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Toxicol Ind Health 1999 15: 119
DOI: 10.1177/074823379901500110

Toxicology and Industrial Health **(1999) 15, 119–132**

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Immunotoxicity of pesticides: a review

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The intricate balance that is the hallmark of the immune system shows vulnerability to any chemical, including pesticides, that can cause structural and functional alterations to the system. The immunotoxic effects of xenobiotics include: histopathologic effects in immune tissues and organs; cellular pathology; altered maturation of immunocompetent cells; changes in B and T cell subpopulations; and functional alterations of immunocompetent cells. Pesticides, including fungicides, herbicides, and insecticides, are the only class of chemicals deliberately released into the environment because of their toxicity. Around the world, millions of people are exposed to pesticides at work and/or in their home. This article reviews evidence, from animal and human studies, on the effects of pesticides on the immune system.

Keywords: *cell-mediated immunity, fungicides, herbicides, humoral immunity, immune response, insecticides, toxicity.*

Introduction

Through evolution, vertebrates developed an effective defense mechanism, the immune system, to protect themselves against potential pathogens (viruses, bacteria, fungi, and parasites) and neoplastic cells. Immunocompetent cells, such as T and B lymphocytes, macrophages/monocytes, and neutrophils, that originate from the hematopoietic bone marrow and the thymus are ubiquitous as they constantly screen the blood, lymph, tissues, and organs for potential pathogens or neoplastic cells.

The intricate balance that is the hallmark of the immune system shows vulnerability to any chemical, including pesticides, that can cause structural and functional alterations to the system. The immunotoxic effects of xenobiotics include: histopathologic effects in immune tissues and organs (bone marrow, thymus, spleen, and lymph nodes); cellular pathology, including abnormal proliferation of stem cells; altered maturation of immunocompetent cells; changes in B and T cell subpopulations; and functional alterations of immunocompetent cells, which are classified as altered humoral-mediated immunity, cell-mediated immunity, or nonspecific responses. Xenobiotics can be immunosuppressive or immunopotentiating. Alterations of the normal immune response can result in increased susceptibility to viral, bacterial, or parasitic infections and to cancers (Krzystyniak et al., 1995).

In this article, pesticides, selected for their wide use around the world and their availability to a wide number of humans and wildlife, are examined for immunotoxicity. These pesticides can be grouped into three general classes: insecticides (specifically, the organochlorines, organophosphates, and carbamates), herbicides, and fungicides.

Immunotoxic effects of organochlorine insecticides

Chlorinated hydrocarbon insecticides are aryl, carbocyclic, or heterocyclic compounds with molecular weights ranging from 291 to 545. They are categorized into five groups:

1. DDT (1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane) and its analogs (DDE, ethylan, methoxychlor, chlorbenzilate, and dicofol);
2. BHC (benzene hexachloride) and lindane;
3. cyclodienes (β-chlordane, heptachlor, aldrin, dieldrin, isodrin, endrin, isobenzan, and α-endosulfan);
4. toxaphene; and
5. mirex and chlordecone.

1. Abbreviations: A, analytical grade; BHC, benzene hexachloride; CFU, colony-forming units; Con A, concanavalin A; CSF, colony-stimulating factor ; CTL, cytotoxic T lymphocytes; HCH, 1,2,3,4,5,6-hexachlorocyclohexane; IgG, immunoglobulins with γ type heavy chains; IgM, immunoglobulins with μ type heavy chains; IL, interleukin; i.p., intraperitoneally; LD_{50}, the dose that kills one-half of a population exposed to a potentially lethal factor within a specified time period; LPS, lipopolysaccharide; MHV-3, mouse hepatitis virus 3; MLR, mixed lymphocyte response; NHL, non-Hodgkin's lymphoma; NK, natural killer (cell); OOS-TMP, *O*,*O*,*S*,-trimethyl phosphorothioate; P, purified; PBMC, peripheral blood mononuclear cells; PCP, pentachlorophenol; PFC, plaque-forming cells; PHA, phytohemagglutinin; SRBC, sheep red blood cells; T, technical grade; w/w, weight ratio (weight per weight)

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The use of many organochlorine insecticides has been widely banned or discontinued because of their persistence in the environment and in human and wildlife tissues. However, the relatively low cost of organochlorine insecticides combined with the unavailability of substitutes for some applications ensure their continued use in many countries. All chlorinated hydrocarbon insecticides can be absorbed through the skin and the respiratory and gastrointestinal tracts.

DDT

DDT was used for agricultural pest and malarial control from the 1940s to the 1960s. The use of DDT was greatly diminished or was discontinued in many countries in the early 1970s because of its persistence in the environment and its harmful effects on wildlife (Banerjee et al., 1986). Nevertheless, DDT is still produced and used in some countries that depend on it for disease vector control.

Studies on DDT have focused mainly on the humoral immune response and few data exist on its effect on the cellular mediated immune response and host response. A summary of data collected for DDT is shown in Table 1.

When xenobiotics are bound to proteins they are believed to be less toxic due to their inability to cross biological membranes. However, from an immunological point of view, protein binding might increase the amount of toxicant available for specific actions. A study (Kaminski et al., 1986) conducted on DDT uptake by macrophages found that DDT bound to serum lipoproteins is more readily absorbed by the cells than free DDT, causing a significant inhibition of phagocytosis by macrophages treated with lipoprotein-sequestered DDT.

BHC (Benzene Hexachloride) and Lindane

BHC is the acronym for the common name benzene hexachloride, whereas HCH is the acronym for the proper chemical name, 1,2,3,4,5,6-hexachlorocyclohexane. Both BHC and HCH are recognized as common names. There are five isomers of BHC: α, β, γ, δ, and ε, and lindane is defined as not less than 99% pure γ-BHC (or γ-HCH). All isomers of BHC accumulate preferentially in fat, although over 30 times more β than γ is stored at equivalent dosage. This explains why the β isomer is more toxic than the γ isomer when administered repeatedly, while the γ isomer is more toxic when given in a single dose (Smith, 1991). The acute toxicity of the isomers of BHC decreases in the order $\gamma > \alpha > \delta > \beta$, whereas the toxicity of repeated doses decreases in the order $\beta > \alpha > \gamma > \delta$ (Smith, 1991).

Lindane, or the γ isomer, is the most studied BHC in toxicology. It has been canceled for use in numerous countries, but it is still used elsewhere for seed protection, treatment of poultry and livestock, and the control of household insects. Lindane can also be used in the form of creams, lotions, and shampoos as a scabicide and pediculicide for humans. This insecticide is rapidly bioaccumulated in animals, with a bioconcentration factor in aquatic organisms from 43 up to 4240, on a wet weight basis (Geyer et al., 1997). In fish, carp seem more resistant than rainbow trout to the immunotoxic effects of lindane (see Table 2).

Immunotoxicological studies indicate a general immunosuppressive effect of BHC as summarized in Table 2. In addition, cytotoxic studies on δ-BCH revealed that this pesticide interacts with cytoskeleton proteins, which can lead to cell lysis (Verma and Singhal, 1991).

Table 1. Summary of the effect of DDT on the immune system

Species	Exposure	Effect	Reference
Chicken	100 ppm for 40 days oral exposure	Decreased weights of thymus, bursa, spleen No effect on anti-SRBC titer	Exon et al., 1987
Chicken	625 ppm for 6–8 weeks oral exposure	No effect on anti-*Salmonella pullorum* titer	Exon et al., 1987
Chicken	100–400 ppm for 5 weeks oral exposure	No effect on anti-BSA titer	Exon et al., 1987
Rabbit	4–150 ppm for 5 weeks oral exposure	No effect on antibody production	Exon et al., 1987
Rabbit	200 ppm for 35 days oral exposure	Suppressed anti-*Salmonella typhi* and anti-ovalbumin IgM and IgG titers	Exon et al., 1987
Guinea pig	15 mg/kg i.p.	No effect on anti-diphtheria titer	Gabliks et al., 1973
Mouse	0.1 LD_{50} (30 mg/kg) by gavage before immunization	No effect on antibody production	Wiltrout, 1978
Rat	0.25 mg/kg for 31 days by gavage	No effect on phagocytosis by neutrophils	Kaliser, 1968
Rat	1, 5, 10 mg/kg i.p.	Decreased phagocytosis by peritoneal macrophages	Kaminski et al., 1982
Human	10 μM *in vitro* exposure of PMN	Decreased chemotaxis	Exon et al., 1987

Abbreviations: BSA, bovine serum albumin; IgG, immunoglobulins with γ type heavy chains; IgM, immunoglobulins with μ type heavy chains; i.p., intraperitoneally; PMN, polymorphonuclear leukocytes; SRBC, sheep red blood cells.

Table 2. Summary of the effect of BHC and lindane on the immune system

Species	Exposure	Effect	Reference
Rat	6.25 mg/kg or 25 mg/kg oral exposure to lindane	Reduced agglutinin titers to *Salmonella typhi*	Dewan et al., 1980
Swiss albino mouse	10 or 100 mg/kg gestational exposure to lindane (pups were tested for their immune response)	Increased anti-SRBC response (PFC) at 10 but no effect at 100 mg/kg Increased proliferation to Con A and LPS at 10 but no effect at 100 mg/kg Increased DTH to SRBC at 10 but depressed at 100 mg/kg	Das et al., 1990
B6C3F1 Mouse	100 or 300 mg/kg of diet oral exposure to β-BHC	No alteration in lymphoid organ weight Decreased proliferation of splenocytes Reduction of NK activity No effect in PFC assay	Cornacoff et al., 1988
Mouse	0.012, 0.12, or 1.2 mg/kg oral exposure to lindane	Biphasic response (stimulation followed by a suppression in a dose response manner) No effect on peritoneal macrophages	Meera et al., 1992
Rabbit	0.1 LD_{50} of lindane daily for 1 month	Decreased phagocytosis	Kopec-Szlezak et al., 1990
Rabbit	0.1, 0.05, or 0.025 LD_{50} of lindane 5 times/week for 6 weeks oral exposure	Decreased antibody titer against *Salmonella typhi*	Desi et al., 1978
Rainbow trout	10 or 50 mg/kg i.p. lindane	Proportion of B lymphocytes reduced 1 month following exposure	Dunier et al., 1995
Rainbow trout	10, 50, or 100 mg/kg i.p. lindane and *Yersinia ruckeri* injection 7 days later	Reduced anti-*Yersinia ruckeri* antibody titer	Dunier and Siwicki, 1994
Rainbow trout	1 mg/kg for 30 days oral exposure to lindane	Decreased chemiluminescent response for up to 1.5 months	Dunier et al., 1994
Rainbow trout	10, 50, or 100 mg/kg i.p. lindane	Reduced B but not T lymphocyte proliferation 45 days after injection	Dunier et al., 1994
Tilapia	20 or 40 mg/kg i.p. lindane	Reduction of total white blood cell counts No effect on phagocytosis or respiratory burst	Hart et al., 1997
Carp	10, 100, or 1000 ppm of lindane for 109 days oral exposure	No effect on anti-*Yersinia ruckeri* antibody production	Cossarini-Dunier et al., 1987

Abbreviations: BHC, benzene hexachloride; Con A, concanavalin A; DTH, delayed type hypersensitivity; i.p., intraperitoneally; LPS, lipopolysaccharide; NK, natural killer cell; PFC, plaque (antibody) forming cell; SRBC, sheep red blood cells.

Cyclodienes (Dieldrin, Chlordane, Heptachlor)

Many of the cyclodiene insecticides have been widely banned or voluntarily canceled and others have been severely restricted. Cyclodiene insecticides include dieldrin, which is used in tropical countries for the control of vectors of disease, mainly malaria, and for soil treatment; aldrin, which is used primarily against soil insects; heptachlor, which has largely been restricted to termite and/or fire ant control in certain situations; chlordane, which is still used in some countries to control insects in vegetable crops and in houses; endrin, which is used as an insecticide and also as a rodenticide to control voles and mice in orchards; and endosulfan, which is still widely used to control agricultural pests and tsetse flies. Dieldrin is found in food, water, air, and soil and has an estimated half-life of 2–8 years. Aldrin, the stereoisomer of dieldrin, is rapidly metabolized into dieldrin so that its toxicity is essentially that of dieldrin. Dieldrin accumulates in red blood cells, and, as aged or damaged erythrocytes are sequestered in the vascular bed of the spleen, dieldrin accumulates in this lymphoid organ, which plays an important role in the inductive phase of the immune response.

Studies on mice exposed i.p. to 0.6 LD_{50} (36 mg/kg) of dieldrin showed a reduction in the number of antibody-producing cells and in the production of antibodies against T cell-dependent (red blood cells) or T-cell-independent LPS antigens (Bernier et al., 1987; Fournier et al., 1988). This toxicity of dieldrin on the humoral-mediated immune response can be explained by the reduced capacity of antigen presenting cells (macrophages) to take and process an antigen, as demonstrated with avidin (Krzystyniak et al., 1989). In another study, some parameters of the T-cell-mediated immune response, such as the mixed lymphocyte response (MLR), proliferation of lymphocytes stimulated by mitogens, and the graft versus host responses, were significantly impaired in mice following a sublethal exposure to dieldrin (0.6 LD_{50}) (Hugo et al., 1988a,b).

The nonspecific immune response is also a target for dieldrin. In mice exposed to 0.6 LD_{50} through i.p. injection, the capacity of macrophages to phagocytose and destroy the bacteria *Salmonella typhimurium* was inhibited for up to 7 and 10 days (Jolicoeur et al., 1988). In other experiments (Krzystyniak et al., 1985, 1986), dieldrin (36 mg/kg) decreased the intrinsic activity of macrophages to restrict the replication of mouse hepatitis virus 3 (MHV-3) and increased the *in vitro* MHV-3 cytolysis of the host cells.

In mice, the direct addition of chlordane (0–10 μM) to cultured spleen cells significantly suppressed the MLR and the proliferative response to T- and B-cell mitogens (Johnson et al., 1987). Antibody response to sheep red blood cells (SRBC) was highly suppressed in the early stages of the response. However, an *in vivo* study on B6C3F1 mice, treated to 0.1, 1.0, 4.0, or 8.0 mg/kg by gavage for 14 days showed no difference in antibody response to SRBC compared to controls (Johnson et al., 1986). However, the proliferation of Con-A- or phytohemagglutinin (PHA)-stimulated splenocytes was significantly increased in a dose-related fashion. Peripheral blood mononuclear cells (PBMC) isolated from a healthy rhesus monkey were exposed to chlordane or heptachlor. At low concentrations (10–40 μM), the pesticides acted as weak mitogens and stimulated production of interleukin-2 (IL-2) from mitogen-stimulated cultures. However, at 80 μM, both pesticides completely suppressed the proliferation and release of IL-2 (Chuang et al., 1992).

A series of experiments were conducted on the effect of prenatal exposure to chlordane in mice. In BALB/c mice exposed prenatally to 8 mg/kg of chlordane, there was no significant change in cytotoxic T lymphocyte (CTL) response. However, natural killer (NK) cell response was increased in females at 100 but not at 200 days. In males, a decrease was observed at 200 days only (Blaylock et al., 1990). In another study, pregnant BALB/c mice were exposed to 4 or 16 mg/kg of chlordane (Blyler et al., 1994). There was a significantly depressed mixed lymphocyte reaction in male but not female offspring, and delayed-type hypersensitivity was depressed at 100 days of age but not at 30 days. To evaluate the effect of chlordane on myeloid cell development, BALB/c mice were exposed prenatally to 8 mg/kg of chlordane. Twenty-one days following birth, myeloid hemopoietic activity of bone marrow cells was evaluated in offspring for colony-forming units in response to an exogenous source of granulocyte/macrophage-colony stimulating factor (CSF), macrophage-CSF and IL-3. There was no difference in the number of viable bone marrow cells but a significant depression of the numbers of bone marrow colony forming units-granulocyte/macrophage (CFU-GM), CFU-IL-3, and CFU-macrophage in female offspring only. The results from these experiments indicate that prenatal exposure to chlordane affects some immune parameters of adult offspring according to age and sex. In BALB/c mice treated topically on the ear with 20 μg/ear of chlordane, reduced contact hypersensitivity to the allergen oxazolone (ear swelling test) was observed (Blaylock et al., 1995).

Many cyclodienes are tumor promoting. One possible mechanism for their tumor-promoting effect is chemical inhibition of communication through gap junction as tested *in vitro* (Trosko et al., 1987). Recently, a study on heptachlor revealed that the toxic effects of this pesticide can be related to its capacity to interact with the phospholipid bilayer structure of cell membranes, whose integrity is

essential for cell functions (Suwalsky et al., 1997). Although never tested on the immune system, it would be interesting to test these mechanisms in relation to the immune response.

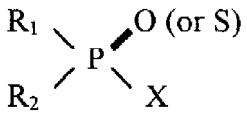
Toxaphene, Mirex, and Chlordecone

Toxaphene is a complex mixture of approximately 177 chemicals formed by the chlorination of technical camphene. It has been used extensively for cotton insects and for a wide range of pests affecting cattle, vegetables, and cereals. In mammals, it was shown (Allen et al., 1983) that mice exposed for 8 weeks to toxaphene (10, 100, or 200 ppm) had depressed IgG antibody production, but there was no effect on phagocytosis. However, offspring of mice fed toxaphene (10, 100, or 200 ppm) through gestation and nursing had a significantly reduced phagocytic ability. This immunosuppression was reversible, since 5 weeks after weaning offspring had a normal level of phagocytic activity.

Mirex and chlordecone are structurally similar to cyclodiene pesticides although they resemble DDT in their toxicity. In rainbow trout exposed for 12 months to mirex (0.5, 5, or 50 ppm), humoral immune response and nonspecific immune response, measured with the plaque-forming cell (PFC) and NK cell assays respectively, were not significantly impaired by the insecticide (Cleland and Sonstegard, 1987; Cleland et al., 1988).

Immunotoxic effects of organophosphate insecticides

Organic chlorine pesticides have been used with less frequency because of their persistence in the environment. Since organic phosphorous pesticides are biodegradable to less harmful products, are less persistent, and are more selective (i.e., they tend to target pests more specifically), they have replaced organochlorine pesticides to some extent. The general formula for anticholinesterase organophosphate compounds is:



All of these compounds can be placed into four main categories depending on the character of the X group:

Group I. X contains a quaternary nitrogen. They are called phosphorylcholines and are powerful inhibitors of cholinesterase as well as being directly cholinergic. As such, some of these compounds are among the most toxic synthetic compounds known. Only very few have been used as pesticides (dimefox and mipafox).

Group II. X contains fluorine. These compounds are known as fluorophosphates.

Group III. X contains some combination of cyanide (CN, OCN, SCN) or a halogen other than fluorine.

Group IV. In this category, the X group is attached by a P–O or P–S bond. The X group may be alkoxy, alkylthio, aryloxy, arylthio, or a heterocyclic analog. Most organic phosphorus pesticides belong to category IV, and their acute toxicity ranges from that of nerve gas to less than that of table salt.

Immunotoxicological studies have been done on the dimethoxy and diethoxy compounds of category IV. Dimethoxy compounds include trichlorfon, dichlorvos, malathion, and methyl parathion, and diethoxy compounds include parathion (or ethyl parathion) as well as many others.

Trichlorfon and Dichlorvos

Trichlorfon is used to control flies and roaches and as an anthelmintic. Vapors from trichlorfon consist of dichlorvos, a degradation product. At a pH higher than 5.5, trichlorfon is transformed to dichlorvos. Dichlorvos itself is used mainly to control pests in closed areas (greenhouses, warehouses, homes, restaurants). When impregnated in polyvinyl chloride resin collars, dichlorvos controls fleas in cats and dogs. A similar formulation prepared in granular form has been tested as an anthelmintic in humans and is used extensively in domestic animals. Trichlorfon and dichlorvos are also used in fish farming for controlling planktonic invertebrates and ectoparasite infections (Gallo and Lawryk, 1991).

Several studies on carp exposed to trichlorfon in baths containing up to 20,000 ppm (concentration used in Polish ponds) revealed a decrease in phagocytosis by neutrophils and a decrease in lysozyme activity (Siwicki et al., 1990), but antibody production against *Yersinia ruckeri* was not affected (Cossarini-Dunier et al., 1990; Cossarini-Dunier et al., 1991). *In vitro* studies on carp indicated that lymphocytes are more sensitive to trichlorfon than to dichlorvos. The proliferation of head kidney leucocytes was significantly inhibited at 12.5 ppm of trichlorfon and 24.5 ppm of dichlorvos (Cossarini-Dunier et al., 1991). The same authors observed the opposite sensitivity of phagocytes to trichlorfon and dichlorvos measured by chemiluminescence, with complete inhibition at 100 ppm and 24.5 ppm, respectively.

One study on human complement indicated that concentrations of dichlorvos ranging from 0.5 to 3.0 mM significantly inhibited the complement-mediated lysis of SRBC (Casale et al., 1989). Dichlorvos (5 to 500 μg/ml) was also shown to interfere with lymphocyte DNA repair processes following ultraviolet irradiation Perocco and Fini, 1980. Following an oral exposure to 1/40, 1/20, and 1/10 of the LD_{50} of dichlorvos, depressed serum antibody titers against *Salmonella typhi* as well as reduced cell-mediated immunity were observed (tuberculin test) (Desi et al., 1980).

In another study, the inhibition of IL-2 dependent proliferation of mouse CTLL2 cells by four organophosphates was shown (Casale et al., 1993). The order of potency for inhibition was dichlorvos > paraoxon > mevinphos > monocrotophos. The authors concluded that the potency to produce acute cholinergic toxicity did not predict the potency to inhibit T-cell proliferation.

Malathion

Malathion was shown to stimulate macrophage functions and the primary humoral-mediated immune response. Malathion given orally to mice (1 to 900 mg/kg) or *in vitro* to mouse or human leukocytes enhanced the respiratory burst and phagocytosis by phagocytes (Rodgers and Ellefson, 1990; Rodgers and Ellefson, 1992). The same researchers later suggested that the stimulation of macrophage functions was possible through degranulation of peritoneal mast cells and the subsequent exposure of macrophages to mast cell mediators (e.g., beta-hexosaminidase) (Rodgers et al., 1996).

Because technical grade malathion is contaminated with *O,O,S,*-trimethyl phosphorothioate (OOS-TMP), one must be cautious when studying the toxicity of malathion not to overlook the toxicity of OOS-TMP. In mice, OOS-TMP (1, 5, 10, 20, or 40 mg/kg) was able to block the generation of CTL and antibody responses, but these effects were reversible (Rodgers et al., 1986). Also, macrophages from OOS-TMP treated animals were less effective in presenting an antigen (Rodgers et al., 1985a), and they tended to exhibit properties similar to those present at inflammatory sites: increased phagocytic functions, IL-1 production, and esterase activity (Rodgers et al., 1985b,c). These studies also showed that OOS-TMP induced the release of an unstable factor by macrophages that inhibit the response of lymphocytes to mitogenic or antigenic stimuli (Rodgers et al., 1985c). Later on, it was demonstrated that OOS-TMP given to mice for 14 days at low concentrations (2 mg/kg) enhanced the generation of IL-2 as well as the generation of CTL, whereas 5 mg/kg suppressed the CTL responses and the production of antibody (Rodgers et al., 1988; Rodgers et al., 1989). When acute doses were administered at concentrations equivalent to a 14-day treatment at 2 mg/kg (20 or 40 mg/kg), immune response was stimulated. However, at 60 and 80 mg/kg, concentrations equivalent to a 14-day treatment at 5 mg/kg, CTL response and antibody production were inhibited.

Methyl Parathion and Parathion

Exposure of the general population to methyl parathion occurs predominantly via food, since it is used to control insects in many field and vegetable crops. It is not persistent in the environment nor is it bioconcentrated and transferred through the food chain. Parathion (ethyl parathion) has been canceled for use on most crops and is not as widely used as methyl parathion.

In vitro studies on human peripheral blood indicate that methyl parathion significantly inhibits the chemotaxis of human neutrophils at levels of 10 μM (Lee et al., 1979). However, no effect was observed on NK and cytotoxic T-cell activity at concentrations ranging from 0.1 to 10 μM of ethyl and methyl parathion (Flaherty et al., 1991). In animal studies, mice given parathion (16 mg/kg), at a concentration causing cholinergic poisoning, had lower numbers of IgM plaque-forming cells (Casale et al., 1984). The authors believe that the cholinergic stimulation may be involved in parathion-induced immunosuppression.

A recent study (Crittenden et al., 1998) evaluated the effect of methyl parathion administered by gavage (1, 3, or 6 mg/kg for 28 days and 6 mg/kg for 7, 14, 21, or 28 days) in mice. The results indicate that at the doses tested, methyl parathion did not significantly alter the CTL response to allogeneic tumor cells nor did it affect the production of antibodies against SRBC. However, the NK cell activity and the nitrite production by macrophages were increased in mice exposed to 1 and 3 mg/kg and to 1, 3, and 6 mg/kg, respectively. The authors also evaluated host resistance and found that exposure to methyl parathion did not significantly decrease host resistance to B16F10 melanoma cells or to *Streptococcus agalactiae*. They concluded that although methyl parathion affects some immune parameters, the immune response seems not to be significantly compromised by subneurotoxic dosages of the pesticide.

Immunotoxic effects of carbamate insecticides

The immunomodulatory functions of carbamates are probably related to the $OC(O)NHCH_3$ group, which is responsible for the acetylcholinesterase effect of carbamates (Luster et al., 1982).

Aminocarb

Aminocarb is used widely in the control of mixed coniferous pests, and studies done on this pesticide revealed route-dependent modulations of the immune response. When aminocarb was administered by oral or dermal routes (0.16 mg/kg) there was a stimulation of the humoral-mediated immune system as evaluated by the production of PFC in response to SRBC (Bernier et al., 1995). Oral exposure to aminocarb (0.08 and 0.31 mg/kg) was also shown to activate B-cell maturation in the bone marrow as evaluated by flow cytometry (Bernier et al., 1990). However, when mice were exposed to aminocarb by i.p. injection (0.16 mg/kg), a suppression of humoral-mediated immunity was obtained (Bernier et al., 1995). The cellular immune response, as evaluated by the mixed lymphocyte reaction, seems to be unaffected by aminocarb regardless of the route of exposure (Bernier et al., 1995). The most relevant endpoint regarding immune responses to xenobiotics is host resistance to pathogens, and aminocarb, given orally by gavage, did not significantly suppress the ability of mice to resist viral (MHV-3) or bacterial (*Salmonella typhimurium*) challenges (1/3 LD_{50}) (Bernier et al., 1988).

Aldicarb

Studies on aldicarb reveal that although it is the most acutely toxic carbamate, it has little effect on the immune response at environmentally relevant concentrations. Mice exposed to aldicarb in water (0.1 to 10 ppb) were not significantly affected in their cellular-mediated immune-system response as evaluated by the MLR (Hajoui et al., 1992) and by the ability of CTL and NK cells to lyse tumor cells (Thomas et al., 1990). As for the humoral-mediated immunity, studies indicate an inhibition in the number of PFC (Olson et al., 1987; Shirazi et al., 1990; Hajoui et al., 1992) or no effect at all (Thomas et al., 1987) following low-level exposures to aldicarb.

However, when administered i.p., aldicarb inhibits T-cell activation to mitogen (Dean et al., 1990a) and the MLR (Dean et al., 1990b). The authors demonstrated that the alteration of macrophage accessory cell function was defective IL-1 production, which was the major cause of T-cell malfunction. In mice injected with aldicarb (0.01, 0.1, 1, or 10 ppb), it was shown that macrophage but not NK-cell-mediated cytotoxicity against LSA tumor cells was impaired (Selvan et al., 1989). The authors observed a stronger suppression following multiple doses than following a single acute dose treatment.

The order of potency of four carbamates to inhibit IL-2 driven T-cell proliferation (0.5, 5.0, or 50 μM) was established as follows: carbaryl > methiocarb > carbofuran > aldicarb (Casale et al., 1993).

Immunotoxic effects of herbicides

Because plants differ markedly from animals, it might be expected that herbicides present little hazard to vertebrates. This belief is strengthened by the high LD_{50} of herbicides, which are generally presented as compounds with low toxicity to mammals. However, chronic exposure to some herbicides has been associated with a number of human health problems, including various cancers (Vineis et al., 1987; Donna et al., 1989; Zahm et al., 1990) and developmental abnormalities (Garry et al., 1996; Munger et al., 1997).

Of the many classes of herbicides, some of the most prevalent are the chlorophenoxy compounds (2,4-D), the bipyridil compounds (paraquat and diquat), the triazines (atrazine and simazine), and the amides (propanil). Although data on their effects on the immune system are scarce, the few studies that exist focus mainly on paraquat and propanil.

Paraquat

Paraquat is a broad-spectrum herbicide known to cause lung injury. Rats injected i.p. with the herbicide (20 mg/kg) experienced a decrease in the percentage of neutrophils in the blood caused by infiltration to the lungs (Suntres and Shek, 1995). Also, in human PBMC treated with 100 μM of paraquat, the synthesis of IL-8 mRNA but not of the protein itself was observed (Bianchi et al., 1993). IL-8 is a neutrophil chemotactic cytokine.

Most studies conducted on the mechanisms of cytotoxicity have been done on hepatocytes. Results of these studies indicate that paraquat, dinoseb, and 2,4-D affect the bioenergetic function of mitochondria (Palmeira et al., 1994). They also reduce the protein thiol level as well as induce lipid peroxidation (Palmeira et al., 1995a). However, no effect on the level of intracellular calcium was observed (Palmeira et al., 1995b). Although these studies have not been conducted on immune cells, one might expect the same effects.

Propanil

Propanil was shown to reduce the number of myeloid stem cells and early myeloid and erythroid progenitor cells in mice acutely exposed to doses between 50 and 200 mg/kg (Blyler et al., 1994). The effect of propanil on the thymus was studied on mice exposed to doses of 100, 150, and 200 mg/kg (Zhao et al., 1995; Cuff et al., 1996), and the results obtained indicate that this herbicide induces thymic atrophy with a significant decrease in the population of immature lymphocytes ($CD3^+ CD4^+ CD8^+$, $CD3^- CD4^+ CD8^+$). However, in adrenalectomized mice no atrophy was observed, suggesting that the immunotoxic

effect of propanil is mediated, in part, by endogenous glucocorticoids.

Immunotoxic effects of fungicides

Fungicides can be classified as dicarboximides (e.g., captan, folpet), substituted aromatics (e.g.,pentachlorophenol (PCP), pentachloronitrobenzene), dithiocarbamates (e.g., mancozeb, thiram), and nitrogen heterocyclic fungicides such as the benzimidazoles (e.g., benomyl, thiabendazole).

Apart from PCP, very few studies have been done on the immunotoxicology of fungicides. In a study on captan (*N*-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide), mice were fed 0.3% w/w of the fungicide for 7, 14, 21, and 42 days. Antibody production against SRBC, as well as the proliferation of splenocytes stimulated with LPS, were significantly inhibited after 14 days but returned to control levels after 42 days (Lafarge-Frayssinet and Decloitre, 1982).

Kerkvliet et al. (Kerkvliet et al., 1985) isolated a dioxin/furan fraction, a chlorinated phenoxyphenol fraction, and a chlorinated diphenyl ether fraction from a solution of technical grade PCP (PCP-T). Mice were then exposed either to fractions or to analytical grade PCP (PCP-A) or PCP-T and immunized with SRBC. The IgM antibody response was then evaluated. Only the dioxin/furan fraction and PCP-T were immunosuppressive, but when the dioxin/furan fraction was added to PCP-A, mice had a reduced humoral response equivalent in intensity to that of PCP-T. Furthermore, the authors provided evidence that the immunosuppression was associated with the induction of cytochrome P450. In another study by the same group (Kerkvliet et al., 1985), they found that the cellular response (NK activity, macrophage activity, MLR) was less sensitive than the humoral response to PCP-T.

Holsapple et al. (1987) treated mice with PCP (10, 30, or 100 mg/kg) or with purified PCP-T (PCP-P; 100 mg/kg). In one case, animals were immunized *in vivo* with SRBC and in another case, cells from treated animals were immunized *in vitro* with SRBC. The results indicated that mice treated with PCP-T had a lower *in vivo* humoral response than mice treated with PCP-P. However, when the antigen was given *in vitro*, the humoral response of mice was similar to the controls regardless of the treatment (PCP-T or PCP-P). According to the authors, the suppression of the response to the antigen given to the whole animal cannot be attributed to a direct effect on immunocompetent cells, because when the antigen is given to splenocytes there is no suppression of the response even if the animal was treated with PCP.

In an *in vitro* experiment (Lang and Mueller-Ruchholtz, 1991), human peripheral blood leucocytes were exposed to PCP-T or PCP-A (10, 20, 30, 40, 80, 160, or 200 μM). The mitogen-induced proliferation of lymphocytes was inhibited by PCP-T and not by PCP-A, whereas the production of IL-2 and the secretion of immunoglobulin were inhibited by both preparations of PCP. The authors concluded that PCP itself is directly immunotoxic to human immune cells and that the T-helper cell subset appears especially sensitive to PCP. In lactating Holstein–Friesian cattle given 0.2 mg kg^{-1} day^{-1} of technical PCP for 135 days, no difference was seen in lymphocyte subpopulations, phagocytosis and respiratory burst by neutrophils, and antibody response against SRBC (Forsell et al., 1981).

The fungicide Vapam (metam-sodium or sodium methyldithiocarbamate) stimulates the production of PFC in response to SRBC in mice following oral exposure (300 mg/kg) (Pruett et al., 1992). However, the authors also observed an inhibition of NK cell activities in mice exposed by oral (200 mg kg^{-1} day^{-1}) or dermal (200 and 300 mg kg^{-1} day^{-1}) routes.

Immunotoxicology of human exposure to pesticides

It is clear from animal studies that some pesticides can alter the immune system either morphologically or functionally. However, in several instances the concentrations or doses tested did not reflect relevant exposure concentrations for humans, making the correlation between immunotoxic effects in experimental animals and man difficult. Furthermore, experimental animals were fed perfectly balanced diets and lived in stress-free environments, while humans exposed to the same chemical might be malnourished and under stress. Nevertheless, acute, subacute/subchronic, or chronic exposure to concentrations or doses higher than those encountered in the environment are necessary to help build the complete toxicological profile of a xenobiotic for safety assessment. In the case of occupational exposure, concentrations of pesticides to which humans are exposed can reach high levels, especially in manufacturing plants and enclosed agricultural areas.

A study of 35 men working in a DDT factory for 11 to 19 years found no greater incidence of illness or cancer (Laws et al., 1967). Concentrations of DDT in fat were measured at 37–647 ppm compared to 8 ppm for the general public. Daily intake was estimated between 17.5 to 18 mg $person^{-1}$ day^{-1} (0.028 mg $person^{-1}$ day^{-1} for the general public). However, in a study conducted among 5000 workers manufacturing DDT and related compounds, an in-

creased mortality due to pancreatic cancer was observed. Cancer risk was 7.4 times greater among subjects who handled DDT in the factory for a mean of 47 months than among those with no exposure (Garabrant et al., 1992).

Also, in a study conducted on workers exposed to organochlorines (between 12–30 years), an increased recurrence of upper respiratory tract infections (tonsillitis, pharyngitis, and bronchitis) compared to controls was revealed (Hermanowicz et al., 1982). Furthermore, some neutrophil functions (phagocytosis, respiratory burst, adhesion) were found to be markedly depressed in 33 workers (average exposure time of 10.9 years). This study is of particular interest since it shows that suppression of immune parameters coincides with increased susceptibility to infections.

In men working in a plant manufacturing HCH in India, higher HCH concentrations, as well as an increase in IgM, was found in workers handling the pesticides than in nonhandlers (Kashyap, 1986). A study done on females working in greenhouses with high pesticide concentrations found some morphological changes in the blood, but the investigators could not detect any alterations of the immune system (Kundiev et al., 1986). Neutrophil chemotaxis and adhesion were inhibited in workers manufacturing organophosphate pesticides, while the prevalence of upper respiratory tract infections was significantly increased (Hermanowicz and Kossman, 1984).

Probably the most insidious type of contamination is from environmental exposure, because the public is often unaware of exposure or toxicity. In people exposed to chlordane (termite control) in their home abnormalities were observed in T- and B-cell subsets. Decreased proliferation response to mitogen and allogeneic human lymphocytes and suppressed antibody dependent cell cytotoxicity were also seen, but there were no effects on NK cell activity (McConnachie and Zahalsty, 1992). Women exposed to aldicarb (potato farming) through drinking groundwater had a decrease in CD8 cell subset and elevated stimulation assay response (Fiore et al., 1986). In another study, twelve individuals exposed to chlorpyrifos were followed 1 to 4.5 years after exposure, and a higher rate of antibiotic sensitivity, CD26 cells, and autoimmunity were observed in exposed subjects (Thrasher et al., 1993).

Three studies on PCP-exposed people were done between 1980 and 1993. In 1980, an increased incidence of chronic respiratory infections and cutaneous inflammatory disorders were observed in workers exposed to PCP as well as increased levels of serum IgM and circulating immature leukocytes (Klemmer et al., 1980). A study done on 38 residents exposed to PCP (1–13 years) in their log home showed that the proliferative responses of blood to mitogens (PHA, Con A, pokeweed mitogen) or antigen (MLR) were significantly depressed, whereas NK cell activity was increased in PCP-exposed women only (McConnachie and Zahalsky, 1991). More recently, a study (Colosio et al., 1993) looked at a high exposure group of 14 workers with a mean PCP plasma concentration of 207.7 $\mu g/l$ compared to 8.9 $\mu g/l$ in a control group (workers from a marble industry in the same area). The investigators found a small albeit significant decrease in the proliferative response of blood lymphocyte to PHA. This response was associated with a significant correlation between the degree of proliferation and PCP-plasma levels.

In immunotoxicology, the most relevant endpoint is host resistance to infections and cancers. In animal studies there are indications that exposure to organochlorine, organophosphate, or carbamate pesticides significantly lowers host resistance to bacteria, fungi, viruses, and tumors (Repetto and Baliga, 1996). For obvious reasons, assessing human resistance to pathogens and cancers following pesticide exposure is impossible.

In the case of non-Hodgkin's lymphoma (NHL), there is a debate whether pesticides may play an important role in its etiology, since in rural areas there is nearly a 60% increase in the incidence of NHL (Cantor et al., 1992). However, there is no evidence to suggest differences in global cancer mortality among pesticide-exposed workers and the general population. Nonetheless, from the review by Zahm and Blair (Zahm and Blair, 1992) on epidemiological studies on NHL, there seems to be a significant increase in risk of NHL (odds ratio from 2 to 8) when one considers patients exposed to phenoxy-acid-derived herbicides only (more specifically, 2,4-D). However, no data can correlate such results with significant and prolonged immune suppression or to direct carcinogenic effects of these substances or their metabolites. It becomes apparent from the data collected so far, that there are immune alterations from occupational and environmental exposures to pesticides.

Immune compensation associated with chemically-induced immune dysfunction

Data accumulated from animal studies and human case studies indicate that some pesticides are immunomodulatory and that they may be a risk for public health. However there are a number of questions that arise, including: 1) Is partial immunosuppression a genuine health concern? 2) Does the immune system have a large reserve capacity to handle such perturbations? 3) Can the immune system compensate for the loss of specific functional components?

The immune system contains three components: humoral immunity, cell-mediated immunity, and nonspecific immunity. These components are usually described as isolated functional units, but they are, in fact, parallel systems that interact and regulate the responses of each other. Alterations of a specific immune function may result in corresponding modulation of other immune functions. Using these feedback mechanisms, the immune system has the capacity to respond rapidly to restore an imbalance. This corrective response may minimize the impact of an immunosuppressed state or it may enhance an undesired response. To fully assess the impact of chemically-induced immunomodulation, it is necessary to evaluate several functional endpoints reflecting a variety of immune responses.

To provide a more realistic assessment of immune dysfunction, it has been recommended that a battery of tests be utilized (Luster et al., 1988). A proper selection of tests within the battery should enable the investigator to enhance the sensitivity and predictability of the evaluation, which will allow for improved risk assessment (Luster et al., 1992; Luster et al., 1993). Using the multitest approach, it is possible to assess overall immunocompetence rather than immunosuppression of simply one or a few defense mechanisms. An imbalance may be more significant from a health perspective than suppression of a single response.

Consequences of Immune Alteration

When there is an alteration in the immune system, the host may attempt to restore normal immune function or to eliminate the immune alteration or imbalance by using compensatory mechanisms. This compensatory activity may create further imbalance, resulting in a loss of self tolerance, a loss of normal immune regulation, or an increased susceptibility to immune-mediated diseases. Possible consequences of primary or secondary immune imbalance subsequent to exposure to immunotoxicants related to infectious disease may include increased susceptibility to infection, increased carrier states, prolonged recovery periods, impaired immunosurveillance mechanisms, and reduced responses to vaccinations or antibiotic therapy. Consequences related to loss of self-tolerance or normal regulatory or compensatory mechanisms, may include hypersensitivity or autoimmunity (Dean et al., 1994; Zelikoff et al., 1994). Possible consequences may be more extensive if the interactions and feedback mechanisms associated with the endocrine and central nervous systems are considered (Husband, 1993; Zelikoff et al., 1994).

Immune Alteration and Compensation

The immune system is a complex network of organs, tissues, cells, and cell products, which act in an ordered manner to generate and sustain proper immunological function and homeostasis. Disruption of this homeostasis may occur upon exposure to immunotoxicants causing altered physiological or biochemical function or causing secondary compensatory responses that attempt to restore the ordered processes. These compensatory responses may occur at several different levels. Table 3 provides examples of immune alterations or compensatory mechanisms that may eventually lead to immune-mediated disease.

Many of the alterations or compensatory responses are interrelated. The loss of a cell population or impaired cell function may also reduce cytokine production. Cytokines function as specific chemical mediators that ultimately regulate growth and differentiation of cells. Cell functions and cell–cell interactions that require specific membrane integrity or receptor recognition may also be controlled by cytokines (Kimber, 1994). The immune alteration as perceived by the host may involve a loss of cells or impaired function.

Ultimately these deficits induce further adaptive or compensatory responses by the host, which, in most instances, will reduce the impact of the deficit on physiological systems. Generally, there is a balance among cell-mediated immunity, humoral immunity, and nonspecific immunity. For example, if cell-mediated immunity is suppressed by an immunotoxicant, the host may augment humoral or nonspecific immune responses to compensate for the suppression. This augmentation may involve increased cell production (cellular proliferation) or altered cytokine production by appropriate cell types. This immuno-enhancement would appear to be beneficial to the host, but the enhanced responses may induce additional immunological responses that prevent desirable responses, potentially triggering autoimmune or hypersensitive predisposition. Initially, toxic damage to the immune system disrupts the balance associated with normal immune function. Follow-

Table 3. Immune alterations or compensatory mechanisms induced by exposure to immunotoxicants that may result in immune-mediated disease

1. Loss of a cell population
2. Induction of a cell population
3. Impaired cell function
4. Impaired cell differentiation
5. Altered cell metabolism
6. Membrane damage
7. Loss of membrane receptors
8. Altered cell surface antigen expression
9. Release of sequestered (hidden) antigens
10. Altered cytokine production
11. Impaired protein synthesis
12. Altered cell oxidation–reduction potential
13. Hapten formation

ing adjustment or compensation by the host, the new balance that is created may result in toxic damage to the host by the immune system.

It is possible to speculate on the development of many different compensatory responses. These responses may occur at the cellular, membrane, and biochemical level, or at a combination of levels. In the vast majority of instances, compensatory responses will result in no adverse effects, which is the intended purpose of such responses. However, adverse effects may occur if the cell type(s) involved in the compensatory response are critical for long-term immunological homeostasis or health. Alterations specifically involving cells with regulatory function (T-suppressor lymphocytes, macrophages) or regulatory cell products (cytokines) have considerable potential to develop immune-mediated disease. The disease may develop directly from exposure to the immunotoxicant or from the subsequent abnormal balance created by the compensatory responses.

Compensation Associated with Immunotoxicants

In most immunotoxicological studies, normal endpoints for evaluation have included humoral immunity, lymphocyte blastogenesis, macrophage function, and phenotypic expression of cell surface antigens. These endpoints may not be sufficient to identify compensatory responses in all instances. In one study (Blankley and Tomar, 1986), cadmium suppressed T-lymphocyte dependent humoral immunity in mice while corresponding T-lymphocyte independent humoral immunity was enhanced. It was suggested that the enhanced T-lymphocyte-independent antibody responses were compensating for the T-lymphocyte-dependent immunosuppression. The nature of the compensatory mechanism was not investigated further.

Compensatory responses, in many instances, may not be straightforward. A suppression of one response such as antibody production may not always lead to an increase in lymphocyte blastogenesis or macrophage function. The presence of both enhanced and suppressed immune responses following exposure to pesticides suggests that the immune alterations are not a generalized cytotoxic effect and specific immunomodulation involving immuno-compensation may be present, although the extent, exact nature, and environmental significance of the compensating action are unknown.

Conclusions

Data accumulated from laboratory animal and human case studies indicate that many pesticides are immunomodulatory and that they may be a risk for public health. Although nontarget aquatic and terrestrial wildlife are affected by pesticide use, few studies have looked at the immunotoxicity of pesticides on these organisms. Even though further research is needed to understand the mechanisms of pesticide immunotoxicity, the data collected so far have helped increase the awareness of the public and governments on the risks associated with pesticide use.

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