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Immunotoxicity induced by pesticides in humans

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ABSTRACT

The evidence that the immune system is affected by pesticides is growing and indicates that pesticide exposure has detrimental health effects and can contribute to increased risks for long-term diseases, including different types of psychiatric disorders, cancers, allergies, autoimmune diseases, and infectious diseases. Motivated by such studies, the present review highlights mechanisms involved in the immunological toxicity of pesticides, as well as the association between pesticide exposure and the predisposition of diseases, caused by perturbation of immune system function. A literature review was performed using the MEDLINE, PubMed, and Scopus databases with publication dates from 1986 to 2016. The following descriptors were used: "immunotoxicity","Pesticides", and"immune system". Pesticides can affect host resistance and can directly affect lymphoid tissues and/or native cells. Disorders such as immunosuppression, hypersensitivity, autoimmunity, and cancers have been cited to result from changes in the immune system. Although public health concerns regarding pesticide exposures are directed primarily at carcinogenic and neurological mutations, these compounds can cause profound effects on the immune system and may trigger several other processes by disruption of function in other physiological systems.

Keywords: Pesticides; Immunology; Cancer; Allergy

1 INTRODUCTION

Pesticides include hundreds of chemicals distributed across broad chemical and functional classes that are used in agriculture for plant protection and in public health for the prevention and control of vector-borne diseases. Although they are widely used, the extensive use of pesticides can have toxic effects on humans and the environment (PARRÓN *et al*., 2014).

The chemical classes of pesticides that pose the greatest threats to public health are organochlorines (DDT, lindane, and chlordane), organophosphates (OPs)

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(malathion, parathion, and diazinon), carbamates (CBs) (aldicarb, carbofuran, and carbaryl), pyrethroids, chlorophenoxy compounds (2,4-dichlorophenoxyacetic acid (2,4-D)], triazines (atrazine and simazine), amides (propanil), and phthalimides (captan, captafol and folpet). This is because these pesticides and their residues are highly persistent in the environment and occupational or environmental exposure is largely unavoidable for humans and other organisms (MOKARIZADEH *et al*., 2015).

Among the systems of the human body affected by pesticides, the immune system represents a great concern because of its close, two-way interactions various organs of the body, including those in the nervous, endocrine, reproductive, cardiovascular and respiratory systems. Because of this, any disturbance of the immune system consequently leads to disturbances of the proper function of these additional systems (CORSINI *et al*., 2012).

Evidence that the immune system is affected by pesticides is growing and shows that pesticide exposure has detrimental health effects and may contribute to increased risks of long-term diseases, including different types of psychiatric disorders, cancers, allergies, autoimmune diseases, and infectious diseases (NTZANI, 2013; PARRON *et al*., 2014).

Motivated by previous studies, the present review highlights potential mechanisms involved in the immunological toxicity of pesticides as well as the association between pesticide exposure and predisposition towards diseases caused by disturbances in immune system function.

2 MATERIALS AND METHODS

A literature review was performed using the MEDLINE, PubMed, and Scopus databases and publication dates from1986 to 2016. The following descriptors were used: “immunotoxicity”, “Pesticides”, and “immune system”. About 35 articles, published in English, fit the proposed theme and were evaluated for this article. Additional articles were retrieved from reference lists of relevant publications.

3 RESULTS AND DISCUSSION

Remodeling, activation, and differentiation of immune system cells is controlled by multiple mechanisms and changes in these processes can lead to cell death or dysfunction. Pesticides and other offenses can affect host resistance mechanisms and can directly affect lymphoid tissues and/or native cells. Immunosuppression, hypersensitivity, autoimmunity, and cancers have all been suggested to result from immune system changes (CORSINI *et al*., 2012; MOKARIZADEH *et al*., 2015).

Xenobiotics can interfere in development, expansion, and cellular signaling, potentially hindering the function and viability of immune cells. The induction of oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and esterase inhibition are considered the main pathways that are directly damaged by pesticides, consequently impacting leukocytes and other cell types (DHOUIB *et al*., 2016).

3.1 Oxidative stress

Oxidative stress can be defined as the excessive production of free radicals capable of causing peroxidation of lipid layers of cells and interfering with antioxidant defenses in the body. The toxicity of many pesticides is associated with the production of free radicals, which are toxic to cells and may be involved in the pathophysiology of many diseases. For example, there is extensive evidence that oxidative stress is an important mechanism partially underlying neurodegeneration in Alzheimer's disease (ABDOLLAHI *et al*., 2004; BUTTERFIELD & LAUDERBACK, 2002).

Oxygen species generated by oxidative stress can damage cellular components, including proteins, lipids, and DNA, in a manner lethal to cells. In addition, pesticides induce carcinogenic mutations due to damage of cellular DNA (SEBASTIAN; RAGHAVAN, 2016). Oxidative stress may also be associated with the pathogenesis of many neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) and may be associated with aging and chronic inflammation (REUTER *et al*., 2010).

3.2 Mitochondrial dysfunction

Multiple pesticides have neurotoxic effects in humans and may interfere with mitochondrial respiratory chain activity and oxidative phosphorylation. Such interference can impair cell function and potentially cause cell death through decreased oxygen uptake and a loss of cellular energy. In addition, mitochondrial dysfunction due to the toxicity of these pesticides may increase the risk of neurological diseases like Parkinson's disease (CHEN *et al*., 2017; ABDOLLAHI *et al*., 2004).

3.3 Endoplasmic Reticulum (ER) Stress

Some pesticides are involved in the induction of endoplasmic reticulum stress and consequent cell damage. As the ER is responsible for synthesis, folding, localization, and post-translational modifications of proteins in eukaryotic cells, any disorder in ER function leads to protein accumulation, resulting in cellular apoptosis (MOSTAFALOU; ABDOLLAHI, 2017; REYNA *et al*. al., 2016).

3.4 Inhibition of Esteratic and Cholinergic Cellular Components

Organophosphates and carbamates are pesticides classified as anticholinergics because of their potential for inhibition of enzymes with esteratic activity. Cells involve in immune system defense responses, especially lymphocytes, express cholinergic components, including acetylcholine, choline acetyltransferase, the high-affinity choline transporter, muscarinic receptors, and nicotinic receptors. In addition, these cells have a self-cholinergic system called the extraneuronal, or non-neuronal, cholinergic system. The existence of a cholinergic extraneuronal system in lymphocytes makes them susceptible to disturbances by organophosphate and carbamate pesticides (BANKS; LEIN, 2012; PREVENTION; MILAN, 2004).

Organophosphate and carbamate classes of pesticides may alter cholinergic signaling of lymphocytes through inhibition of the enzyme acetylcholinesterase, disrupting cellular homeostasis and leading to apoptosis. Organophosphates have a greater disposition for causing acute intoxication, which favors the overstimulation of

cholinergic receptors by accumulated acetylcholine and can cause functional alterations in the lymphocytes. Cancer and certain types of infections are possible consequences of chronic intoxication by organophosphates (DIAZ-RESENDIZ; TOLEDO-IBARRA; GIRÓN-PEREZ, 2015). Steroid inhibition may compromise lymphocytes and other cells of the immune system. For example, compromised neutrophil function and natural killer cell function has been observed in patients exposed to pesticides, increasing the risk of cancer and viral infections. Macrophages can also undergo impairment of their phagocytic function, and dendritic cells can also suffer damage to their antigen presenting function (THOMAS, 1995; WANG, 2010).

3.5 Pesticides associated with cancer

The World Health Organization (WHO) characterizes cancer as encompassing a broad group of neoplastic diseases that can affect every part of the body. Cancer is the result of interactions between genetic and environmental factors, which can be triggered by exposure to biological, physical, and chemical stimuli (WHO, 2015). The association of exposure to cancer incidence with different classes of pesticides, including insecticides, herbicides, and fungicides, has been prominent in many recent published studies. For example, the herbicide glyphosate is associated with breast cancer (THONGPRAKAISANG *et al*., 2013), pesticides containing alkylureas and amines are associated with brain tumors (ALAVANJA; HOPPIN; KAMEL, 2004), anddieldrin causes tumors of the lung, liver, lymphoid tissue, uterus, thyroid, and mammary glands in test animals at doses as low as 0.1 ppm (STERN, 2014).

A meta-analysis showed that an increased risk of prostate cancer in farmers is associated with exposure to the highly toxic pesticide 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). By 2006, five studies were conducted that studied 26,706 people exposed to this pesticide and showed positive correlations between pesticide exposure and death from prostate cancer (Kabir; Zaydehdel; Tayefeh-RAHIMIAN, 2018). Pestana *et al*. (2015) investigated the role of organophosphorus pesticides in the development of breast cancer in two cell lines, MCF-7 (estrogen receptor-positive) cells and MDA-MB-231 (estrogen receptor negative) cells. Concentrations of 50nMto

1μM were used, and a decrease in proliferation and viability of MCF-7 cells was observed, while no alteration in MDA-MB-231 cell proliferation or viability was observed. In addition, cell invasion was induced in the MCF-7 lineage.

There is increasing evidence suggesting a relationship between exposure to organochlorine pesticides and an increased risk of developing non-Hodgkin's lymphoma. In a meta-analysis, the risk of pesticide exposure and development of non-Hodgkin's lymphoma was studied and positive associations were found for exposure to the pesticides dichlorodiphenyldichlorethylene, hexachlorocyclohexane, chlordane, and hexachlorobenzene (LUO *et al*., 2016). In another meta-analysis, an association between non-Hodgkin's lymphoma occurrence and exposure to organophosphoruspesticides was found (HU *et al*., 2017).

3.6 Pesticides associated with allergies

Several epidemiological studies indicate an increasing prevalence of allergies in recent decades. Evidence suggests that chemicals, especially pesticides, may potentiate allergens and play an important role in the development of allergy-based diseases (Yaganagwa *et al*., 2008). Certain pesticides contribute to the degranulation of mast cells and basophils by triggering the production of cytokines, such as IL-4 and IL-13, which promote IgE secretion by B cells. After binding of IgEto the Fc receptor of mast cells and/or basophils, cross-linking of IgE receptors by allergens triggers cellular degranulation. Mediators of allergic responses are then released, including histamine, heparin, serotonin, cytokines, proteases, leukotrienes, and prostaglandin, which then contribute to a number of allergic reactions, including blood vessel dilation, mucus secretion, and smooth muscle contraction. This process may help to explain the development of IgE antibodies against dichlorodiphenyldichloroethylene (DDE) and pyrethrins in exposed individuals (El-Magd, SABIK, SHOUKRY, 2011, KARMAUS *et al*., 2005).

Exposure to pesticides was also linked to the risk of asthma development. Sunyer *et al*. (2006) showed that early exposure to DDE is associated with asthma in children of 4 to 6 years of age. Weselak *et al*. (2007), in an exploratory retrospective

study, found associations between persistent pesticide exposure during pregnancy and the rate of developing bronchitis or asthma in resulting offspring. In addition, exposure to any type of pesticide (herbicide, fungicide, or insecticide) during pregnancy is significantly associated with the development of allergies and hay fever in the populations studied.

4 CONCLUSIONS

Although public health concerns regarding pesticide exposure primarily focus on the potential for carcinogenic and neurological mutations, pesticides can also have profound effects on the immune system and may trigger several additional processes via disruption of the function in many physiological systems.

Immunological changes caused by pesticides alter the function of various immune cells and can even lead to apoptosis of these cells, facilitating the occurrence of pathological processes and contributing to the development of psychiatric disorders, cancer, allergies, autoimmune diseases, and infectious diseases.

Cancer resulting from exposure to pesticides can be caused by alterations to the immune pathway, interference with immune surveillance components (especially killer natural cells), or by the induction of innate immune system dysfunction. However, cancer can also result from the damage that pesticides cause in DNA.

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REFERENCES

ABDOLLAHI, M.; RANJBAR, A.; SHADNIA, S.; NIKFAR, S. Pesticides and oxidative stress: a review. [s. l.], n. June 2014, 2004.

ALAVANJA, M. C. R.; HOPPIN, J. A.; KAMEL, F. H EALTH E FFECTS OF C HRONIC P ESTICIDE. [s. l.], 2004.

BANKS, C. N.; LEIN, P. J. NeuroToxicology Review A review of experimental evidence linking neurotoxic organophosphorus compounds and inflammation. [s. l.], v. 33, p. 575–584, 2012.

BUTTERFIELD; LAUDERBACK. Serial Review: Causes and Consequences of Oxidative Stress in Alzheimer's Disease Guest Editors: Mark A. Smith and George Perry DISEASE BRAIN: POTENTIAL CAUSES AND CONSEQUENCES INVOLVING. Free Radical Biology & Medicine, [s. l.], v. 32, n. 11, p. 1050–1060, 2002.

CHEN, T.; TAN, J.; WAN, Z.; ZOU, Y.; AFEWERKY, H. K.; ZHANG, Z. Z. and T. *et al*. Effects of Commonly Used Pesticides in China on the Mitochondria and Ubiquitin-Proteasome System in Parkinson's Disease. Journal of Molecular Sciences, [s. l.], v. 12, n. 18, p. 2507, 2017.

CORSINI, E.; SOKOOTI, M.; GALLI, C. L.; MORETTO, A.; COLOSIO, C. Pesticide induced immunotoxicity in humans: A comprehensive review of the existing evidence. Toxicology, [s. l.], 2012. Disponível em: http://dx.doi.org/10.1016/j.tox.2012.10.009

DHOUIB, I.; JALLOULI, M.; ANNABI, A.; MARZOUKI, S. From immunotoxicity to carcinogenicity: the effects of carbamate pesticides on the immune system. [s. l.], 2016.

DÍAZ-RESENDIZ, G.; TOLEDO-IBARRA, G.; GIRÓN-PÉREZ, M. I. Modulation of Immune Response by Organophosphorus Pesticides: Fishes as a Potential Model in Immunotoxicology. Journal of Immunology Research, [s. l.], p. 1–10, 2015.

EL-MAGD, S. A. A.; SABIK, L. M. E.; SHOUKRY, A. Pyrethroid Toxic Effects on some Hormonal Profile and Biochemical Markers among Workers in Pyrethroid Insecticides Company. [s. l.], v. 8, n. 1, p. 311–322, 2011.

HU, L.; LUO, D.; ZHOU, T.; TAO, Y.; FENG, J.; MEI, S. The association between non-Hodgkin lymphoma and organophosphate pesticides exposure: A meta-analysis*. Environmental Pollution, [s. l.], v. 231, p. 319–328, 2017. Disponível em: http://dx.doi.org/10.1016/j.envpol.2017.08.028

KABIR, A.; ZENDEHDEL, R.; TAYEFEH-RAHIMIAN, R. Dioxin Exposure in the Manufacture of Pesticide Production as a Risk Factor for Death from Prostate Cancer: A Meta-analysis. [s. l.], v. 47, n. 2, p. 148–155, 2018.

KARMAUS, W.; BROOKS, K. R.; NEBE, T.; WITTEN, J.; OBI-OSIUS, N.; KRUSE, H. Environmental Health: A Global Immune function biomarkers in children exposed to lead and organochlorine compounds: a cross-sectional study Methods: [s. l.], v. 10, p. 1–10, 2005.

LUO, D.; ZHOU, T.; TAO, Y.; FENG, Y.; SHEN, X.; MEI, S. Exposure to organochlorine pesticides and non-Hodgkin lymphoma: a meta-analysis of observational studies. Nature Publishing Group, [s. l.], n. May, p. 1–11, 2016. Disponível em: http://dx.doi.org/10.1038/srep25768

MOKARIZADEH, A.; FARYABI, M. R.; REZVANFAR, M. A.; ABDOLLAHI, M. A comprehensive review of pesticides and the immune dysregulation: mechanisms, evidence and consequences. Toxicology Mechanisms and Methods, [s. l.], v. 00, n. 00, p. 1–21, 2015. Disponível em: http://dx.doi.org/10.3109/15376516.2015.1020182

MOSTAFALOU, S.; ABDOLLAHI, M. Pesticides: an update of human exposure and toxicity. Archives of Toxicology, [s. l.], v. 91, n. 2, p. 549–599, 2017.

NTZANI, E. E. Literature review on epidemiological studies linking exposure to pesticides. [s. l.], p. 1–159, 2013.

PARRÓN, T.; REQUENA, M.; HERNÁNDEZ, A. F.; ALARCÓN, R. Environmental exposure to pesticides and cancer risk in multiple human organ systems. Toxicology Letters, [s. l.], v. 230, n. 2, p. 157–165, 2014. Disponível em: http://dx.doi.org/10.1016/j.toxlet.2013.11.009

PREVENTION, H. R.; MILAN, P. U. The lymphocytic cholinergic system and its modulation by organophosphorus pesticides. [s. l.], v. 17, n. 3, p. 325–337, 2004.

REUTER, S.; GUPTA, S. C.; CHATURVEDI, M. M.; AGGARWAL, B. B. Free Radical Biology & Medicine Oxidative stress, in fl ammation, and cancer: How are they linked? Free Radical Biology and Medicine, [s. l.], v. 49, n. 11, p. 1603–1616, 2010. Disponível em: http://dx.doi.org/10.1016/j.freeradbiomed.2010.09.006

REYNA, L.; FLORES-MARTÍN, J.; RIDANO, M. E.; GENTI-RAIMONDI, S.; GENTI-RAIMONDI, S. Chlorpyrifos induces endoplasmic reticulum stress in JEG-3 cells. Toxicology in Vitro, [s. l.], 2016. Disponível em: http://dx.doi.org/10.1016/j.tiv.2016.12.008

SEBASTIAN; RAGHAVAN. Mini-Review Molecular mechanism of Endosulfan action in mammals. Journal of Biosciences, [s. l.], v. 1, n. 42, p. 149–153., 2016.

SIGURS, Nele *et al*. Severerespiratorysyncytialvirusbronchiolitis in infancyandasthmaandallergyat age 13. American journalofrespiratoryandcriticalcare medicine, v. 171, n. 2, p. 137-141, 2005.

SUNYER, Jordi *et al*. Prenataldichlorodiphenyldichloroethylene (DDE) andasthma in children. Environmental health perspectives, v. 113, n. 12, p. 1787-1790, 2005.

STERN, A. H. Hazard identi fi cation of the potential for dieldrin carcinogenicity to humans $. Environmental Research, [s. l.], v. 131, p. 188–214, 2014. Disponível em: http://dx.doi.org/10.1016/j.envres.2014.02.007

THOMAS, P. T. Pesticide-induced Imm u notoxicity : Are Great Lakes Residents at Risk ? [s. l.], v. 1, n. December, p. 55–61, 1995.

THONGPRAKAISANG, S.; THIANTANAWAT, A.; RANGKADILOK, N.; SURIYO, T.; SATAYAVIVAD, J. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food and Chemical Toxicology, [s. l.], v. 59, p. 129–136, 2013. Disponível em: http://dx.doi.org/10.1016/j.fct.2013.05.057

WANG, C. H. I. H. U. N. G. Early onset pneumonia in patients with cholinesterase inhibitor poisoning. [s. l.], p. 961–968, 2010.

YANAGISAWA, R.; TAKANO, H.; INOUE, K.; KOIKE, E.; SADAKANE, K.; ICHINOSE, T. Effects of Maternal Exposure to Di- (2-ethylhexyl) Phthalate during Fetal and / or Neonatal Periods on Atopic Dermatitis in Male Offspring. [s. l.], v. 1136, n. 9, p. 2004–2009, 2008.