protein adducts are promising as biomarkers for epidemiological and long term continuous exposure to low levels of pollutants including the hazardous agrochemicals. Increased rate of hepatic biosynthesis of protein, DNA, and RNA are indicative of the inductive effect which activates cytotoxicants (El-Sebae *et al.*, 1988). The specific potential of agrochemicals to bind with DNA and RNA can be used as a criterion to predict for their cytotoxicity. DNA and protein adducts also can be used to measure exposures that cause other non-genotoxic adverse health effects. Protein adducts could be a better reliable measurement of exposure dose levels than DNA adducts because the protein adducts are not repaired and tend to persist for the life of the protein which reaches 17 weeks in the case of hemoglobin in humans. The protein adducts are therefore useful as a biomarker of exposure because they fulfill the criteria of linear dose-response

relationships for single exposures (Snell, 1990). Hemoglobin adducts were successful biomarkers for blood levels of exposure to ethylene oxide and lead (Golkan *et al.*, 1990). Recently, there was evidence that rats, serum protein profile reflects electrophoretic gradient changes inducted by the dermal administration of malathion to rats (Abou Zeid *et al.*, 1993). Similar data were reported showing specific alterations in the serum protein profile as a result of *in vivo* application of a sublethal dose of cyanophos. In vitro incubation of rat serum with a sublethal level of a number of cyclodiene and lindane insecticides, PCB,s and trichloroethane showed characteristic changes in the rat serum protein profile as shown by SDS-PAGE followed by laser integration scanning and by FPLC chromatography. Preferential binding of rat serum transferring with albumin cations showed another example of using specific blood protein as specific biomarker for detection and quantification of Al³⁺ cation intake during occupational or medical treatments (El-Sebae *et al.*, 1994). It can thus be concluded that most DNA, hemoglobin, albumin, and blood proteins are selective sensitive biomarkers of exposure and effective dose (Timberell *et al.*, 1994).

7. Immune Dysfunction as a Biomarker for Exposure to Toxic Chemicals

Immunotoxicology is the study of adverse effects on the immune system that result from exposure to toxic chemicals including industrial, agrochemicals, pharmaceuticals, and environmental pollutants. In these instances, the immune system act as a nonspecific target of the xenobiotic, which may lead to an increased incidence or severity of infections disease or neoplasia because of an inability to respond to an invading agent.

The sensitivity of the immune system to reflect the environmental stress and particularly the xenobiotics, suggests using the immune response and its suppression as a biomarker for long term health adverse effects subsequent to exposure to hazardous agrochemicals including pesticides. However, it is a real challenge to distinguish homeostatic changes from pathogenomic ones. Several investigators in the last decade have used the immune system marker to indicate biological response for low doses of toxic substances (Burger *et al.*, 1987). In one of the studies, some of the strengths and limitations in using markers are the effect on the immune activation

and autoantibodies in persons who have long term inhalation exposure to formaldehyde. Four groups of exposed patients were compared with controls. The four exposed groups have shown higher antibody titer to antibodies to formaldehyde-human serum albumin (HCHO-HAS) conjugate; and increases in Tal+, IL2+, B cells, and autoantibodies were recorded (Thasher *et al.*, 1990). It was found to be much better to use a collection of immune system marker because no single marker will accurately reflect the state of the immune system as a whole. Two pesticide fertilizer mixtures were examined for their ability to induce immunotoxicity in mice. This mixtures were made to resemble ground water contaminations from agrochemicals in either California (aldicarb, atrazine, dibromochloropropane, dichloropropane, ethylene dibromide, simazine, and ammonium nitrate); or Iowa (alachlor, atrazine, cyanazine, metalochlor, metribuzin, and ammonium nitrate. No consistent suppression was shown for either mixture, however, a slight but significant suppression of the bone marrow progenitor cells occurred after 90 days exposure to the high dose of the California mixture (Thomas *et al.*, 1991).

Another type of molecular biomarker for adverse effects can be the cytogenetic investigation with peripheral blood lymphocytes, splenocytes, and pulmonary cell culture to monitor genotoxic effects of low level mixture or single toxicant. However, this research area is not yet fully developed and needs further exploration for standardization (Kilgerman *et al.*, 1987).

In a recent review on biomarker in toxicology, biomarkers of effect were emphasized to include several examples of different aspects. Inhibition of blood enzymes such as d-aminoleuvolenic acid dehydratase (ALAD) by lead. Number and damage of blood cells, e.g., presence of sister chromatic exchanges due to potential damage of chromosomes in workers exposed to ethylene oxide. Lack of particular lymphocytes indicating immune suppression caused by dioxin (TCDD). Similar, induction of cytochrome P450 isozymes, as a biomarker of the effect of many types of chemicals particularly organochlorine pesticides, polycyclic hydrocarbons and related chemicals. As a biomarker for long term exposure, it is suggested that we can make use of the urinary markers for cytochrome P450 induction by measuring the increased excretion of D-glucuronic acid and the 6-b-hydroxycortisol/17-hydroxycorticosteroids ratio

(Timberll *et al.*, 1994). A recently suggested biomarker for toxic effects are the stress proteins. Immunocytochemistry might be one of the best methods to quantify the specific heat shock protein HSP 72 which is found normally in minute levels. Heat shock proteins proved to be induced by various chemical stresses, and any increase can be easily related to the type of environmental stress (Hugget *et al.*, 1992). Although NMR has been used only recently to study biological systems, it has been proven to be a powerful technique and direct proton NMR of biological fluids such as serum bile and urine has been developed. The use of sophisticated techniques such as two dimensional correlation spectroscopy (COSY) analysis allows separation of overlapping resonances and greatly improved resolution of spectra. This new technique has the advantages of providing structure and quantitative information, it is rapid and not preselective. Therefore, any xenobiotic in body fluids can be detected and quantified (Nicholson *et al.*, 1989).

Chemicals induced immunosuppression may result through multiple mechanisms including cellular depletion or functional alternation in which the cells do not respond adequately to an antigen. Hypersensitivity is the result of an appropriate immune response directed against chemical agents that bind to host tissues and are recognized as foreign antigenic agents by the immune system. Such chemical-host tissue complex may lead to respiratory tract allergies (e.g. asthma or rhinitis) or allergic disorders. The chemical agents known to cause allergic disorders include anhydrides, aldehydes, isocyanates, organophosphate insecticides and some antibodies. Bautoimmunity, which has similarities to the hypersensitivity response is characterized by an immune response against self-antigens. However, several environmental chemicals e.g. vinyl chloride or trichloro ethylene and certain metals e.g. mercury, generate immune responses that may lead to the production of autoantibodies, although not necessarily to symptomatic autoimmune diseases (Nicholson *et al.*, 1989).

8- Immune Dysfunction as a Biomarker for Chronic Exposure to Organophosphate

A large number of epidemiological studies of organophosphate (OP) exposed populations revealed that farmers succumb more frequently lymphomas or hematopoietic tumors than would be

expected in healthy nonfarming populations (Luster *et al.*, 1990) and (Dean *et al.*, 1989) . Such data have been documented not only for farmers residing in the USA, but also for those in other countries (Rosenthal *et al.*, 1994). An excess of lymphomas has been recently reported in Italian farmers (Burmeister , 1981). Studies by epidemiologists from the National Cancer Institute in the USA have reported that the farm worker who acquire liver tumors in excess have been exposed to pesticides, which are postulated as the cause for the development of such tumors in exposed workers in the fields or grain mills treated with pesticides. Malathion, an OP insecticide was one of the identified chemicals by workers exposed to pesticide-treated grain. Several recent studies have shown OP-induced abnormalities in human cytotoxic T-lymphocyte, natural killer cell and cytotoxic monocyte functions that regulate human immune surveillance Lee and Waters (1985). Both chromosomal aberrations and cell-mediated immunity can be readily assessed using peripheral blood samples from populations at risk. In addition to OP- induced defects in natural killer cell and cytotoxic T-lymphocyte activities; the inhibition constants of human monocyte carboxyl esterase and plasma butyl cholinesterase, were compared. The data suggest that immune cell esterases may be a more sensitive marker of organophosphate exposure than plasma butyryl-cholinesterase, which is a standard biomarker currently used to detect OP exposure. Recent studies also showed that chronic OP exposures causing an impairment in esterase-dependent immune surveillance systems, may facilitate oncogenic virus infection, an increase in the frequency of lymphocyte mutations and the subsequent development of lymphomas (Pearce *et al.*, 1985). This is one of the good examples to demonstrate that chronic exposure to pesticides might lead to higher susceptibility to genotoxic and infections diseases. Several in vitro studies have also shown OP-induced mutations in human peripheral blood lymphocytes and human lymphoid cell lines B-cell origin (Alvauga *et al.*, 1990). The frequency of hybrid antigen-receptor genes in peripheral blood lymphocytes of agricultural workers has been determined to higher during pesticide application times than before or after the pesticide use, and significantly higher than controls. Thus, such functional OP-induced cytotoxic immune-toxic changes may represent sensitive

biomarker of chronic OP exposure and effect when integrated with duration and intensity of exposure.

9- Biomarker for susceptibility

There is an increasing interest in the role of genetic variation in toxic responses. Therefore, variation in human susceptibility and development of relevant biomarker are of increased importance. An example of the variation in metabolism can be described under the acetylator phenotype. The ability to acetylate and detoxify amines, hydrazines, and sulphonamides vary between individuals. Slow acetylators have mutations responsible for less functional N-acetyltransferase enzyme. There are correlations between slow acetylator phenotype, bladder cancer and occupational exposure to aromatic amines. On the other hand, different types of cancers (colorectal) have been linked to the fast acetylator phenotype. With the advancement of molecular biology we will be able to differentiate between these phenotype by gene analysis, rather than by biochemical reactions. It has been suggested also that taurine levels may be a useful biomarker of susceptibility. Urine taurine level reflects taurine status in the liver as shown in animal studies (Timberell *et al.*, 1994). Taurine in the liver is protective and when its levels are reduced, the liver will be rendered more susceptible to toxicants. This finding is crucial because humans normally do not biosynthesize taurine and depend on its dietary sources. Individuals with relatively less taurine in their liver will be at higher risk. Current risk assessment models fail to consider genetic predisposition that make people more sensitive or resistant to exogenous exposure and endogenous processes. Cytochrome P450 enzymes activating carcinogens show wide genetic polymorphisms and differ widely among various ethnic and genetic groups. In addition to the inherited factors for detection of susceptible individuals, determination of the effective dose of carcinogen will help in setting the risk assessment evaluation. DNA adducts will be an accumulative measure of exposure, absorption, metabolic activation, detoxification and DNA repair process. The combination of type and abundance of adduct and genotyping assays will reflect the interaction between exogenous and endogenous factors along the term exposure to carcinogens. Such criteria for risk assessment will be useful to differentiate between the level of cancer risks between individuals, and genetic traits by making the more vulnerable people.

A biological marker of susceptibility, the alpha-lantitrypsin ZZ allele, has been found to be associated with the disease emphysema. People with the ZZ homozygote are 30 times at the risk of developing emphysema than the general population. However, because emphysema has various causes, the heterozygous state—although genetically factors exist: e.g. pollution by cadmium, ozone, or cigarette smoke. Generally, the use of biomarkers of susceptibility in environmental epidemiology has the advantage of increasing both the precision and reliability of risk assessment and correlation between exposures and health diseases in populations without neglecting the highly susceptible section in the population which is diluted by the majority of the nonsusceptible.

Future extensive research is still needed to reach more sensitive measures and critical biomarkers that define the wide variation in susceptibility in a population, to protect those who are at high risk because they are more susceptible for one reason or another.

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