ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Our everyday immune system and today's pesticides

Nosso sistema imune de cada dia e os agrotóxicos de hoje

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ABSTRACT

Beginning in the 1950s, massive pesticide use began in what is called the "Green Revolution", a quest for increased agricultural productivity and modernization. In the 1960s, the Brazilian National Program of Agricultural Defense was created to facilitate the introduction of agrochemicals, leading the country to become one of the world's largest pesticide users by 2008. These substances have deleterious effects on the immune response of exposed individuals, mainly related to macrophages and B, T, and NK cells. This affects phagocytosis and antigen and antibody production, inducing production of oxygen free radicals and mitochondrial dysfunction, which results in oxidative stress and cellular DNA damage, excess apoptosis, cell cycle mutations, regulatory disorders, and, consequently, immunodeficiency. Thus, the development of immune-mediated diseases, such as asthma and chronic obstructive pulmonary disease (COPD), is closely linked to pesticides, since these varied mechanisms of toxicity to the immune system induce respiratory manifestations, such as cough, wheezing, irritation and inflammation. Pesticide use is also related to non-immune-mediated diseases because exposure alters the normal function of thyroid hormones, androgens, and estrogens. To evaluate their impact, the present study performed an integrative review of the literature, which, due to the growing and uncontrolled use of pesticides, is of great relevance and demonstrates the need for greater epidemiological, environmental, and worker health surveillance.

Keywords: Agrochemicals, pesticide exposure, immune diseases, respiratory tract diseases.

RESUMO

O uso massivo dos agrotóxicos nas lavouras deu-se a partir de 1950 com a "Revolução Verde", como resultado da busca por aumento da produtividade e modernização dos campos agrícolas. Diante disso, na década de 1960, foi criado o Programa Nacional de Defensivos Agrícolas (PNDA), que veio para facilitar a introdução dos agroquímicos, colaborando para que, a partir de 2008, o Brasil passasse a ser o país com maiores percentuais de uso destes produtos. Essas substâncias geram efeitos deletérios sobre a resposta imune dos indivíduos expostos, principalmente relacionada aos macrófagos, células B, T e NK. Isso afeta a capacidade de fagocitose, apresentação de antígenos e produção de anticorpos, além de induzir a geração de radicais livres de oxigênio e disfunção mitocondrial, resultando em estresse oxidativo e danos ao DNA celular, apoptose em excesso, mutação no ciclo celular, desordem de regulação e, consequentemente, imunodeficiência. Dessa forma, o desenvolvimento de doenças imunomediadas, como asma e doença pulmonar obstrutiva crônica (DPOC), está estreitamente ligado aos agrotóxicos, uma vez que esses variados mecanismos de toxicidade ao sistema imune induzem, dentre outras, manifestações respiratórias, tais como tosse, sibilo, irritação e inflamação. Além disso, estes pesticidas estão relacionados com doenças não imunomediadas ao alterar a função normal dos hormônios da tireoide, andrógenos e estrógenos. A fim de avaliar estes impactos, o presente estudo consiste em uma revisão integrativa da literatura e, diante da crescente utilização descontrolada dos agrotóxicos, assume grande relevância, refletindo a necessidade de maior atuação da vigilância epidemiológica, ambiental e da saúde do trabalhador.

Descritores: Agroquímicos, exposição a praguicidas, doenças do sistema imunitário, doenças respiratórias.

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Introduction

The use of chemical compounds in farming was initiated after the end of the world great wars, and started to be massively applied in the 1950s, with the so-called "Green Revolution." The quest for increased agricultural productivity and modernization resulted in the creation of the National Program of Agricultural Defense in the 1960s. This program facilitated the introduction of agrochemicals throughout the years, which led Brazil to become the world leader in the use of these products in 2008.[1-3]

Numerous types of agrochemicals are currently used in Brazil, and notably most of them are banned in European countries and in the United States. Herbicides, insecticides, fungicides, and bactericides stand out as the most used of types of agrochemicals and, despite their high impact on control of agricultural plagues, the development of resistance to the toxins applied has led to the use of increased doses and to the search for new, more potent compounds, resulting in serious impacts on human health.[1,4]

Exposure to agrochemicals produces several effects, such as impaired immune response in exposed individuals, which has drawn the attention of health care professionals.[3] Recent investigations showed that these agrochemicals affect especially macrophages, B cells, T cells, and natural killer (NK) cells, leading to changes in the cell cycle, decreased antigen presentation capacity, reduced phagocytic capacity, and induction of apoptosis.[3]

In this context, it is observed that some exposed individuals will develop an immunodeficiency state, since cell responses and antibody production will fail; therefore, these individuals will become less resistant to infectious processes. Moreover, there will be failures in immunological surveillance of tumors and immune regulation disorders, facilitating the development of neoplastic processes and immune diseases.[3]

Airway involvement caused by such chemicals also has been much observed, because they promote respiratory mucosa irritation and local epithelial inflammation, favoring the onset of diseases such as asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD).[4] Furthermore, cardiovascular, hematological, neurological, cutaneous, and ocular changes have also been correlated to the use of pesticides.[4-6]

Therefore, in view of the several impacts and damages both to workers exposed to chemical products in farming and to the general population through water, soil and air contamination, the present article aims to describe the main influences observed in the immune system resulting from exposure to pesticides.

Methods

This is an integrative literature review conducted on the following databases: National Library of Medicine (PubMed), Latin American and Caribbean Health Sciences Literature (LILACS), and Scientific Electronic Library Online (SciELO). Articles were selected using Descriptors in Health Sciences (DeCS) and Medical Subject Heading (MeSH), using the following descriptors: "agrotóxicos," "doenças do sistema imunológico," "doenças respiratórias," "exposição a produtos químicos," "agrochemicals," "immune system diseases," "respiratory tract diseases," and "chemical compound exposure." Inclusion criteria were full articles in Portuguese and English and published from January 2000 to April 2021. Exclusion criteria consisted of experience reports, opinion articles, and editorials.

Discussion

Overview of pesticides in Brazil

Agrochemicals, agricultural defensives, pesticides, medicines for plants, venom are some of the numerous terms linked to the group of chemical compounds used in the sector of production, storage, and processing of agricultural products, in pastures, in protection of forests, and in urban, water, and industrial environments. Their main purpose is to change the composition of flora and fauna in order to preserve them from harmful action of living beings and chemicals.[7]

As provided by Law n. 7,802, dated of July 11th, 1989, 3rd article, pesticides, their components, and related products may only be produced, exported, imported, marketed, and used if previously registered with a federal agency, in compliance with the directives and requirements of health federal agencies.[8]

For pesticides to be marketed in the Brazilian territory, information on their labels must be clear; therefore, the presence of specific labelling and package leaflets, written in Portuguese. In the case of accidents, there must be explicit instructions, including warning symptoms, first aid, antidotes, and recommendations for physicians.[8] Hence, for classification purposes, pesticides are divided

according to regulations provided by the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA). There were changes in 2017, and pesticides reclassified according to the level of toxicity, as shown in Table 1.[9]

In addition to the classification according to toxicity, as recommended by ANVISA, pesticides may be classified according to their chemical properties. Among them, herbicides are represented by chlorophenoxy (2,4-D; 2,3,5-T; and MCPA), urea derivatives, triazines, amide, bipyridyls, and glyphosate.[4] Insecticides are represented by organochlorines, cyclohexanes, chlorinated benzenes, cyclodienes, chlordecone, organophosphates, carbamates, pyrethroids, rotenone, Bacillus thuringiensis (protein compound).[4]

Fungicides, in turn, include dithiocarbamates, captan, captafol, pentachlorophenol, iprodione, and sulfur, and, with regard to bactericides, triazine-S-triones, chlorine-releasing agents, chlorine, and dichloronitrobenzene stand out. Rodenticides are represented by coumadin and derivatives, anticoagulants, strychnine, sodium fluoroacetate; and, finally, methyl bromide, aluminum/zinc phosphide, and sulfur are examples of fumigants.[4]

Another known classification is linked to the mechanism of action of pesticides, which may present neurotoxic properties, such as organochlorines and organophosphates, or properties similar to those of vegetal hormones, such as phenoxy herbicides. Other substances may act as endocrine disruptors, such as the herbicides atrazine and urea, or interfere with physiological processes, promoting changes in coagulation cascade by reducing vitamin K synthesis, such as coumadin, among several other types of mechanisms of action.[4]

All forms of classifying these substances show the danger of their excessive use. However, the reality of consumption shows to be contradictory since, despite the known hazards of excessive exposure, the Brazilian market occupies a prominent position in the global ranking, being the largest consumer of pesticides in the world since 2008, according to ANVISA.[1,10] Herbicides are the most commonly used products, accounting for approximately 45% of the total amount used, followed by fungicides (14%) and insecticides (12%).

In addition to intense use of registered agrochemicals, another concern is related to smuggling of these products. An analysis of samples collected in 2011 by the Program for Analysis of Pesticide Residues in Food, developed by ANVISA, showed that 78% of them were contaminated, even with two pesticides that have never been registered in Brazil, azaconazole and tebufenpyrad, which

Table 1
2017 reclassification according to levels of pesticide toxicity

Category	Toxicity	Examples
Category 1	Extremely toxic product	2,4 D and methomyl
Category 2	Highly toxic product	Chlorpyrifos and diazinon
Category 3	Moderately toxic product	Acephate, diuron, malathion, and mancozeb
Category 4	Little toxic product	Glyphosate

Sources: Brazilian Health Surveillance Agency, 2019; International Agency for Research on Cancer, 2018; United States Environmental Protection Agency, 2019.[9]

suggests lack of control of public policies on the use of agrochemicals in the country.[10]

In this context of intense production and consumption, it is worth emphasizing that the use of pesticides is a major public health problem, due to the size of the exposed population in pesticide plants and surrounding areas, in farming, in fighting endemics, in the vicinity of farming areas, and, ultimately, those who consume contaminated food,[10] requiring specialized attention for its control.

Agrochemicals and non-immune-mediated diseases

Studies associate exposure to agrochemicals with hormone deregulations and diseases in humans.[11] These impacts have been studied since these products began to be used in the 1960s. Currently, it is know that agrochemicals have compounds capable of deregulating the endocrine system, inhibiting cholinesterases, such as AchE (acetylcholinesterase) and ChP (butyrylcholinesterase), and acting as a substance with carcinogenic potential.[11,12]

Deregulation of the endocrine system occurs by altering the physiological function of thyroid hormones, androgens, and estrogens. Some agrochemical compounds are capable of interrupting signaling pathways, mimicking the interaction of endogenous hormones with nuclear receptor. Consequently, they interfere with synthesis, response, and degradation of peptide and steroid hormones.[2,11,13,14] Furthermore, epidemiological data have associated exposure to agrochemicals with increased incidence of hormone-dependent tumors, which are closely linked to endocrine deregulation.[11]

Moreover, the fact that interruption of hormone synthesis may be a factor that precedes changes in human brain functions has been also an object of study.[11,14] In humans, neuronal death caused by agrochemical compounds is caused by oxidative stress, mitochondrial dysfunction, failures in endoplasmic reticulum function, damages to signaling molecules, protein degradation, and other mechanisms.[14]

Exposure to pesticides, such as organophosphates, may lead to acute and even chronic manifestations, depending on time and extent of exposure. Therefore, when a test is performed to measure biological exposure indicators, the levels of cholinesterases, AchE, and ChP are reduced. Consequently, in poisoning, people may present with muscarinic, nicotinic, motor, and neurosensory effects, as well as cognitive disorders.[12] Furthermore, studies that used epidemiological data and analyzed cell models established the relationship between exposure to agrochemicals and brain neurodegeneration, with Parkinson's disease being the main neurodegenerative disease.[14]

From this perspective, contact with toxic agents is practically inevitable, since consumption of industrialized products and interaction with nature go hand in hand with contact with several chemical entities. Therefore, it is also worth highlighting the carcinogenic potential of agrochemicals, due to the heterogeneity of compounds and chronic exposure to these substances experienced by a large portion of rural workers. However, chronic effect is linked to the several absorption pathways, such as dermal, digestive, and respiratory ones, and, when associated with fat-soluble toxins, leads to increased risks for cell mutation, due to bioaccumulation generated in the body. Thus, brain neoplasms, non-Hodgkin lymphoma, cutaneous melanomas, digestive and urinary tract cancers become the reality of the population in contact with such chemicals.[2]

Agrochemicals, immune system, and immune-mediated diseases

Immune response to pathogens and to diseases results from the joint action of several cell and hormone components. It can be divided into innate or adaptive immune responses, with the first represented mainly by neutrophils, macrophages, and NK cells, and the latter by T and B lymphocytes and antibodies.[3] The effects of agrochemicals in this system result from their immunotoxicity potential, a term first used in 1970 that covers any deleterious effect in immune function, both innate and adaptive.[15] These effects deregulate the body protective system, thus impairing defensive response.

Agricultural defensives are present in food, in fluvial waters, in the air, and in the soil; therefore, there are several forms of contamination. Moreover, since various agrochemicals are used concomitantly and each mechanism has specific actions, different cell groups are affected, resulting in multiple immunity failures.[3] These failures include deficiencies in phagocytosis capacity, in antigen presentation, and in antibody production, induction of excess apoptosis, cell cycle mutations, regulatory disorders, and, consequently, immunodeficiency.[3,15] These deleterious effects become even more intense during

spraying seasons, since inhalation of pesticides is shown to be an important contamination pathway.[3]

Organophosphorus compounds, organochlorines, carbamates, triazines, and chlorophenols are the most used chemical groups in Brazil and, as previously mentioned, each group has different mechanisms of immunotoxicity, with a direct action on cells and consequences to the development of immune-mediated diseases. Together with these mechanisms of direct action to the cells, reactive oxygen species (ROS) are produced, which results in oxidative stress and cellular DNA damage, inducing changes in signaling and proapoptotic state.[3] In this context, the effect of glyphosate was observed in tests of specific cell lines, confirming significant cell mortality resulting from mitochondrial damage due to increased amount of ROS.[16]

Furthermore, a study conducted in the United States observed a significant genotoxic effect on B and T lymphocytes caused by pesticides among farmers during one pesticide spraying season.[17] Workers were chronically exposed to several pesticides, making it difficult to attribute the genotoxic effect to one specific class or chemical compound. However, this form of exposure was shown to induce DNA damages, such as simple- and double-stranded DNA breaks, resulting in deficient B and T cell repair. Fungicides, such as chlorothalonil, carbendazim, and methyl thiophanate may play a greater role in inducing these DNA damages in T lymphocytes.[17] Chlorothalonil exhibited strong cytotoxicity against specific cell lines, resulting in high cell mortality after 24 and 48 hours of contact[18] and cytogenetic effects on lymphocytes, leading to an increased number of chromosome aberrations.[19]

Mitochondrial dysfunction, another mechanism, is characterized by damaging effects to the endoplasmic reticulum, causing deficiency in protein production and also in cell apoptosis.[3] An example of this phenomenon is the negative effect on anti-cancer proteins, specifically NK-92CI cells, which are highly cytotoxic to tumor cells. This effect is characteristic of the carbamate class, such as carbaryl (insecticide), maneb (fungicide), thiram (fungicide), and ziram (fungicide). Therefore, the findings of the study suggest that this class significantly reduces intracellular levels of proteins in this cell line, in a dose-dependent manner to their immunotoxic effect, predisposing individuals to the development of cancer.[20]

Deregulation of signaling mechanisms is also common, caused by agrochemicals such as atrazine, one of the most used herbicides in Brazil but banned in the European Union because it induces positive modulation of regulatory T cells, preventing the production of cytokines such as interferon-gamma and weakening immune response.[21] This results in toxic effects in fertility, nervous system, and fetal development.[3] Similarly, bendiocarb, a carbamate insecticide, causes dose-dependent changes in homeostasis and immune cell function, including changes in regulatory TCD4 cells and in adjustment of cytokines and chemokines.[22]

However, the most serious problem is that bendiocarb may be absorbed by pregnant women and transferred to the fetus. Therefore, intra-uterine exposure to this chemical has unequivocal effects on the fetus immune system, due to an exacerbated inflammatory response, which may be critical to maintain maternal-fetal tolerance and leads to adverse effects during pregnancy. Furthermore, it brings important biological consequences to child's development and health, since these changes are still detectable in childhood.[22]

All these mechanisms may negatively influence the potential of the body to defend itself against external pathogens, including viruses. Cellular damages may worsen clinical conditions, a fact that is particularly important in a pandemic scenario such as that of COVID-19. In this context, individuals with comorbidities such diabetes mellitus, hypertension, obesity, and immunosuppression were considered as a risk group.[3,23] Thus, it can be inferred that the impact of these chemicals on the immune system extends to the ability of responding to viral infections, including SARS-CoV-2 infection, either directly or not.[3]

Development of immune-mediated diseases is also closely linked to agrochemicals. These varied mechanisms of toxicity to the immune system induce, among others, respiratory manifestations such as cough, wheezing, and airway irritation and inflammation. These manifestations derive from immune-mediated lung diseases, and may be divided into type 1 reactions, which are predominantly IgE-mediated, such as occupational asthma, type 3 and 4 reactions, which are caused by hypersensitivity, such pneumonitis, and those mediated by innate immunity, such as CPOD.[15]

Organophosphates consist of an important chemical group extensively used worldwide since, in addition to the previously mentioned effects on the central nervous system in non-immune-mediated reactions, these compounds have also peripheral

effects, especially for airways. Their mechanism of action is based on the inhibition of acetylcholinesterase, whose function is degrading acetylcholine, resulting in accumulation of this neurotransmitter in the respiratory system. As a consequence of chronic exposure, excess muscarinic response occurs, characterized by induction of hyperresponsiveness and bronchoconstriction, justifying its relationship with asthma.[3-5,24]

Considering that the use of organophosphates is not restricted to farming areas, also including peri-urban and urban areas, their ability to worsen asthma and other immune-mediated diseases extends both rural and urban workers and residents.[5,24] Moreover, organophosphates have another mechanism of direct action on the immune system: they inhibit serine hydrolases, enzymes able to hydrolyze immune signaling chemicals. Therefore, several previously mentioned defense cells, such as neutrophils, macrophages, NK cells, antibodies, and lymphocytes, undergo negative immune modulation, generating an immunodeficiency state again.[25]

Asthma is defined as an inflammatory lung disease characterized by intermittent, reversible bronchoconstriction, hypersecretion, and airway hyperreactiveness, with repercussions in the presentation of respiratory symptoms and reduced quality of life.[5,15,24] It was shown that one fifth of cases of adult-onset asthma results from occupational factors and that, in nearly 90% of these cases, immunological factors are involved.[26] This pathophysiology is justified by the action of mastocytes, eosinophils, lymphocytes, IgE, and mediators such as histamine, which act causing edema and inflammation after exposure to allergens. However, due to low antigenicity of pesticides, asthma induced or worsened by these chemicals is possibly due to the immunological effect of Th1/Th2 imbalance, so as to induce release of ROS and cause cellular damage.[27] Therefore, exposure to vapors of chemicals may result in cough and chronic expectoration, leading to exacerbation of pre-existing disease[4] and to the development of adult-onset asthma.[4,28]

Rhinitis is, by definition, an inflammation of nasal mucosa, and may be caused by direct action of agrochemicals, also known as irritant rhinitis, or be immune-mediated, known as allergic rhinitis, which is much more common in the context of rural workers.[27] Clinical presentations of this disease include rhinorrhea, sneezing, itching, and nasal obstruction.[27,29] The use of 2,4-D pesticide was associated with development of allergic rhinitis and wheezing in the long term compared to workers not exposed to this chemical. Similar results were obtained with the use of carbamates and pyrethroids.[29]

Hypersensitivity pneumonitis (HP) is an interstitial lung disease characterized by inflammation concomitant with fibrosis resulting from constant inhalation of antigens and, consequently, sensitization.[27,30] In Brazil, it is the second most common interstitial lung disease, and inhalation of low-molecular weight chemical compounds, such as organochlorines, carbamates, and pyrethroids, are among the several causes for the development of HP.[24] One of the most remarkable forms of HP is "farmer's lung," a type of allergic pneumonitis caused by a type 3 and 4 hypersensitivity reaction resulting from inhalation of dust and agricultural products; thus, increased levels of inflammatory interleukins such as IL-1, IL-6, and TNF-alpha potentiate defensive response and cause noncaseating granulomas, alveolar destruction, and fibrosis.[15] Because of these changes, this disease is manifested as fever, chills, cough, dyspnea, and chest pain, in the acute stage, and cough and chronic expectoration when sequelae remain.[30]

Finally, COPD is characterized by chronic small airway limitation in association with inflammation and loss of lung elasticity. Occupational exposure to pesticides may be related to the development of COPD, and organophosphates, organochlorines, carbamates, and herbicides are the classes more related to chronic bronchitis.[4] Therefore, it is possible to observe the extent and severity of the influence of agrochemicals on the immune system and on the development of immunodeficiency.

Conclusion

In view of the growing and uncontrolled use of agrochemicals, this study addressed information on the existing relationship between high consumption of pesticides in Brazil and diseases they cause in the entire body, either immune-mediated or not. Therefore, it is possible to understand the relevance of the immune system with regard to the other body systems, because, in cases of immunodepression or agrochemical poisoning, the other systems are also affected and, thus, the entire physiology will be impaired, focusing, in this study, on the consequences to the nervous, endocrine, and respiratory systems.

Therefore, the main importance of the present study lies on its aim of subsidizing measures to protect the most vulnerable individuals in the context of harm to human physiology, notably to the immune system. In this sense, it bears noting the importance of developing studies and research projects involving such issues, so as to better understand the existing relationship between agrochemicals, with all their immunotoxicity effects, and the immune system, as well as the other body systems and, based on this, develop control measures regarding the use of agrochemicals in Brazil.

From this perspective, it is possible to understand beforehand that the impact of agrochemicals on the body and on the environment demonstrates the need for a better health promotion and prevention, and, concomitantly, for greater monitoring and mapping of agrochemical poisoning, either acute or chronic, in order to promote health surveillance actions, focusing on those of epidemiological, environmental, and notably worker health surveillance.

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