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Immunomodulatory effect of Xenobiotics

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Abstract

Rapid industrialization and anthropogenic activities end up with xenobiotics exposure to the environment. There are many chemicals currently used for various applications such as pesticides, herbicides, polycyclic aromatic hydrocarbons, polyphenols and heavy metals, etc., classified as toxic pollutants due to their hazardous properties to diverse life forms. A variety of xenobiotics are responsible for many immune system disorders by altering the humoral and cellular immune response(s). Xenobiotics induce various immunological alterations such as immune-suppression or hypersensitivity which ultimately provide an opportunity for initiation of autoimmunity, neoplasm induction and infection. Immunotoxic effect of xenobiotics determined by measuring immunological parameters such as cytokine profile, proliferation of immune cells, immunoglobulin production, activity of T cells, NK cells and activation of macrophages/ dendritic cells. Collective information and analysis of available immunotoxicity data assists in prediction of xenobiotic exposure to the biosphere. This review gives a brief overview of xenobiotics interference with the immune system functions.

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Key words

toxins; xenobiotics; pesticides; immune response; inflammation

Introduction

Xenobiotics are natural or synthetic compounds usually not involve in metabolic pathways and act as foreign molecules to an organism. Industrial as well as agricultural developments during the last century have resulted in non-judicious production and usage of extremely hazardous xenobiotic pollutants leading to an alarmingly high level of contamination in the biosphere. The severity of the xenobiotic pollution is devastating as most of the xenobiotic pollutants are toxic to most forms of life ranging from simple prokaryotes to highly complex organisms, including human beings.[1-6] A large number of the anthropogenic substances were developed during the early nineteenth century; however, their noxious consequences could be realized only after the detailed toxicological studies were performed on environmental samples contaminated with these xenobiotics only during last 2-3 decades.[7-9] Epidemiological and animal studies have proven the effect of pesticides; industrially synthesize chemicals, polycyclic aromatic hydrocarbons, mycotoxins and metals etc. on the immune system.[10-14] Immunotoxicity involves alteration in any function of innate and adaptive immunity involving suppression/ activation of immune reactions, hypersensitivity and induction of autoimmune disorders (**Fig. 1**). Exposure of xenobiotics can have suppressive impact on the immune functions which consequently causes depletion in the host resistant towards severe pathogen encounters. However, activation of immune system induced by xenobiotic causes hypersensitivity reaction initiation and production of autoantibodies leading to autoimmune disorders. Direct effect of xenobiotics on immune response can be determined by several classical *in vitro* based assays including proliferation of immune cells, cytotoxic activity of T calls and NK cells, dendritic cells activation, antibody production and cytokine profile.[15]

Effects of xenobiotics on immune system depend on physio-chemicals properties such as dose, size, complexity, solubility, duration of persistence, reactivity towards macromolecules. Subsequently, host condition such as age, gender, basal metabolic rate, polymorphism in detoxifying enzymes, nutrition availability, lifestyle, status of the immune system also determine the vulnerability towards xenobiotic. In this article we summaries the effect of xenobiotics (Polycyclic aromatic hydrocarbons, Polyphenols, Pesticides, Polyhalogenated Aromatic hydrocarbons and heavy metals) on immune functions.

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Immunological response alteration by Polycyclic Aromatic Hydrocarbons (PAHs)

A polycyclic aromatic hydrocarbon (PAHs) consists of three or more combined benzene rings formed during incomplete combustion of fossil fuels in automobile emissions, chimney soot and tobacco smoke. Consortium of PAHs is ubiquitously found throughout the environment which induces adverse clinical manifestations including cancer.[16] Carcinogenic potential of PAHs are well studied in experimental murine system and skin papillomas are easily developed by applying PAHs alone or in combination with other xenobiotics.[17] Generally, PAHs shows resistant towards biodegradation but metabolize into diol and epoxide derivative by cytochrome-450 dependent monooxygenase[18] and aldo-keto

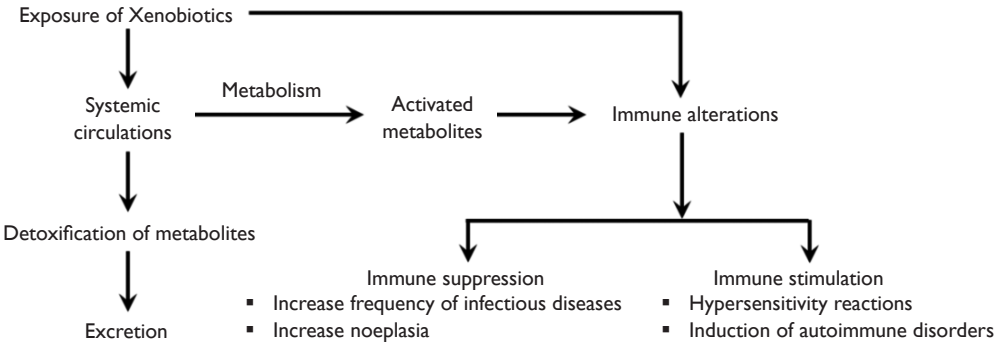

Figure 1. Immune alterations induced by Xenobiotics.

Table 1. Polycyclic Aromatic Hydrocarbons effect on immune system

S.N.	Name of Compounds	Immune Responses	Reference
A.	Polycyclic Aromatic Hydrocarbons (PAHs)	▪ Impairment of humoral and cell-mediated immune function.	22, 62
		▪ Immunosuppressive agent.	62
1.	Benzo[a]pyrene	▪ Immunosuppressant and immunotoxicants.	63
		▪ Diminish humoral immunity, increases T cell mitogenic activity.	64-66
		▪ Induce pro-inflammatory cytokines production (IL-1β, iNOS).	22, 67
		▪ Inhibited the up-regulation of markers such as CD1a, CD80 and CD40 found in dendritic cells during monocyte differentiation into dendritic cells upon the action of GM-CSF and IL-4.	68 69
		▪ Modulate Vitamin-D3 signaling via activating Aryl hydrocarbon receptor.	70
		▪ Increases IL-4 mRNA expression.	71
2.	7,12-Dimethyl benzo [a]anthracene (DMBA)	▪ Suppress splenocytes proliferation up to 90% during mitogen and alloantigen-induction.	72
		▪ Repression of in vitro humoral immune response of murine splenocytes.	73
3.	Benz[a]anthracene	▪ Induces oxidative DNA damage in lymphocyte.	74
4.	3,6-bis(2 piperidinoethoxy) acridinetrihydrochloride	▪ Immunomodulator, enhances cytotoxic activity of Natural killer cells.	75

reductases[19] where as their detoxification is accomplished by glutathione transferase.[20] Active derivatives of PAHs have ability to bind with nucleic acids and adduct formation.[21] Exposure to PAHs has been found to interact with immune system and induce many inflammatory reactions (**Table 1**). Dimethyl benz(a)anthracene (DMBA) exposure causes suppression of both branches of immune system, humoral as well as cell mediated. Extended suppression of immune system provides an opportunity for tumor progression and become clinically visible neoplasm.[22] However, PAHs induced cancer is influenced by various factors like metabolically active derivative formation, variation in genetic pattern (polymorphisms in the Ah receptor locus and in the Major Histocompatibility Complex loci), DNA adduct formation and presence or absence of TLR-4.[23] Several PAHs (DMBA, Benzo(a) pyrene, and 3-methylcholanthrene) are contact allergens when applied on the skin where as continuous exposure of pyrene was linked with asthma in children.[24]

Immunological response alteration by Poly-phenolic compounds

Polyphenols are micronutrients present in normal diets, categories into flavanoids (phenolic amine) and non-flavanoids (phenolic acids). Poly-phenols frequently used in food industry applications (color and flavor enrichment) due to their anti-oxidant properties[25] as well as prevention of disease linked with oxidative stress such as neurogenerative,[26] cardiovascular,[27] cancer[28] and others.[29] Anti inflammatory effect of polyphenols are widely attributed.[30] However, exact mechanism of their action is not fully determined. The anti-oxidant property, involves clearance of reactive oxygen species, protection from oxidative stress, stabilization of thiol redox reaction and reduction in membrane lipid peroxidation.[31] Polyphenols are also involved in immune response alteration upon their exposure (**Table 2**). Polyphenols modulate the immune response (activation and differentiation of immune cells) by altering the epigenetic processes like DNA methylation, modification of histone proteins and post translational modifications.[32] Regulation of epigenetic mechanism achieved by polyphenols involves alteration of histone deacetylase and histone acetyltransferase activity. Polyphenols such as EGCG, genistein, curcumin and quercetin act as histone deacetylase inhibitor where as genistein acts as histone acetyltranferase activators and EGCG, curcumin as histone acetyltransferase inhibitor.[33] Polyphenols also bring about alteration through epigenetic mechanism that includes expression of miRNA in immune cells.

Table 2. Effect of Polyphenols on immune system

S.N.	Name of Compounds	Immunological responses	Reference
1.	Polyphenols	▪ Proliferation of the immunocompetent cells, including T helper 1 (Th1), natural killer cells, dendritic cells (DCs) and macrophages in secondary lymphoid organs.	76
		▪ Increasing splenic T and B cells populations.	77
	Flavanols	▪ Suppression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) as well as cytokines TNF-α, IL-1-β and IL-6 from macrophage.	78
	a) Epigallocatechin-3-gallate	▪ Foxp3 and IL-10 gene expression increases in Jurkat T cells.	79
		▪ Increases regulatory T cells proliferation in spleen, pancreatic lymph nodes and mesenteric lymph nodes. Decreases the Th1 and Th17 populations and lower the expression of T-bet and ROR-γt in animal models of experimental autoimmune encephalomyelitis.	80
		▪ Decreases the Th9 cells proliferation along with decreased expression of the PU-1.	81
		▪ Immunosuppressive and Decreases IFN-γ production in vitro.	82
	b) Baicalin	▪ Under TGF-β stimulus, increase the Foxp3 gene expression and also induction of functional Treg from splenic CD4+CD25− T cells in HEK 293 T cells.	83
		▪ Decreases expression of IL-17 during Th17 differentiation.	84
	c) Procyanidin C1	▪ Decreases the secretion of TNF-α, IL-1-β and IL-6.	85
	d) Fisetin	▪ Inhibits the expression of IL-6 and TNF-α in THP-1 monocytes cells exposed to high osmolarity.	86
	e) Theaflavin	▪ Decreases the expression of IL-6, Monocyte chemoattractant protein-1 (MCP-1) and Intracellular adhesion molecule-1 (ICAM-1).	87
	f) Curcumin analog 3,5-Bis(2-pyridinylmethy lidene)-4-piperidone (EF31)	▪ Inhibits secretion and expression of TNF-α, IL-1-β and IL-6.	88
	g) Propolis	▪ It can act as vaccine adjuvant.	89
	h) Resveratrol	▪ Reducing the levels of pro-inflammatory cytokines TNF-α, IL-1-β, and IL-6 and inflammation.	90
		▪ Increases proliferation CD19+ cells and Immunoglobulin synthesis in B lymphocytes.	91
	i) Resveratrol analog RVSA40	▪ Increases anti-inflammatory cytokine IL-1-β together with down-regulation of TNF-α and IL-6.	92
	j) 7-O-Methylnaringenin	▪ Down regulate TNF-α, IL-6 and IL-1-β expression in a dose dependent manner.	93
2.	Pentachlorophenols	▪ Enhances B and T-lymphocyte blastogenesis.	94
		▪ Decreases antibody titers and Delayed type hypersensitivity response and increases induced peritoneal macrophage count.	95
3.	Hydroquinone	▪ Inhibits IFN-γ production and increases Th2 response mediated allergic diseases. Enhances IL-4 production in CD4+ T cells and also increases Age levels in antigen-primed mice. Blocks the IL-12 production via suppression of NF-κB activity.	96
		▪ Inhibition of the production of IL-1-β, IL-2, and NO.	97, 98
		▪ Suppresses the production of TNF-α, IL-1-β and IL-6. Inhibits production of NO and ROS, phagocytic uptake of FITC-labeled dextran. Induces production of costimulatory molecules.	99
4.	Glabridin	▪ Suppresses expression of CD40, CD80, CD86, MHC-I and MHC-II during maturation of dendritic cells (DCs).	100
5.	Quercetin	▪ Decreases TNF-α IL-1-β, IL-6, macrophage inflammatory protein 1α m-RNA level macrophage. Induces nitric oxide synthase activity.	101

Immunological responses alteration by Pesticides (Organophosphate/Organochlorine /Carbamate compounds)

Pesticides used worldwide for enhancing crop yields, have been widely accepted because of their ubiquitous availability, application easiness, efficiency and economic profits. But their mutagenic property leads to great cost to human health. However, in underdeveloped and developing countries, irregular applications of pesticides results in worldwide contamination of food and environment. Immunosuppressive effects of pesticides cause by their direct impact on lymphoid organs. Pesticide exposure linked to decrement in the number of immune cells which subsequently cause impaired functions of the immune system (**Table 3**). Organophosphate compounds (OPs) widely used for control of pest includes insecticides (parathion, malathion, diazinon, ethion, fenthion, chlorpyrifos, dichlorvos etc), herbicides (tribufos, merphos), nerve agents (G-series includes tabun, sarin, soman, cyclosarin and v-series comprises VE, VG, VM, VR, VX), ophthalmic agents (echothiophate, isoflurophate) and antihelmintics (trichlorfon). Due to their wide application, metabolites of OPs are reported across the world's different populations.[34-37] Fundamental mechanism of organophosphate is to effect transmission network of neurons by inhibition of acetylcholinesterase (AChE) and serum cholinesterase activity.[38] However, OPs can directly or indirectly produce immune alteration including deregulations of macrophage and neutrophil activity,[39] antibody production,[40,41] cytokine production, complement system, T cell proliferation.[42] OPs produce their

Table 3. Effect of Pesticides on immune system

S.N.	Name of Compounds	Immunological responses	Reference
1.	Organophosphate		
	Chloropyrifos	▪ Increases CD26 expression on cytotoxic T cells. ▪ Decreases CD15 cells production (Autoantibody producing B cells). ▪ Reduces mitogenesis immune cells in response to concanavillin and phytohemagglutinin. ▪ Amplifies autoantibodies production.	102
	Diisopropyl methyl phosphonate	▪ Inhibits activity of human and murine NK cells and murine cytotoxic T cells.	103
	Malathion	▪ Suppresses of NO production and LPS-induced TNF-alpha generation. ▪ Increases antibody production following immunization with a T-lymphocyte dependent antigen and macrophage function and led to mast cell degranulation.	104 41
2.	Carbamate		
	Aldicarb	▪ Increases T8 lymphocytes population and decreases T4:T8 cell ratio. ▪ Increases lymphocytes proliferation and alters macrophage functions by decreasing with IL-1 production.	105 106
	Dimethoate	▪ Decreases total serum IgG and IgM and T-cells in the thymus, forming autologous rosettes.	107
	Sodium methyl dithiocarbamate	▪ Inhibits expression of IL-1α, IL-1β, IL-18, IL-12, IFN-γ, p35, p40 m-RNA level and macrophage migration inhibitory factor (MIF) whereas increases IL-10 m-RNA level.	108
	Mancozeb	▪ NO production decreases with the in vitro exposure. Suppresses TNF-γ secretion in vitro where as enhance release detected in ex-vivo experiment.	109
	Carbendazim	▪ Decreases B lymphocytes proliferation and serum IgG, IgM and IgA levels.	110
3.	Organochlorine		
	Endosulfan	▪ Decreases IgA and IgG production.	111
	Methoxychlor	▪ Decreases in IgM splenic plaque-forming cell responses, splenic T-cell (CD3+) populations and germinal center (GC) B-cell (CD19+PNA+) populations.	112
	Hexachlorocyclohexane	▪ Increases population of CD3 (+) CD4 (+) T-lymphocytes and expression of CD45RO (+) on CD4 (+) and CD8 (+) T-lymphocytes. ▪ Decreases CD4(+) CD25(+) T-lymphocytes and level of IL-2 and IFN-γ in SLE patients.	44
	o,p'-Dichlorodiphenyl -trichloroethane (DDT)	▪ Increases the percentages of CD3(+)CD4(+) T-lymphocytes and IL-10 level. ▪ Decreases CD4(+) CD25(+) T-lymphocytes and level of IL-2 and IFN-γ in SLE patients.	44

effect at cellular level of immune system by oxidative damage, inhibition of serine hydrolase including complement system, change in signal transduction pathways, altered metabolism and decrease in humoral/cell mediated immunity.[43] Carbamate compounds (CMs) are carbonic acid derived esters that are used alternatively in place of organophosphates. CMs also reversibly inhibit activity of acetylcholinestrase (AChE). Organochlorine compounds (OCs) are lipophilic and thus, easily bioaccumulate in fatty tissues. Immune system irregulations during chronic exposure of OCs could be linked to immunesuppression, reduction in immunoglobulin level, alteration of macrophage phagocytic function and the progression of autoimmune diseases such as systemic lupus erythematosus.[44]

Immunological responses alteration by Polyhalogenated Aromatic hydrocarbons

Polyhalogenated aromatic hydrocarbons (PHAHs) are worldwide environmental toxins and known as endocrine disrupter. Members of PHAHs family: polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), polybrominated diphenyl ethers (PBDEs), 1,1-dichloro-2,2-bis(4-chlorophenyl) ethylene (p,p'-DDE), polychlorinated dibenzofuran, polychlorinated dibenzo-p-dioxins etc. PHAHs cause various hazardous effects on organ system like hepatic, nephritic, nervous and cardiovascular. PCBs exhibit resistance towards biodegradation and eventually bioaccumulate in food chain due to high lipophilicity. Biomagnifications properties of PHAHs make them a serious threat to the marine environment.[45] Effect on immune function by PCBs attracted a lot of attention during the last decade and their immunosuppressive effect was determine by *in vitro* assays and experimental animal studies (**Table 4**).[46-50] Among all polyhaloginated aromatic hydrocarbon, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most potent and resistant environmental toxin that exerts the effect by binding to aryl hydrocarbon receptor complex (AhRC). TCDD along with aryl hydrocarbon translocator binds to DNA and regulates expression of various signal transduction pathway molecules. Effects of TCDD include suppression of humoral and cellular immunity and increases susceptibility towards infectious diseases and neoplasm.[51]

Immunological responses alteration by heavy metals exposure

Metals essentially required in trace amount, act as cofactors in various biologically important processes. However, non essential heavy metals (arsenic, lead, mercury, cadmium, vanadium, platinum and palladium) effect the immune functions which ultimately increase susceptibility towards pathogen encounter, hypersensitivity, autoantibody production, inflammation and neoplasia (**Table 5**). Cadmium a major environmental pollutant comes from industrial activities (fossil fuel combustion,

Table 4. Effect of Polyhalogenated Aromatic Hydrocarbon on immune system

S.N.	Name of Compounds	Immunological responses	Reference
1.	2,3,7,8-Tetrachloro -dibenzo-p-dioxin (TCDD)	▪ Increases the expression of genes involve in antigen processing and presentation. It also increases expression of genes of dendritic cell maturation pathways.	113
2.	Polychlorinated Biphenyls	▪ Immunosuppressive.	49
	2,2',4,4',5,5'-hexachlorobiphenyl	▪ Deceases CCL22 gene expression.	114
3.	Polybrominated diphenyl ethers	▪ Decreases peripheral blood monocytes, NK cell activity and splenic CD4 (+) CD8 (+) proliferation. Increases T and B cell proliferation on mitogen stimulation.	115
		▪ Decreases proinflammatory cytokine production (TNF-γ and IL-6).	116

Table 5. Effect of Heavy metals on immune system

S.N.	Name of Metal	Immunological responses	Reference
1.	Cadmium	▪ Increases production of NO.	117
		▪ Inhibits synthesis of IgE by B cells or PBMCs upon IL-4/aCD40 stimulation and decreases proliferation of B cells or PBMCs.	118
		▪ Increase production of chemoattractant Leukotriene B4 from neutrophils and monocytes.	119
2.	Lead (Pb)	▪ Decreases NO production in cytokine-induced cell lines.	120
		▪ Induces production of TNF, IL-6 and IL-12 and decreases IL-10 production.	121
3.	Mercury (Inorganic)	▪ Increases IL-12, IL-17, IFN-γ and TNF-α production.	122
		▪ Overexpression of CD86 and HLA-DR and production of TNF and IL-8 in vitro.	123
4.	Arsenic	▪ Decreases IL-2, IL-4, IL-5, IL-10, TNF-α and IFN-γ secretion from T cells.	124
		▪ Increases IgG, IgA and IgE level.	125

industrial discharge, phosphate fertilizer synthesis). In terms of immune response alteration, cadmium is found to effects various immunological functions by increasing production of reactive oxygen species (ROS) in immune cells.[52,53] Subsequently, oxidative activation of NFkB and AP-1 directs synthesis of IL-6, IL-8 and TNF in alveolar macrophages which attract neutrophils to inflammation site due to increased expression of adhesion molecules on endothelial cells.[54] After Cadmium, Lead is most extensively studied found to have wide range of physiological consequences. Even though Lead has hazardous role in neurological, gastrointestinal, nehprological and cardiovascular system, it also affects immune system adversely. Epidemiological studies show compromised immune responses towards *Candida albicans* infection and neutrophilia in workers exposed to Lead and smoking habits, respectively.[55,56] Environmental distribution of Mercury (both organic and inorganic states) is observed to be associated with immune response alterations.[57,58] Different categories of Arsenic compounds are human carcinogens and also they effect immune functions and increase rate of cancer incidences, chronic infection, autoimmune reactions etc.[59-61]

Discussion

Immune system, a defense mechanism evolves to provide protection against pathogens and neoplasm. Metabolism of xenobiotics generates activated metabolites involve in severe pathophysiological conditions including immune alterations, neurological interruptions, cardiovascular, nephrological and ultimately changes in body homeostasis. Xenobiotics can obstruct the regular functioning of immune system and such immunocompromised conditions provide opportunity for pathogen encounter and tumor progression. Suppression of immune response upon exposure of xenobiotics can increases the vulnerability towards viral, bacterial and parasitic infections and also increases the incidence of neoplasm. On the other hand activation of immune responses can leads to initiation of autoimmune reactions or non specific tissue damages. Diversity in physio-chemical properties of xenobiotics leads to initiation of different molecular event(s) in immune cells. Oxidative stress induction by production of ROS is major mechanism involve in immune response alterations. Carcinogenic mechanism of polycyclic aromatic hydrocarbons includes adduct formation and ROS productions. These mechanisms also lead to destruction of genomic integrity of immune cells and affect their functions. Dietary polyphenols (secondary metabolites) act as anti-oxidants and decrease the ROS production in immune cells, but modulate immune response by modifying epigenetic mechanisms. Worldwide application of pesticides have wide array of immunomodulatory effects. Mechanism of pesticides induced immunotoxicity involves ROS production, caspase-3 activation, and mitochondrial dysfunction and transcription factor activity alterations. Certain xenobiotics such as dioxins, biphenyls and dibenzofurans modulate immune response via binding to aryl hydrocarbon receptor (AhR). Binding with AhR receptor leads to increase production of xenobiotic metabolizing enzymes and IL-22 from Th17 cells. Action of xenobiotic metabolizing enzymes generates protein reactive derivatives of xenobiotics. Among these derivatives of xenobiotics some act as neoantigen and promote T cell activation. Activated T cell and increased IL-22 production exacerbates conditions for autoimmune diseases. Furthermore, environmental and occupational exposures of heavy metals contribute a major factor in irregulation of immune responses which maximizes the risk of inflammation and pathogen encounter. The complete mechanism involved in metal toxicity to immune system is underestimated and a multidisciplinary approach is needed for treatment in both low as well as high level exposure of heavy metals. Exact mechanism involved in xenobiotic

induced immune alteration may not be completely understood but their physiological consequences are well defined. Therefore, it is time to combine and analyze the epidemiological as well as animal studies based data to construct definite toxicity map of a xenobiotic metabolism. Computational molecular docking of xenobiotic metabolism and their derivatives will provide huge information in combating xenobiotic immunotoxicity. Additionally for unavoidable conditions such as smoking, drinking and handling, proper monitoring and rapid detection of symptoms during xenobiotics exposure is highly recommended.

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