Mechanistic Overview of Immune Modulatory Effects of Environmental Toxicants

Haji Bahadar[1], Mohammad Abdollahi[*,1,2,3], Faheem Maqbool[1], Maryam Baeeri[1] and Kamal Niaz[1]

[1]*Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, International Campus, Tehran, Iran*

[2]*Department of Toxicology and Pharmacology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

[3]*Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

Mohammad Abdollahi

Abstract: The immune system is an integrated organization, comprising of specific organs, cells and molecules playing a crucial role in the maintenance of health. The purpose of this paper is to give a mechanistic overview of toxic effects of various chemicals and pharmacological agents, and their interaction with the various components of the immune system that leads to modulation of the immune responses. Studies suggest that many chemical agents present in the environment like; heavy metals, agrochemicals, and various types of hydrocarbons possess immune toxicity and cause either structural, functional or compositional changes in various components of the immune system that alters immune response. There is present a complex bidirectional relationship between central nervous system (CNS) and the immune system. And receptors for neuropeptides, neurotransmitters, and hormones are located on lymphoid organs. Therefore, we are of the opinion that Endocrine Disrupting Chemicals (EDCs) present in our environment may be indirectly involved in causing immune toxicity *via* neuroendocrine channels, and *vice versa* many neurological disorders may be associated with environmental pollutants utilizing immuno-neuroendocrine pathways.

Keywords: Environmental pollutants, heavy metals, immunotoxicity, immunosuppression, pesticides.

INTRODUCTION

The immune system is an integrated organization comprising of specific cells and molecules. The cellular components of the immune system are derived from hematopoietic stem cells in bone marrow, which include polymorphonuclear (PMN) leukocytes and lymphocytes. PMN leukocytes are further classified as basophils, eosinophils, neutrophils, mast cells, monocytes, dendritic cells and macrophages. And lymphocytes include B- and T-lymphocytes, and natural killer (NK) cells. Plasma cells which secrete antibodies are derived from B-lymphocytes. And in thymus the T- lymphocytes are differentiated into distinct types of cells, CD4 T-helper cells, and CD8+ cytotoxic T-cells [1].

ENVIRONMENTAL POLLUTANTS AND IMMUNE SYSTEM

Heavy industrialization and scientific developments have led to the addition of detrimental chemicals to the environment in the form of heavy metals, agrochemicals, and various types of hydrocarbons posing constant health threat. According to various toxicity studies, it has been indicated that the immune system is a potential target for toxic assault of many chemicals present in our environment. These pollutants have the ability to modulate the normal physiology of immune system in humans and experimental animals and compromise the host defense mechanisms [2-4].

MECHANISMS OF IMMUNOTOXICITY LINKED TO VARIOUS ENVIRONMENTAL POLLUTANTS

Environmental pollutants induce immunotoxicity by disturbing the homeostasis. They cause structural, functional, and compositional changes in various components of the immune system or indirectly show an effect on various metabolic and hormonal pathways. The outcome, as a result of altering the normal homeostasis may be either suppression or stimulation of the immune system. We focused on toxic effects of pollutants which cause structural, compositional, and functional changes in the immune system.

COMPOSITIONAL CHANGES IN IMMUNE SYSTEM

Compositional changes include alteration in the profile of colony forming unit (CFU) in bone marrow, changes in hematologic cellular parameters, alteration in circulating immunoglobulins level, alteration in CD3+, CD4+, CD8+ B220+, in spleen and alteration in CD4+/CD8+ or CD4-/CD8-, ratio in thymus [5]. T- Lymphocytes, B-lymphocytes and NK cells, present in the blood and lymphatic system are responsible for the specific adaptive immune response. Any type of toxic effect experienced by lymphocytes leads to

*Address correspondence to this author at the Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran; Tel/Fax: +98-21-66959104;
E-mails: mohammad.abdollahi@utoronto.ca, mohammad@tums.ac.ir

2212-4055/14 $58.00+.00

alteration in immune response of the host. The most important among all particulate air pollutants is asbestos having immunotoxic properties in exposed populations. Exposure to asbestos has been reported to decrease T-lymphocytes and elevate serum immunoglobulins. Furthermore, asbestos exposure also increases inflammation by elevating the activity of interleukin-1 (IL-1) interleukin-2 (IL-2), interleukin -6 (IL-6) and, interleukin-8 (IL-8). High IgE level, low activity of NK cells, along with B-cells lymphoproliferative disorders are some of the toxic effects of asbestos exposure [6-10]. Gases (nitrogen dioxide, sulfur dioxide, and tobacco smoke) present in the environment have also been found in many epidemiological studies to cause an increase in the incidence of respiratory diseases and infections [11-13]. Polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans have caused decreased in serum IgM and IgA, in a population of more than 2000 peoples exposed to these chemical pollutants by consuming contaminated rice oil [14]. Other environmental pollutants which have been reported to affect the immune system are mercury (Hg), arsenic (As), cadmium (Cd), certain aromatic hydrocarbons and pesticides [15-20]. Benzene is one of the ubiquitous volatile organic compounds present in the environment. In experimental studies, it has been reported that benzene exposure causes a dose dependent suppression of both B- and T-lymphocytes along with a decrease in thymus and spleens. While, some epidemiologic reports suggest that chronic benzene exposure cause reduction in immunoglobulins, B-lymphocytes and CD4 T-cells [16, 21, 22]. Heavy metals, like As, Hg, Cd and lead (Pb) are important environmental toxicants. Inorganic As exposure causes a direct cytotoxic effect on lymphocytes, elevated rate of sister chromatids exchange, reduction in various macrophagic surface markers, alteration in endocytosis and phagocytosis [23-25], while Pb has been noted to adversely affect the number of B- and T-lymphocytes, TCD4+, and CD8+ cells in exposed population [26-29], while, Hg exposure has been noted to cause apoptosis and suppression of T-lymphocytes [19, 30].

Pesticides are the only chemicals that are deliberately released to the environment. Many studies are available showing pesticides immunotoxic properties. They exert immune system toxicity in the form of affecting lymphocyte distribution, disturbing cellularity, decrease in thymus and spleen weight, decrease in neutrophils and CD4+, CD4/CD8, CD19+ and MHC-II+ cells along with a decline in immunoglobulins [18, 31-33]. In experimental animals, decline in bone marrow function, B cell population and IgM has been shown as a result of exposure to a mixture of herbicides, 3,4-dichloropropionanilide (Propanil) and 2,4-dichlorophenoxy acetic acid (2,4-D) [34]. Whereas, Propanil alone has been reported to reduce the number of T- and B-cells in the bone marrow along with the suppressed function of NK cells and macrophages [35]. In this regard, Pb is another environmental immunotoxic agent which exerts its immunotoxicity by affecting myeloperoxidase activity of neutrophils and subsequently decrease neutrophils function. Besides, Pb exposure decreases T-helper lymphocytes, IgG, IgM, C3 and C4 complement levels [36-38]. Polycyclic aromatic hydrocarbons (PAH), present abundantly in our environment, possess immunosuppressant properties by directly affecting T-cells. In addition to suppression of B-cells, they also affect differentiation, maturation stages, and functions of monocyte derived dendritic cells and macrophages [39-41]. Moreover, exposure to benzene has been reported to induce immunotoxicity by reducing peripheral blood leukocytes, and lymphocytes [42].

Interleukins are a group of proteins having an important role in immunity. Any compositional and functional deviation in in these proteins leads to an altered immune response. In experimental and epidemiological studies, it has been shown that interleukins remained the targets of some of the environmental pollutants like asbestos, pesticides, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) [6, 43, 44].

STRUCTURAL CHANGES IN IMMUNE SYSTEM

These changes in the immune system include alteration in surface receptors, alteration in expression of receptors, and histopathologic changes in lymphoid organs [5]. Phenol is a metabolite of benzene, which is abundantly available in our environment released from many sources. There are reports from certain experimental studies that phenol exposure causes histologic changes in lymphatic organs, increase splenic megakaryocytes, decrease splenic follicles, and increase the thickness of reticular layers of adrenal glands [45]. Reports from other chemical agents with regard to structural changes in the immune system are lacking.

FUNCTIONAL CHANGES IN IMMUNE SYSTEM

The function of the immune system is compromised as a result of both compositional and structural deviations as described earlier. Functional changes include altered antibody response, alter cell mediated response, change in the release of mediators and cytokines, and alter host resistance, decreased production of antibodies, modification in proliferation and differentiation, and processing and presentation of antigens or reduction the killing potential of NK cells [5].

DISCUSSION AND CONCLUSION

The immune system plays an important role in the maintenance of health of an individual. Experimental and some epidemiological studies suggest that the immune system is very sensitive to the toxic effects of environmental chemical pollutants, causing changes, ranging from the organ level to cellular components. A number of environmental chemicals, like heavy metals, some pesticides, various hydrocarbons, PCBs have been documented to possess immunotoxic effects, which ultimately leads to either immune suppression or immune stimulation. Immunosuppression may result in decreased host resistance to infections or growth of tumor cells, whereas immune stimulation might result in hypersensitivity or some autoimmune diseases. The interaction of various types of chemical agents with the components of the immune system leads to modulation in the immune response. As a result of these toxic attacks, alteration in lymphocyte population, decrease in the size of lymphoid organs, and decrease in immunoglobulins lead to decreased host resistance along with a change in specific immune response. In order to reflect on the toxicities caused by various biological and

chemical agents on the immune system, a separate discipline known as immunotoxicology exists within the society of toxicology.

Receptors for neuropeptides, neurotransmitters, and hormones are located in lymphoid organs. And there is present a bidirectional relationship between central nervous system (CNS) and immune system [5, 46-48]. Furthermore, the autonomic and neuroendocrine outflow interacts with the immune system *via* pituitary gland, modulating immune functions, and there seems a crucial link of CNS-immune interaction and autoimmune diseases [47, 49]. As already mentioned, the link between the CNS and the immune system is bidirectional, and it has been noted that activation of the immune system leads to changes in hypothalamic, autonomic and endocrine functions. Body peak antibody production causes an increase in the firing rate of neurons in the ventromedial nucleus of hypothalamus and subsequently leads to enhanced sympathetic activity in spleen, increase activity of adrenocorticotropic hormone and cortisone. These evidences show that signals generated by an activated immune system are received and processed by CNS [47, 50]. So on the basis of these experimental studies, it may reasonably be assumed that some environmental pollutants may cause immune toxicity indirectly *via* neuroendocrine channels, and *vice versa* many neurological disorders may be associated with environmental pollutants. Therefore, many Endocrine Disrupting Chemicals (EDCs) present in our environment may be indirectly involved in immune assault.

Experimental and epidemiological evidences gathered in this review suggest that environmental toxicants cause changes in immune system ranging from an organ to cellular components (Fig. **1**). Particularly, the lymphocytes have been shown to be the most sensitive elements of the toxic action of these chemical pollutants. A number of environmental chemical pollutants like benzene, heavy metals, pesticides, PCBs, and polycyclic aromatic

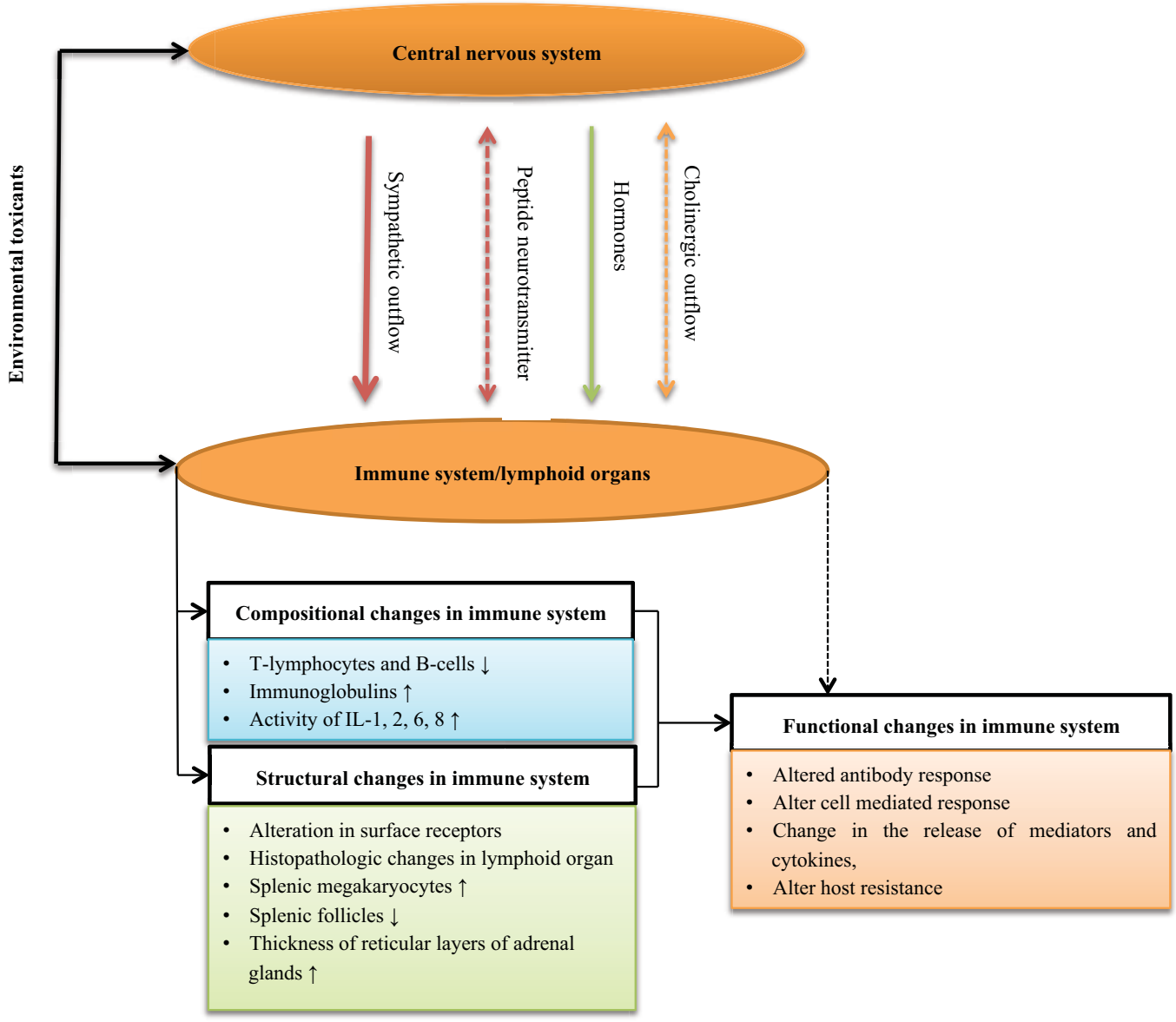

Fig. (1). Illustration of CNS and immune system communication and a mechanistic overview of environmental toxicants induced immune dysfunctions

hydrocarbons directly affect these important components of the defense system. But, indirect mechanisms affecting the immune system like increased production and releases of corticosteroids, autonomic output, have remained an understudied subject in the context of pathology of immunotoxicity and CNS disorders. Moreover, extensive research has been conducted on environmental chemical pollutants with respect to their toxicity on the immune system. But so far, no detailed study has been done to find out a relationship of chemical toxicants induced toxicity on immune system with certain diseases having immunologic background. Therefore, further objective research on the bidirectional relationship between CNS and immune system might be helpful in understanding the role of environmental toxicants in the incidence of certain immunologic disorders.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This review is the outcome of financially non supported study.

REFERENCES

[1] Janeway, CA.; Jr, Travers. The Immune System in Health and Disease. New York: Garland Science; 2001. Available from: http://www.ncbi.nlm.nih.gov/books/NBK27092.

[2] Mokarizadeh, A.; Faryabi, M.; R.; Rezvanfar, M.A.; Abdollahi, M. A comprehensive review of pesticides and the immune dysregulation: mechanisms, evidence and consequences. *Toxicol. Mech. Methods,* **2015**, 1-21 [Epub ahead of print].

[3] Veraldi, A.; Costantini, AS.; Bolejack, V.; Miligi, L.; Vineis, P.; Van Loveren, H. Immunotoxic effects of chemicals: A matrix for occupational and environmental epidemiological studies. *Am. J. Ind. Med.,* **2006**, *49*, 1046-1055.

[4] Tryphonas, H. Approaches to detecting immunotoxic effects of environmental contaminants in humans. *Environ. Health Perspect.,* **2001**, *109* (6), 877-844.

[5] Kaminski, NE.; Faubert, K.; Holsapple, MP. Toxic responses of the immune system. *Casarett & Doull's Toxicology The Basic Science of Poisons*, **2008**, *12*, 485-555.

[6] Kagan, E.; Solomon, A.; Cochrane, J.; Kuba, P.; Rocks, P.; Webster, I. Immunological studies of patients with asbestosis. II, Studies of circulating lymphoid cell numbers and humoral immunity. *Clin. Exp. Immunol.,* **1977**, *28* (2), 268-275.

[7] Kagan, E.; Jacobson, RJ.; Yeung, KY; Haidak, DJ.; Nachnani, GH. Asbestos-associated neoplasms of B cell lineage. *Am. J. Med.,* **1979**, *67*, 325-330.

[8] Hartmann, D.; Georgian, MM.; Oghiso, Y.; Kagan, E. Enhanced interleukin activity following asbestos inhalation. *Clin. Exp. Immunol.,* **1984**, 55, 643-650.

[9] Kubota, M.; Kagamimori, S.; Yokoyama, K.; Okada, A. Reduced killer cell activity of lymphocytes from patients with asbestosis. *Br. J. Ind. Med.,* **1985**, *42*, 276-80.

[10] Ilavská, S.; Jahnová, E.; Tulinská, J.; Horváthová, M.; Dušinská, M.; Wsolová, L.; Kyrtopoulos, SA.; Fuortes, L. Immunological monitoring in workers occupationally exposed to asbestos. *Toxicology*, **2005**, *206*, 299-308.

[11] French, JG.; Lowrimore, G.; Nelson, WC.; Finklea, JF.; English, T.; Hertz, M. The effect of sulfur dioxide and suspended sulfates on acute respiratory disease. *Arch. Environ. Health: An. Intl. J.*, **1973**, *27*, 129-133.

[12] Neas, LM.; Dockery, DW.; Ware, JH.; Spengler, JD.; Speizer, FE.; Ferris, BG. Association of indoor nitrogen dioxide with respiratory symptoms and pulmonary function in children. *Am. J. Epidemiol.,* **1991**, *134*, 204-219.

[13] Yarnell, JWG.; St Leger, AS. Respiratory illness, maternal smoking habit and lung function in children. *Br. J. Dis. Chest.,* **1979**, *73*, 230-236.

[14] Chen, PH.; Wong, CK.; Rappe, C.; Nygren, M. Polychlorinated biphenyls, dibenzofurans and quaterphenyls in toxic rice-bran oil and in the blood and tissues of patients with PCB poisoning (Yu-Cheng) in Taiwan. *Environ. Health Perspect.,* **1985**, *59*, 59-65.

[15] Reynaud, S.; Deschaux, P. The effects of polycyclic aromatic hydrocarbons on the immune system of fish: a review. *Aquat. Toxicol.,* **2006**, *77*, 229-238.

[16] Bahadar, H.; Mostafalou, S.; Abdollahi, M. Current understandings and perspectives on non-cancer health effects of benzene: A global concern. *Toxicol. Appl. Pharmacol.*, **2014**, *276*, 83-94.

[17] Savabieasfahani, M.; Lochmiller, R.; Rafferty, D.; Sinclair, J. Sensitivity of wild cotton rats (Sigmodon hispidus) to the immunotoxic effects of low-level arsenic exposure. *Arch. Environ. Contam. Toxicol.,* **1998**, *34*, 289-296.

[18] Mostafalou, S.; Abdollahi, M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicol Appl Pharmacol.,* **2013**, *268*, 157-177.

[19] Shenker, B.; Rooney, C.; Vitale, L.; Shapiro, I. Immunotoxic effects of mercuric compounds on human lymphocytes and monocytes. I. Suppression of T-cell activation. Immunopharmacol. *Immunotoxicol.,* **1992**, *14*, 539-553.

[20] Das, K.; Debacker, V.; Pillet, S.; Bouquegneau, J. Heavy metals in marine mammals. *Toxicol. Marine Mamm*., **2003**, 135-167.

[21] Aoyama, K. Effects of benzene inhalation on lymphocyte subpopulations and immune response in mice. *Toxicol. Appl. Pharmacol.,* **1986**, *85*, 92-101.

[22] Wierda, D.; Irons, RD.; Greenlee, WF. Immunotoxicity in C57BL6 mice exposed to benzene and Aroclor 1254. *Toxicol. Appl. Pharmacol*., **1981**, *60*, 410-417.

[23] Lemarie, A.; Morzadec, C.; Bourdonnay, E.; Fardel, O.; Vernhet, L. Human macrophages constitute targets for immunotoxic inorganic arsenic. *J. Immunol.,* **2006**, *177*, 3019-3027.

[24] Sakurai, T.; Kaise, T.; Matsubara, C. Immunotoxicity of organic arsenic compounds in marine animals. *Appl. Organometallic Chem.,* **1996**, *10*, 727-732.

[25] Burgdorf, W.; Kurvink, K.; Cervenka, J. Elevated sister chromatid exchange rate in lymphocytes of subjects treated with arsenic. *Human Genetics.,* **1977**, *36*, 69-72.

[26] Jaremin, B. Blast lymphocyte transformation (LTT), rosette (E-RFC) and leukocyte migration inhibition (MIF) tests in persons exposed to the action of lead during work. Report II. *Bull. Inst. Marit. Trop. Med. Gdynia.,* **1983**, *34*, 189-197.

[27] Fischbein, A.; Tsang, P.; Luo, JCJ.; Roboz, JP.; Jiang, JD.; Bekesi, JG. Phenotypic Aberrations of CD3+ and CD4+ Cells and Functional Impairments of Lymphocytes at Low-Level Occupational Exposure to Lead. *Clin. Immunol. Immunopathol.,* **1993**, *66*, 163-168.

[28] Coscia, G.; Discalzi, G.; Ponzetti, C. Immunological aspects of occupational lead exposure. *La Medicina del lavoro.,* **1986**, *78*, 360-364.

[29] Li, S.; Zhengyan, Z.; Rong, L.; Hanyun, C. Decrease of CD4+ T-lymphocytes in children exposed to environmental lead. *Biol. Trace Elem. Res.,* **2005**, *105*, 19-25.

[30] Shenker, BJ.; Guo, TL.; Shapiro, IM. Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction. *Environ. Res.*, 1998, *77*, 149-159.

[31] Filipov, NM.; Pinchuk, LM.; Boyd, BL.; Crittenden, PL. Immunotoxic effects of short-term atrazine exposure in young male C57BL/6 mice. *Toxicol. Sci.*, **2005**, *86*, 324-332.

[32] Blakley, B.; Brousseau, P.; Fournier, M.; Voccia, I. Immunotoxicity of pesticides: a review. *Toxicol. Ind. Health*, **1999**, *15*, 119-132.

[33] Lee, W.; Lim, CS.; Lee, KS.; Chang, SH. Immunotoxicity among farmers exposed to pesticides. *Korean J. Prevent. Med.,* **1999**, *32*, 347-354.

[34] De la Rosa, P.; Barnett, J.; Schafer, R. Loss of pre-B and IgM+ B cells in the bone marrow after exposure to a mixture of herbicides. *J. Toxicol. Environ. Health A*, **2003**, *66*, 2299-2313.

[35] Salazar, KD.; Ustyugova, IV.; Brundage, KM.; Barnett, JB.; Schafer, R. A review of the immunotoxicity of the pesticide 3, 4-dichloropropionanalide. *J. Toxicol. Environ. Health*, *B Crit. Rev.*, **2008**, *11*, 630-645.

[36] Ündeğer, Ü.; Başaran, N.; Canpmar, H.; Kansu, E. Immune alterations in lead-exposed workers. *Toxicology*, **1996**, *109*, 167-172.

[37] Ündeğer, Ü.; Başaran, N. Effects of lead on neutrophil functions in occupationally exposed workers. *Environ. Toxicol. Pharmacol.,* **1998**, *5*, 113-117.

[38] Valentino, M.; Governa, M.; Marchiseppe, I.; Visona, I. Effects of lead on polymorphonuclear leukocyte (PMN) functions in occupationally exposed workers. *Arch. Toxicol.*, **1991**, *65*, 685-688.

[39] Laupeze, B.; Amiot, L.; Sparfel, L.; Le Ferrec, E.; Fauchet, R.; Fardel, O. Polycyclic aromatic hydrocarbons affect functional differentiation and maturation of human monocyte-derived dendritic cells. *J. Immunol*., **2002**, *168*, 2652-2658.

[40] Davila, DR.; Romero, DL.; Burchiel, SW. Human T cells are highly sensitive to suppression of mitogenesis by polycyclic aromatic hydrocarbons and this effect is differentially reversed by α-naphthoflavone. *Toxicol. Appl. Pharmacol*., **1996**, *139*, 333-341.

[41] Van, Grevenynghe, J.; Rion, S.; Le Ferrec, E.; Le Vee, M.; Amiot, L.; Fauchet, R. Polycyclic aromatic hydrocarbons inhibit differentiation of human monocytes into macrophages. *J. Immunol.,* **2003**, *170*, 2374-2381.

[42] Hsieh, GC.; Sharma, RP.; Parker, RD. Subclinical effects of groundwater contaminants. I: Alteration of humoral and cellular immunity by benzene in CD-1 mice. *Arch. Environ. Contam. Toxicol.,* **1988**, *17*, 151-158.

[43] Chuang, L.; Liu, Y.; Killam, Jr K.; Chuang, R. Modulation by the insecticides heptachlor and chlordane of the cell-mediated immune proliferative responses of rhesus monkeys. *In Vivo*, **1991**, *6*, 29-32.

[44] Badesha, JS.; Maliji, G.; Flaks, B. Immunotoxic effects of prolonged dietary exposure of male rats to 2, 3, 7, 8-tetrachlorodibenzo- p-dioxin. *Eur. J. Pharmacol: Environmen. Toxicol. Pharmacol.,* **1995**, *293*, 429-437.

[45] Monfared, AL.; Jaafari, A.; Sheibani, MT. Histological and histometrical evidences for phenol immunotoxicity in mice. *Comp. Clin. Path.*, **2012**, 1-6.

[46] Ader, R.; Felten, D.; Cohen, N. Interactions between the brain and the immune system. *Annu. Rev. Pharmacol. Toxicol.,* **1990**, *30*, 561-602.

[47] Ader, R.; Cohen, N.; Felten, D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet*, **1995**, *345*, 99-103.

[48] Davis, SL. Environmental modulation of the immune system *via* the endocrine system. *Domestic Animal Endocrinol*., **1998**, *15*, 283-289.

[49] Solomon, GF. Psychoneuroimmunology: interactions between central nervous system and immune system. *J. Neurosci. Res*., **1987**, *18*, 1-9.

[50] Besedovsky, H.; Sorkin, E. Network of immune-neuroendocrine interactions. *Clin. Exp. Immunol.*, **1977**, *27*, 1.

Received: April 19, 2015 **Revised: May 26, 2015** **Accepted: May 28, 2015**