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Immunomodulation of Host as a Predictive Bio-Indicator of Toxicity in the Mammalian System

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ABSTRACT

Immune system is complex in nature, consisting of multi organ involvement in its activity. It is one of the most sensitive systems in the body. Any foreign material i.e. chemicals, drugs and micro-organisms, if enters in the body, may produce alteration in the function of the immune system. Only recently information has been generated that many environmental chemicals and drugs can produce modulation of the immune system in even low doses of exposure and for a short period. Some chemicals in low doses produce severe immunotoxicity well before producing any sign of overt toxicity to the other system. This can be only predicted by using immunotoxicological tests. The chemicals that enhance the immune response may predispose the host to auto-immune disease or lymphoreticular disorders resulting in allergic or hypersensitivity reactions. On the other hand, the chemicals that suppress immunity may sufficiently disrupt the immunoregulatory network, resulting in increased susceptibility to infection or to develop cancer.

In the recent past toxicological assessments were done by using lethal dose (50%) evaluation, use of biochemical and pathological examination of different organs, which gives information only about the cell number or degree of cellularity. The early effect of chemicals on the cell function may be missing in that type of study. Currently, the inclusion of immunological assessment parameters in toxicity evaluation of chemicals have made it possible to test the toxicity at the cellular level.

It has been well known that many of the environmental chemicals at very low doses can modulate immune system without producing any clinical sign or symptoms of the disease or disorders. It is of importance that assessment of immunomodulation can be used as a sensitive bio-indicator for predicting the toxicity caused by environmental chemicals, since immunotoxicity can be determined with much smaller dosages of chemicals than is needed for toxicity evaluation of chemicals using animals.

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1. INTRODUCTION

Toxicologists are asked to predict the toxicity of chemicals for certain animal species from time to time. It has been found that the immunobiological indicators are more sensitive than the biochemical tests for evaluating the toxicity of chemicals. In some countries, it is recognized that the interactions of environmental chemicals such as pesticides with the immune system of the host, have potential impact on public health. But the public health authorities are not alerted to these possibilities. Immune system, the body's own natural defence mechanism, is responsible for the well-being in many ways, including (a) rejection and destruction of both living and non-living foreign material, (b) neutralization of toxins of pathogens like virus, bacteria, parasites etc., and (c) the destruction of tumor cells. In a healthy individual, the immune system carries out its protective role with remarkable efficiency. When an individual's immune system is altered by infections, a number of serious disorders can result.

Recent investigations have shown that many chemicals and metals which persist in environment as environmental pollutants or formed as an impurity during their production, food and food additives and particulate pollutants, etc., are responsible for modulating defence system of the host.

2. EFFECT OF PESTICIDES AND INSECTICIDES

Pesticides are reported to be immunosuppressive in nature and may also be responsible for increased susceptibility to infections. They can also cause auto-immune diseases in exposed humans and animals. The presence of auto antibodies was considered to be a significant indicator of early pathologic process. Liver auto antibodies were detected in a group of persons having contact with organochlorine and organophosphorus pesticides.[1] Auto antibodies and tissue specific auto antibodies were found in humans and guinea pigs exposed to Caprolactam, Methapheniclene diamine, Polychloropinene, Thiram, Chlorophos, BHC and Methyl mercaptophos.[2,3] Anthio and Milbex were found responsible for anti hepatic, anti kidney, anti stomach and anti intestinal antibodies in goats.[4] Anti hepatic auto antibodies were also reported in mice and rats treated with Methyl mercaptophos, Phosphamide, Aldrin or Monuron.[5]

It has been found that occupational workers especially farm workers develo pallergic symptoms when sensitized with pesticides. It was confirmed by 'Patch test' and characterized by erythema, edema and eczema. Cases of photo allergy caused by pesticides have also been reported. Three cases of contact dermatitis related to flori-culture were reported. One case was reported from a flower shop and two from an office decorated with flowers and plants. In these cases fungicide, Meneb was found to be the source of allergen which was confirmed by patch test. The workers involved with cutting tops of unflowering Chrysanthemum plants, developed itching and burning sensations in arms, face, neck and abdomen. The plants were sprayed 2 hr before with a mixture of the insecticide Naled, fungicide Captan and the miticide Dicofol.[6]

Table 1. Effect of pesticides and insecticides on immune system.

Pesticide/Insecticide	Effect	References[56-61]
	Suppressed antibody titre	
Malathion, Paraquat, Thiophanatemethyl, Chlorothalomil, Menab, Trifluralin, Captafol	Allergic	
Namatin, Maneb	Dermatitis and sensitized lymphocytes	Matsushita et al.
Sevin, Dicresyl, Jalan, Tillam, Eptam, Maneb, Carbofuran, Methyl parathion.	Increased susceptibility to E.coli, S.typhimurium or Staphylococcal infection	Street & Sharma; Fan
Paraquat, Diqual	Decreased macrophage viability	Styles.
Carbofuran, Methyl parathion, DDT	Thymic atrophy, Suppressed tuberculin hypersensitivity, Reduced germinal centres in spleen	Street & Sharma; Fan
DDT, Mirex	Decreased IgG, Reduced activity of bursal, spleenic & thymic lymphocytes	Glick; Subha Rao & Glick.

Recently, attention has been drawn to study the effects of DDT on immune system, because it is known that DDT persists in environment and accumulates in animal tissues. Studies indicate that DDT exposed animals are more susceptible to infections and it can also alter antibody response in exposed animals. The effects of pesticides and insecticides on some of the immune parameters are shown in Table 1.

3. INDUSTRIAL CHEMICALS

3.1 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a highly toxic chemical, formed as an impurity during the production of some chlorinated phenols or chemicals, synthesized from compounds such as 2,4,5-T, a herbicide. Exposure to TCDD occurs indirectly after the application of 2,4,5-T as a defoliant.[7]

First report of thymic atrophy caused by TCDD came from Buu Hoi et al.[8] in 1972. Vos and his co-workers did extensive work on immuno-suppression caused by TCDD in experimental animals (mice, rat and guinea pig). Their study indicate a suppression in cell-mediated immunity in exposed animals. Thymic atrophy was one of the most sensitive parameters of TCDD exposure.[9-11]

3.2 Vinyl Chloride

It was observed that immune complexes were generally present in workers exposed to high concentrations of vinyl chloride.[12] It is believed that these immune complexes

may be responsible for its toxic symptoms. The symptoms of vinyl chloride toxicity are dermal induration, acro osteolysis, splenomegaly and thrombocytopenia.[13,14] Long duration of exposure may also lead to hepatic fibrosis or portal hypertension and angiosarcoma of liver.[15] Vinyl chloride may also develop various types of tumors in experimental animals.[16] Immunofluorescence studies of biopsy material of vinyl chloride exposed workers showed hyper immunoglobulinemia, cryoglobulinemia and cryofibroinogenemia along with anti tissue antibodies indicating the presence of immune complex disorders. It is suggested that a reactive metabolite may become antigenic after binding with the tissue protein and the binding of macromolecules in hepatic tissue was also found.[17,18] The increased level of carcino-embryonic antigen, present in exposed workers, may be used as a diagnostic test.[19]

3.3 Organotin Compounds

Organotin compounds are mainly used as heat stabilizers in PVC plastics, biocidal compounds for the preservation of wood, paper and textile, agricultural fungicides, miticide and acaricide, anti-fouling paints and as a catalytic agent in various industrial processes.[20-22]

These compounds may enter into human body by leaching of stabilizers from plastic into food, beverages and drinking water or from plastic medical devices into fluids. They may enter into environment by use in agriculture and by leaching from plastic disposables.[23] Therefore, the organotin pollution in environment can not be ruled out.

The toxicity of organotin compounds has been studied after a French tragedy known as 'Stalion affair' in which 217 people were affected, out of which 100 died. It was caused by a preparation 'Stalinon' which is used in the treatment of furuncles and staphylococcal infections.[24,25]

Organotin compounds affect thymus by decreasing the number of thymocytes and the thymus- dependent areas of peripheral lymphoid organs. Endotoxin mortality assay showed that the rats treated with di-n-butyltin dichloride (DBTC) or di-n-octyltin dichloride (DOTC) at 150 ppm dose level, were susceptible to Listeria monocytogenes.[26] Plaque forming cell (PFC) assay showed a reduction in the number of PFC of spleen and a reduction of hemolysin titre against SRBC in the serum of DBTC and DOTC exposed rats. Suppression of tuberculin hypersensitivity, skin graft rejection, graft vs host reaction and the mitogen responsiveness were dose related. A dose related decreases in lymphocyte blast transformation was found by PHA and Con A but LPS did not affect blast transformation. *E.coli* (LPS) stimulated spleen cells, did not show impairment in ^{3}H-thymidine uptake. Macrophages are not affected by organotin compounds, as shown by phagocytosis of carbon particles. This shows that dialkyl tin suppress the various sub-populations of *T*-cells without affecting the *B*-cells.[27-29]

4. METALS

Many metals such as lead, cadmium, mercury, zinc, arsenic etc. are known for their immuno modulatory effects. Some metals are toxic to animals and humans after

Table 2. Effect of metals on immune system.

Metal	Parameter	Effect	References[62-94]
Lead, Cadmium, Mercury Zinc, Arsenic, Cobalt, Nickel, Di-n-butyltin dichloride (DBTC), Di-n-octyltin dichloride (DOTC)	Susceptibility to E.coli, S.enteriditis, S.typhimurium or EMC virus	Increase	Sely et al.; Cook et al.; Rippe & Berry; Hemphill et al.; Koller; Gainer & Pry; Tripathy & Mackness
Lead, Cadmium, Mercury, Zinc, Arsenic, Magnesium, Platinum	Antibody synthesis-SRBC	Decrease	Luster et al. Koller & Kovacic; Koller et al.; Blakley et al.; Bozelka et al.; Ohi et al.; Luecke et al.; Fraker et al.; Fernandes et al.; Elin & Berenbaum
Lead, Cadmium, Mercury	Mitogen PHA	Decrease	Faith et al.; & Gaworski & Sharma
Lead	Delayed type hypersensitivity	Decrease	Faith et al. & Muller, et al.
Lead, Cadmium, Zinc, Nickel	Phagocytosis	Decrease	Filkins & Buchanan; Trejo et al.; & Loose et al.
Lead	Tumor growth-FBPA, MSB Sarcoma & Rauscher leukemia virus	Increase	Hinton et al.; Kerkvliet et al.; (in press) & Gainer, I
Cadmium	Tumor growth-MSB Sarcoma	Decrease	Karvliet et al.
Mercury	Tumor growth-Rauscher leukemia virus	None	Koller
Zinc	Tumor growth-PYB 6	Decrease	Mulhern
Lead, Cadmium	EAC-C_3 receptor, B-cell	Decrease	Koller & Brauner
Mercury	EAC-C_3 receptor, B-cell	Increase	Koller et al.

acute and chronic exposure, leading to disease or death. However, recent experiments have shown that chronic low level exposure to certain metals may induce subtle changes within the host, including alteration of immune system. The metals which are considered to be environmental pollutants and hazardous to public health are lead, cadmium, mercury, zinc etc. Table 2 shows the effects of some metals on immune system.

5. FOOD AND FOOD ADDITIVES

Available reports indicate that foods, food colours and food additives can also modulate immune system of host.

5.1 Caffeine

Caffeine is extensively used as a therapeutic agent and is widely ingested in the form of caffeine containing beverages, yet very little is known about its effects on the immune system. For the first time, detailed immunological investigations were conducted on the effects of caffeine by Saxena et al.[30] Their studies indicate that

caffeine administration did not produce any conspicuous change in the organ/body weight ratio, histology, total cell count or viability of cells of various lymphoid organs except moderate atrophy of thymus. However, the functional studies in mice pretreated with caffeine have revealed modulation of the immune system. Higher dose level of caffeine caused significant suppression of humoral, cell mediated and indirect immunity together with increased susceptibility to endotoxin shock. However, immuno stimulation was observed at a low dose level of caffeine. Singh et al.,[31] showed that there was no change in the cellularity of bone marrow but caffeine caused a dose dependent reduction in the viability of cells both under *in-vivo* and *in-vitro* conditions. There was also a significant depression in the ^{3}H-thymidine incorporation in DNA of bone marrow cells of caffeine treated mice.

5.2 Butylated Hydroxyanisole (BHA)

BHA is commercially used as an anti-oxidant in foods. It has immuno-suppressent activity at the level not cytotoxic.[32] It exerted an inhibitory effect on the primary immune response to thymus-independent antigen, *E.coli*. It inhibits the PFC response to SRBC and *E.coli*. It appears that BHA affects both *B*- and *T*-cell functions.

5.3 Gallic Acid

Gallic acid is a metabolite of food additives Propyl gallate and Tannic acid. Gallic acid is immuno suppressive for PFC response to thymus-dependent antigens and exerts its suppressive effects on *T*-lymphocyte functions via macrophage.[33]

6. PARTICULATE POLLUTANTS

6.1.Silica

In silica exposed animals, serum agglutinin activity was found lowered.[34-36] Lymphoproliferative response of *T*-cells in spleen by mitogen Con A was found enhanced while in mesenteric lymph nodes, it was lowered. Silica can also alter the macrophage functions. Phagocytic activity of macrophages to *E.coli* was found lowered in silica exposed mice.[35,37]

6.2 Asbestos

Variations were found in host susceptibility to asbestos exposure.[38,39] Histocompatibility antigen (HLA) B_8 was found more frequent in anti nuclear antibody (ANA) positive group of asbestos workers.[40] Low proportions of *T*-cells and impaired skin reaction to recall antigens were also found which indicate that asbestos can also alter the cellular immune response.[41-44]

6.3 Coal Dust

Increased levels of IgA, IgG, C_3 and α_1-anti trypsin were reported in coal workers' pneumoconiosis.[45,46] Preliminary investigations revealed impairment of both *T* and *B* cells in the higher categories of pneumoconiosis.[47] Intratracheal administration of coal

Table 3. Effect of silica, asbestos and coal on immune system.

Parameter	Effect	References[95-106]
Susceptibility to infection	Increase	Bailey et al.; Miller and
Skin hypersensitivity	Delayed	Zarkower; Schuyler et al.
Skin graft rejection	Delayed	Merchant et al.; Turner-warwick; Cate and Burrell.
Rheumatoid factor,	Present	Schroeder et al.; Kitaev and
Anti-nuclear antibodies,	Present	Tyurebayeva; Bailey et al.
Lung auto antibodies.	Present	Johnson et al ; Turner-warwick; Turner warwick & Parkes; Lange et al.; Pernis et al.; Säuter et al., Benedek, et al.; Kang et al. and Lippman, et al.

mine dust in experimental animals showed, lesions in spleen and tracheobronchial lymph nodes but significant changes in the total cell count or viability of thymus, spleen and lymph nodes were not found.[48] Mice exposed to coal mine dust, intra peritoneally, over a period of 30 days had significant suppression of primary (19 S or IgM) and secondary (7 S or IgG) immune response as evinced by reduction in the number of antibody secreting cells in spleen and haemagglutination titre in the serum.[49] Table 3 summarises the effects of silica, asbestos and coal on some of the immune functions.

6.4 Agate Dust

Recent epidemiological survey conducted by ITRC, in agate industries at Khambhat (Gujarat) showed various categories of pneumoconiosis in workers, Here agate stones are processed for making ornaments and scientific instruments. The incidence of pulmonary infection especially tuberculosis was considerably high. The effect of intratracheal administration of respirable agate dust on the immune system was assessed in rodent models. It has been found that the exposed animals become more sensitive to endotoxin of *E.coli* Lipo polysaccharide (LPS), than the controls. Agate dust also affected the macrophage chemotaxis under *in-vivo* conditions. Furthermore, considerable decrease in IgM and IgG secreting plasma cells in spleen with a corresponding decrease in serum haemagglutination titre was observed in agate exposed animals.[50]

7. CONCLUSION

This paper reviewed the effects of environmental pollutants on the immune system. It has become clear from the above reported literature that many of the environmental chemicals at very low dosages can modulate immune system without producing any clinical sign of the disease. It is therefore, clear that immunomodulation can be used as a sensitive indicator for assessing the toxicity caused by environmental chemicals.

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