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Hum Exp Toxicol 2008; 27; 671

DOI: 10.1177/0960327108094509

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Effects of pesticide exposure on the human immune system

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Epidemiological evidence from Western countries indicates that the prevalence of diseases associated with alterations in the immune response, such as asthma, certain autoimmune diseases and cancer, are increasing to such an extent that it cannot be attributed to improved diagnostics alone. There is some concern that this trend could be, at least, partially attributable to new or modified patterns of exposures to chemicals, including pesticides. The purpose of this article is to review the evidence on pesticide immunotoxicity in humans. Overall, the available data are inadequate to draw firm conclusions on the immunotoxic risk associated with pesticide exposure. The available studies on the effects of pesticides on the human immune system have several limita-

tions, including limited data on exposure levels, heterogeneity of the applied methods, and difficulties in assessing the prognostic significance of observed slight changes and in the interpretation of the reported findings. Further studies are needed and preferably as prospective studies, comparing pre- and post-exposure data in the same group of subjects and including an appropriate non-exposed control group. More knowledge is required regarding the prognostic significance of the small changes observed.

Key words: immune system; immunotoxicity; pesticides

Introduction

The aim of immunotoxicology is to study the potential effects of xenobiotics on the immune system. An immunotoxic compound is defined as a compound that can alter one or more immune functions resulting in an adverse effect. The two main adverse effects are:

- 1) decreased immunocompetence (immunosuppression), a decreased capacity to neutralize external organisms, which may result in repeated, more severe, or prolonged infections as well as the development of cancer;
- 2) immunoenhancement, an exaggerated expression of the immune response, which, as an adverse effect, may lead to immune-mediated diseases, such as hypersensitivity reactions, or autoimmune diseases like allergy.

Although not associated with specific immunity, a third common effect is an inflammatory response

in which immune cells and mediators actively participate.

At least two properties make the immune system vulnerable to chemical or physical insults: (1) the immune system develops rather late in life (thymus development continues at least until puberty), and bone marrow-derived immune components are continuously being renewed and (2) each response to a pathogen attack, including immune surveillance, demands a delicate control of the balance between activation, silencing and regulation of immune reactivity.

It has been hypothesized that altered immune function may be an early indicator of immunotoxicity, eventually having an effect on immunologically based diseases, such as cancer, hypersensitivity, and autoimmunity.¹ Industrialized countries have been facing and have faced a significant increase in some of these conditions over the past few decades, although the rate of increase has recently slowed. Although the levels of evidence differ, these diseases can, potentially, be attributed to an environmentally related alteration of the immune system function. Thirty-five million people in the USA suffer from allergic diseases, 2–5% of which occurred due to occupational exposure.¹ Asthma prevalence

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in European children has risen to 4.5%^{2,3} and the prevalence of diseases, such as rhinitis, atopic eczema and urticaria, is generally increasing.³⁻⁵ With respect to autoimmunity, the USA is facing higher incidences of rheumatoid arthritis, autoimmune thyroid diseases, and uveitis.⁶ Environmental and occupational exposures to xenobiotics have been implicated as the possible causes of these trends.⁶ Moreover, with regard to immunosuppression, epidemiological data suggest that cancer patterns are changing over time, with increases in melanoma, prostate cancer, non-Hodgkin lymphoma, and multiple myeloma.⁷ The possibility that such trends could be associated with changing patterns of exposures to xenobiotics needs to be evaluated. Unfortunately, time trends for infectious diseases are thought to be unreliable because of the substantial improvement in diagnostic techniques, and improved survival.

Several animal studies have identified a number of chemicals with a potential to cause immunosuppression, including agents that are commonly used in the workplace such as pesticides, metals, and industrial chemicals. The possibility that environmental pollutants may interfere with immune functions in humans has been raised in a growing number of studies focusing on subjects accidentally or occupationally exposed to industrial or environmental chemicals.¹ Besides the vast amount of data accumulated on these specific compounds, including solvents, heavy metals, pesticides, persistent organic pollutants, etc., the question pending is whether occupational and environmental pollutants affect the immune response and thereby increase the incidence of sensitization to ubiquitous antigens, the onset of autoimmune diseases, or the development of cancer. Xenobiotics may play an important role in genetically susceptible individuals, where they may initiate, facilitate or exacerbate pathological immune processes, resulting in autoimmunity, asthma, and cancer. Theoretically, they can do so by the induction of mutations in genes coding for immunoregulatory factors, modification of immune tolerance and regulation, or by immunostimulation and immunosuppression.

Pesticide immunotoxicity in humans: existing evidence

The term "pesticide" is a contraction used to define a variety of agents that are classified on the basis of their potential to kill living organisms. They include insecticides, herbicides, and fungicides. It is estimated that annually approximately 7000 metric tons (Mt) of herbicides, 8000 Mt of insecticides,

and 9000 Mt of fungicides are used worldwide.⁸ As they are addressed at controlling living species, pesticides are biologically active substances, and due to their ubiquitous presence in the living and working environment, they are source of exposure for most of the human population and such exposure cause concern. These compounds differ from all other chemical substances in that they are deliberately spread in the environment, and, as they are designed to interfere with certain living organisms, they are inevitably characterized by variable levels of toxicity. There is some evidence suggesting that the immune system may be a target for the toxic effects of some pesticides.⁹⁻¹²

The current evidence on the immunotoxicity of pesticides in humans following occupational or environmental exposures is summarized in Table 1. The table clearly shows that the available data are incomplete (the majority of data are relative to old pesticides and, only few immune parameters have been investigated) and that, sometime, the results are contradictory or difficult to understand, i.e. lindane poisoning caused an increase in serum interleukin IL-2, IL-4, and tumour necrosis factor TNF- α but a decrease in interferon IFN- γ . In some instances (i.e. chlordane, hexachlorobenzene, chlorpyrifos), a decrease in cell-mediated immunity was associated with increased allergic reactions and autoimmune diseases, suggesting that pesticide-induced immunosuppression may have an impact on individual's ability to evoke an allergic response. Pesticides, although not antigenic themselves, may alter or prime the immune system's response to antigens, including self-antigens, skewing the Th1/Th2 balance. Pesticides can alter immune functions, however, in many instances the observed effects are very slight and, unfortunately, the current scientific literature does not offer a sufficient basis on which to draw conclusions about the risks to human health. That is, might a mild immunosuppressive effect bring about an increased risk of infectious diseases or cancer? On the other hand, might a mild immunostimulation or a change in Th1/Th2 balance cause an increase in allergies, or autoimmune diseases? Exceptions are concordant evidence on the immunosuppressive effects exerted by pentachlorophenol¹²⁻¹⁶ and the finding of an increased immune response after hexachlorobenzene exposure.^{17,18} Moreover, in the case of mancozeb, there is interesting agreement between the immunoenhancement observed in field studies and the well known immunomodulator potential of other dithiocarbamates, which had been proposed by clinical immunologists for the treatment of different conditions of immunodeficiency as T-cell-specific immunostimulants.¹⁹⁻²¹ We have recently investigated the effects of

Table 1 Immunomodulatory effects of pesticides in humans

Compound	Trend	Effect	Type of exposure	Ref
Aldicarb (carbamate)	Decrease	CD4/CD8 ratio due to increase in CD8 cells	Environmental (groundwater)	52,53
Atrazine (herbicide)	Decrease	NK cell activity	<i>In vitro</i>	54
Chlordane (organochlorine)	Increase	Hypersensitivity, allergic rhinitis, serum IL-1, IL-5, IL-6, IL-8, RANTES, and TNF- α , staphylococcal skin and viral upper respiratory tract infections	Human bystander	55
	Decrease	Cellular immunity	Indoor & workplace	56
	Increase	IL-2, IL-3, IL-7, IL-9, IL-11 IL-12, IL-15, IFN- γ , CD1 lymphocytes, autoantibodies	Indoor	56
	Decrease	CD45RA/T4 cells, proliferative response to mitogens	<i>In vitro</i>	57
	Increase	Incidence of sinusitis and bronchitis	Indoor	59
	Decrease	NK cell activity	Residential	59
Chlordane/heptachlor	Increase	Autoantibodies	Occupational	59
Chlorpyrifos (OP)	Increase	Atopy and antibiotic sensitivity	Environmental	59,60
	Increase	CD26 cells, autoantibodies and autoimmunity	Occupational	24
DDT & G-HCH (organochlorine)	Decrease	CD5 cells, proliferative response to mitogens		
	Decrease	Neutrophil function		
	Increase	Incidence of infections		
	Decrease	Neutrophil function		
	Decrease	IL-2 production		
DDT	Increase	Plasma IL-4		
DDT	Decrease	CD16 cells, mytogen proliferation, CD4/CD8 ratio, serum IgM		
DDE (organochlorine)	Decrease	Serum IgG		
	Decrease	Serum IgM and IgG	<i>In vitro</i>	61
	Increase	Autoimmune-type diseases	<i>In vitro</i>	62
	Decrease	Neutrophil functions	Occupational	63
	Decrease	IFN- γ production	Human bystander	64
HCB (fungicide)	Decrease	Serum IgM	Occupational	65
	Increase	Neutrophil functions	Occupational	17
	Decrease	IFN- γ production	Human (accidental poisoning)	18
Hexachloro cyclohexane	Increase	Serum IgM	Occupational	66
Lindane (organochlorine)	Increase	Serum IL-2, IL-4, TNF- α	Occupational	67
	Decrease	Serum IFN- γ	Poisoning	68
	Increase	Allergic contact dermatitis		69
Malathion (OP)	Increase	Proliferative response to T-cell mitogens, IL-2 production	Occupational	70
Mancozeb (fungicide)	Decrease	LPS-induced TNF- α production, CD25 cells	Occupational	71
	Increase	Proliferative response to T-cell mitogens, B cells	Occupational	22
	Decrease	TNF- α production		
OP	Increase	Asthma and atopic reaction	<i>In vitro</i>	39
	Increase	Infections of the upper respiratory tract	Occupational	72
	Decrease	Neutrophil functions	Occupational	22
	Decrease	NK and CTL cells activity		
OP by products of sarin (DIMP and DEMP)	Decrease	NK and CTL cells activity	<i>In vitro</i>	73
Pentachlorophenol (fungicide)	Decrease	Lymphocyte proliferative response to mitogens	Human (accidental poisoning)	74
	Decrease	Lymphocyte proliferative response to mitogens, blood monocytes, serum IL8, CD4/CD8 ratio, CD4 cells	Occupational	15
	Decrease	Lymphocyte proliferative response to mitogens, MLR, serum immunoglobulins, Anti-smooth muscle antibodies, CD10 cells, NK cell activity (females)	Unspecified	17
	Decrease	Immature blood lymphocytes, basophils, low grade skin and upper respiratory tract infections	Occupational	14
	Decrease	T-cells, CD8 cells, NK cells, lymphocyte proliferative response to mitogens	Occupational	13
	Decrease	NK cells activity	Occupational	75
	Decrease	IFN- γ production, expression of STAT6, Lymphocyte proliferation, monocytes antigen presentation, monocytes HLA-DR expression	<i>In vitro</i>	58
Pyrethroids	Decrease	NK cell activity	<i>In vitro</i>	76
	Decrease	Neutrophil function		
Tributyltin (fungicide)	Decrease	NK cell activity and binding to target cells	<i>In vitro</i>	77
Triphenyltin (fungicide)	Decrease		Occupational, acute poisoning	78
Ziram (fungicide)	Decrease		<i>In vitro</i>	77,79

OP, organophosphate pesticides; DDT, dichlorodiphenyltrichloroethane; GHCH, gamma-hexachlorocyclohexane; DDE, dichlorodiphenylethylene; DIMP, diisopropyl methylphosphonate; DEMP, diethyl methylphosphonate; HCB, hexachlorobenzene; MLR, mixed lymphocytes response.

mancozeb on the immune system in a group of agricultural workers. The levels of urinary excretion of ethylene thiourea, the major metabolite of mancozeb, confirmed that the absorption of the fungicide took place during application. The investigation of serum, cellular and functional immune parameters suggested that mancozeb exerts a slight immunomodulatory effect characterized by: (i) an increase in total leukocyte counts and in the proliferative response to mitogens; (ii) an increase in the percentage and absolute number of CD19⁺ cells; (iii) a reduction of CD25⁺ cells, and (iv) a pattern of cytokine production characterized by a significant reduction in lipopolysaccharide (LPS)-induced TNF- α release.²² Organophosphate pesticides (OP) cause a reduction in neutrophil function (phagocytosis, respiratory burst, adhesion) accompanied by increases in upper respiratory tract infections (tonsillitis, pharyngitis, and bronchitis) in exposed subjects.^{23,24}

It has been suggested that pesticides may interfere with normal immune surveillance, which may affect recognition and destruction of abnormal cells, and may increase the incidence of tumors associated with oncogenic viruses. Interestingly, in a study in corn farmers addressed at investigating changes in immune function in relation to farming activities and pesticide exposure (61 different active compounds), decreases in natural killer (NK) cells and in CD69 and CD25 T-cell activation markers were observed. These may be relevant for immunosurveillance.²⁵ These data are consistent with the evidence of decreased NK-cell activity induced by several of the pesticides shown in Table 1. Natural killer cells play a central role in immune defense against viral infections and the formation of primary tumors. Thus, interference with their numbers or activity could increase the risk of tumor development and/or viral infections.

Despite the substantial number of studies on cancer and agricultural chemicals, the potential of pesticides as causative agents in human carcinogenesis is still poorly understood.²⁶ Cancer is a multifactorial disease with contributions from genetic, environmental, and life style factors. Pesticides have on occasion been reported to be associated with hematopoietic cancers, and cancers of the prostate gland, pancreas, liver, and other body systems.²⁷ However, epidemiological studies do not show any consistent associations. In a large prospective cohort of pesticides applicators,²⁸ the overall cancer incidence was significantly lower than expected as a result of a low overall smoking prevalence and other lifestyle factors, whereas excess cancers of the prostate and ovaries were observed. This result

is consistent with a meta-analysis published in 2004 by Van Maele-Fabry and Willems,²⁹ which showed a possible relationship between pesticide exposure and prostate cancer. Sixty years after the introduction of DDT and despite its extensive use, the evidence remains too sparse to support an association between organochlorine pesticides and breast cancer.³⁰

Occupational exposure to some pesticides, including phenoxy herbicides, organochlorine and organophosphorous insecticides, has been associated with an increased risk for non-Hodgkin's lymphoma, but these associations remain to be confirmed.^{31,32} Furthermore, maternal and perinatal exposure to pesticides has been associated with an increased risk for lymphoma.³³ The evidence, however, is too weak and inconsistent to draw any conclusions. Discordant results may be related to variations in susceptibility factors, such as genetic polymorphisms in genes involved in pesticide metabolism, i.e. CYP1A1 and glutathione-S-transferase,³⁴ gender and age.³⁵ In most studies, however, adjustments were made for gender and age. Methodological shortcomings, such as recall and information biases, may account for the inconsistent findings. Mechanistic data in both animal and epidemiological studies, combined with improved exposure assessments, may contribute significantly to the understanding of the potential cancer risk of individual pesticides. Given the current inconsistent research findings, it is likely that if there is a cancer risk at all, it is small.

Despite the ability of several pesticides, including pentachlorophenol, chlordane, chlorpyrifos and hexachlorobenzene (Table 1), to increase the levels of autoantibodies, few studies have evaluated the possible role of pesticides as risk factors for autoimmune diseases. A weak association (Relative Risk <2.0) has been reported for pesticide exposures and rheumatoid arthritis.³⁶

Overall, despite the evidence of immunotoxic effects generated under experimental conditions, there are no convincing results from human studies in which alteration of immune function caused by low-level pesticide exposure can be judged to pose a risk for human health. This represents an urgent future challenge, because answering this question could help to establish whether environmental and occupational immunotoxicants contribute to the burden of immune-related diseases.

The consequences of pesticide-induced immunosuppression may be particularly relevant in many developing countries, where, compared with the industrialized world, much larger fractions of the population still live in the countryside and work

on farms and compounds in conditions that have been banned or restricted in industrialized countries.

In immunotoxicity studies of pesticides in humans, particular attention should be given to those compounds for which there is convincing laboratory evidence for an effect on the immune system. The question that arises is, however, whether prolonged exposure to relatively low concentrations of different chemicals showing immunotoxicity in experimental models can affect the human immune system in real life conditions. This is a critical issue, because extrapolation from high doses used in laboratory models to low doses of mixtures of compounds in environmental and occupational exposures, can be very difficult and is based on substantial assumptions. It is also important to remember that most of the toxic effects exerted by chemicals are characterized by the presence of a threshold, under which no effect is anticipated. At this regard, it is also important to consider that the immune system also possesses functional reserve and redundancy in response to xenobiotics. Even if immunotoxicology never went far than hazard identification, immunosuppression and, possibly hypersensitivity, demonstrated a threshold.

Molecular mechanisms of pesticide-induced immunotoxicity

Due to increased knowledge of the immune system and better understanding of the mechanisms of action of the immunotoxic compounds, there is a need to revise the current approaches to the investigation of immunotoxicity in humans including, when appropriate, new tests. For a better understanding of immunotoxic risk, studies on the molecular mechanisms of action of immunotoxic compounds can prove to be of great value. Recognition of cell structures and their components that can be modified may help to identify specific and sensitive markers for immunotoxic effects. The majority of immunotoxic chemicals directly interact with immunocompetent cells and cause immunotoxic effects by affecting multiple targets.³⁶ Several mechanisms of immunosuppression can be described. Xenobiotics can disrupt T-cell maturation in the thymus, cause cytotoxicity, inhibit cell proliferation, and may interfere with metabolic, receptor/ligand interactions and signal transduction pathways. As pesticides include compounds with different chemical structures, different targets and mechanisms of action can be anticipated.

The understanding that carbamates and organophosphate insecticides share the same mechanism of action, achieved by the inhibition of acetylcholinesterase, a serine hydrolase, and that the serine hydrolase activity is probably linked to several immune functions, may give a more clear picture of the potential immunotoxicity of these compounds.³⁷ Immunotoxicity may be direct via inhibition of serine hydrolases or esterases in immune cells, through oxidative damage to immune organs, or by modulation of signal transduction pathways. Indirect effects include modulation by the nervous system or effects of altered metabolism/nutrition in immune organs. Moreover, some dithiocarbamates and organophosphorous compounds are thought to derive their immunotoxic potential from the induction of oxidative stress. Modulation of nuclear factor- κ B (NF- κ B) activation could explain some of the immunotoxic effects described for dithiocarbamates and for propanil.^{38,39} It was recently demonstrated that mancozeb, by modulation of lipopolysaccharide (LPS)-induced reactive oxygen species generation, prevented I κ B degradation and NF- κ B nuclear translocation, which in turn resulted in decreased TNF- α production in monocytes.³⁹ Furthermore, the knowledge that corticosteroids mediate part of their anti-inflammatory effect by inhibiting NF- κ B nuclear binding and through the induction of the inhibitor I κ B α ,^{40,41} the finding of chemicals inducing corticosteroids or corticosteroids-like molecules, suggests that they may elicit their immunotoxic effect through such a pathway.

An approach for immunotoxicity studies in humans

Because of its potential detrimental effects to health and its potential association with morbidity and mortality,⁴² immunotoxicity is of considerable importance to the toxicologist involved in identifying and characterizing human health hazards. There is a need to describe an approach to study the immune systems of humans occupationally and environmentally exposed to xenobiotics. The rationale for such an approach should be established based on laboratory experience.

Over 20 years ago, the development of laboratory testing strategies and methods to assess immunotoxicity based on a "tiered" approach was advocated.^{43,44} A similar approach should be adopted for human studies. However, the study of the human immune response to xenobiotics is more complicated than that of laboratory animals, due to difficulties in recruiting subjects for repeated

sampling, the fact that only noninvasive tests can be carried out and because estimates of the levels of exposure, particularly over time, are often very poor.

Immune changes can be subtle and reversible, with values returning to normal after termination of exposure.⁴⁵ Immunotoxicology studies, therefore, should preferably be carried out on recently exposed populations, as immunotoxic effects may “fade out” after termination of exposure.⁴⁶ The difficulties of controlling for confounding factors and the variability of the immune response⁴² emphasizes the need of carrying out, where possible, longitudinal studies in humans and comparing pre- and post-exposure findings with non-exposed populations.

Various reference institutes and organizations have addressed the need to perform clinical immunology tests in humans. Several approaches have been proposed, including the testing scheme proposed by WHO⁴⁷ and another proposed by a panel of the US National Academy of Sciences.⁴⁸

As a general rule, all of the proposed approaches are based on the measurement of serum, cellular, and functional immune parameters. Serum parameters include autoantibodies (non-organ and organ-specific), inflammation markers, total immunoglobulins (IgA, IgG, IgE, IgM), serum levels of cytokines and soluble receptors. Cellular parameters include total and differential blood cell counts and the determination of different lymphocyte subpopulations. The functional immune parameters include proliferative responses to mitogens and antigens.⁴⁷ The above-mentioned approaches, with some adaptations and changes, have been used in some studies on pesticide immunotoxicity. The results have been inconclusive showing slight immunotoxic effects or no effects at all.

We believe that a tiered approach may be applicable to human studies as well. This should be based on three steps: (1) the potential of immunomodulation following human exposure; (2) the refinement of the results of the first step and collection of information on functional alterations in immune response, and (3) when required, the further refinement of the collected information and point out concordance with other parameters, including longitudinal prospective studies, and molecular investigations.

The first phase of immunotoxicity studies should include the determination of CD3, CD4, CD8 (CD4/CD8 ratio), CD19 and CD16/56 positive cells. The results obtained from this simple test panel are sufficient to display the balance between lymphocyte subpopulations and highlight possible alterations. In Tier 1, autoantibodies, inflammation markers, total IgG, IgA, IgE, IgM, and allergen-specific IgE,

and complement factors, are also evaluated together with clinical routine parameters, such as complete and differential blood cell counts, erythrocyte sedimentation rates and C-reactive protein.

The determination of functional immune parameters, including proliferative responses to mitogens and antigens, cytokine production under stimulation, immunoglobulin production, and NK activity should be performed in Tier 2 phase. The assessment of cytokine production seems a very promising tool, able to provide information on the immune functionality of an individual at the time of sample collection and improving the interpretation of Tier 1 results. The determination of selected cytokines, characteristic for Th1 and Th2, should therefore be also carried out in Tier 2. The analysis of the messenger-RNA coding for different cytokines may give additional information regarding the expression of genes possibly affected by exposure to xenobiotics. In parallel, the determination of cytokine soluble receptors and of soluble surface markers could provide information on the status of activation of the parent cells.⁴⁹

In laboratory animals, an appropriate way to assess the effects of chemicals on the immune system is to study their effects on antigen-specific immune responses, such as antibody production in response to T-cell-dependent antigens.^{50,51} This probably also applies to human studies.⁴⁶ Some authors have indeed proposed, as a functional assay, the determination of the response of the immune system, in the form of antibody titers, following vaccination against an agent with which the subjects have never been in contact with, for example the hepatitis B vaccine.⁴⁹ However, as with any other immune response, antibody production following vaccination is subject to the same individual variability present in “non-responders”. Provided that these factors are corrected for, a study that shows an association between exposure to a given agent and diminished vaccination responses may indicate suboptimal function of the immune system and clinically relevant diminished resistance to pathogens. The assessment of vaccination responses, where possible, should therefore be included in Tier 2 assays. The choice of immune parameters in Tier 3 should take into accounts the results of Tier 2. Typically, Tier 3 should include research aimed at characterizing the molecular mechanism of action as well as epidemiological investigation to point out any correlation with clinical relevant outcomes.

In the interpretation of the results, it is necessary to take into account that single alterations in single immune functions are rarely biologically significant. However, changes in two or more parameters

assessed, when concordant, may indicate that the effects may be relevant; performance of next tier of tests should then be initiated. This means that deviations in a single parameter only should not be interpreted as indicating immunotoxicity.⁴⁵

Based on differences in study designs, different hypotheses can be assessed. For example, in the case of a prospective study, a change between baseline and post-exposure measurements in the exposed group may indicate a transient change, while such a difference between the exposed and controls may suggest the presence of a more persistent change. Of course, it is necessary to keep in mind that even the most well-conducted cross-sectional study can only highlight changes in selected immune parameters that, when concordant and significant, may generate hypotheses on the types and mechanisms of a possible immune disruption. The question which remains unanswered is whether these effects are adaptive only, and therefore "not adverse" at all, or, on the contrary, are early signs of disruption that could develop further, up to a clinical impairment. This critical question will receive an answer only from prospective controlled epidemiological studies, in which the incidence of selected diseases observed in populations with well-defined patterns of pesticide exposure is compared with appropriate reference groups. Such studies are very complicated due to the presence of multiple exposures, the ubiquitous presence of pesticides and their residues in the general and working environments, and the difficulties usually encountered in retrospective exposure characterization.

Furthermore, questions that have not yet received appropriate attention are whether especially sensitive populations exist and what are the roles of aging, gender, and ethnicity in immune diseases?

Conclusions

The assessment of immunotoxicity in human populations is a very difficult task and the assessment of the immunotoxicity of pesticides in agricultural settings, where co-exposures to several compounds is common, is even more demanding. However, there is some concern about a possible relationship between chemical exposure and the new patterns of diseases emerging in industrialized countries. Due to the paucity of data, particularly with respect to new pesticides, it is clear that there is a need to continue to improve immunotoxicology studies. A concerted effort is required to organize and standardize, where possible, the study protocols, starting with the proposed approaches and taking into

account the new knowledge on the molecular mechanisms of action discussed in this article.

One of the most difficult aspects of immunotoxicology studies is the drawing of conclusions on the prognostic significance of slight changes observed in human immunotoxicity studies. The only way to overcome this limitation is to validate the hypothesis generated by means of epidemiological studies. Due to the difficulties associated with the collection of sound exposure data in retrospective cohort studies, the most useful option could be longitudinal prospective studies with good quality exposure assessments to generate reliable exposure-response data that focus on individual pesticides. These studies are quite complicated and expensive, and provide results after a long period of study. But this is the only way to collect data and to compare, the two key elements of any toxicological study, which are the absorbed dose and the observed effects. Multi-disciplinary collaborations will allow more rapid progress. In the meanwhile, national surveillance systems should be implemented to identify populations at high risk and to promote exposure-control programs.

Acknowledgments

This study was financially supported by the European Union (Contract QLK4-CT-2001-00211, EUROPIT).

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