PESTICIDES AND THE IMMUNE SYSTEM: The Public Health Risks

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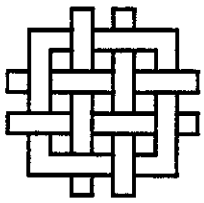

WORLD RESOURCES INSTITUTE

March 1996

Resource ID#: 4166

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III. Pesticide Exposure

Introduction

The public health risks of pesticide-induced immunosuppression depend not only on how toxic various compounds are, but also on how many people are exposed, what their risk-related demographic, socioeconomic and health profile is, what kinds of pesticides they are exposed to, and the extent and routes of exposure. Pesticide use patterns indicate that three large groups are potentially exposed: 1) farmers and farmworkers occupationally exposed to pesticides; 2) other members of farm households, especially in areas of intensive pesticide use; and 3) populations exposed to persistent pesticides that bioaccumulate in food.

Unfortunately, assessing exposure is difficult. No one is systematically measuring exposures, even among small farmers and farmworkers, the largest group at risk. Measuring the pesticide dose would be difficult anyway, since recommended monitoring techniques are expensive and the dose can vary widely depending on the crop, equipment, wind conditions, and the precautions taken.

However, descriptive studies discussed below show that farmworkers and other workers are actually liberally dosed when they use pesticides. Clinical reports of pesticide intoxication demonstrate that moderate and heavy exposure is commonplace. Pesticide residues on foodstuffs and in water demonstrate potential non-occupational exposure. Pesticide residues in blood serum, breast milk, or urine confirm occupational and non-occupational exposure, even though certain pesticides break down quickly in blood, and the liver and kidney break down and expel pesticides in urine. Cholinesterase depression provides another important biomarker of exposure to organophosphate pesticides, although depression is transient and normal values vary across individuals (He, 1993; Brewster, 1992; Krieger, 1992). The evidence in this chapter taken as a whole confirms that hundreds of millions of people are exposed significantly to pesticides each year.

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Occupational Exposure

Almost half of the world's 6.5 billion people live in rural areas, mostly in farm households. Of the roughly 2 billion workers in the world in 1990, 1.1 billion—over half—are farmers, the largest occupationally exposed group. Of these, 95 percent live and work in developing countries (WRI, 1994; FAO, 1986). Most exposed workers are agricultural laborers and small farmers in areas of plantation or intensive agriculture.

Although lapses in safety precautions also occur in developed countries, in the developing world inadequate safety and hygiene practices are the norm in applying, formulating, storing, transporting and manufacturing pesticides. There, most farmworkers are not trained in safe pesticide use, and the few regulations that address farmworker safety are unrealistic or unenforced.

A recent comparative study of pesticide use and exposure patterns in Brazil, Costa Rica, Ecuador, Paraguay, Venezuela, Egypt, South Africa, India, and Malaysia concluded that "in Third World countries, pesticides cannot be used with safety. Health and safety issues are exacerbated by a general lack of hazard awareness; the lack of protective clothing, or difficulty of wearing protective clothing in tropical climates; shortage of facilities for washing after use, or in case of accidents; the value of containers for re-use in storing food and drink; illiteracy; labelling difficulties relating either to language, complexity or misleading information; lack of regulatory authorities; and lack of enforcement" (Dinham, 1993, 38).

Pesticide warning labels do not ensure safe use. Often, they are printed incorrectly or in the wrong language and many users are illiterate. A survey by the Thai Division of Toxic Substances found that 44 percent of randomly selected pesticide formulations had the active ingredients incorrectly labelled (Tayaputch, 1988). Three fifths of Kenyan farmers, many of whom are literate, could not understand the instructions written on pesticide containers (Mwanthi, 1993a). Mexican farmworkers in the state of Chiapas poisoned by paraquat "did not know the proper dilution for paraquat use; they learned to use paraquat from friends, rather than from qualified authorities" (Tinoco, 1993, 80).

Even when instructions are readable, workers are exposed—usually through the skin—when using improper equipment to mix or spray pesticides. Organophosphates and carbamates are particularly capable of absorption through the skin, even if cotton clothing is worn (Grissom, 1992). Kitchen spoons, matchboxes, tin cans, and bottles are often used to mix active ingredients, which allows highly concentrated chemicals to touch bare skin (Chester, 1993; Castaneda, 1988).

Observations of Malaysian plantation workers identified several exposure routes. Knapsack sprayers, often using leaking and outdated hand sprayers, averaged 27.84 ml of dermal exposure per hour of application and spraying machine operators averaged 31.78 ml. Mixers' hands were also highly exposed, since many wore no protective gloves. When sprayers were refilled while still attached to their operators, pesticides spilled onto workers' backs. It was common for "operators to walk through the spray mists before the droplets settled on the target and also to walk into the sprayed areas, particularly where foliage was thick" (Tan, 1988, 411).

In tropical climates, sprayers rarely wear uncomfortable and costly protective clothing. Only 3 percent of a sample of Filipino rice farmers wore full protective clothing (long pants, long sleeves, mask and gloves) when spraying. One in five sprayed into the wind (Rola, 1993). In the northern Philippines, farmers spraying pesticides wore masks in only one quarter of spraying operations and never wore gloves or boots (Alba, 1988). In Sri Lanka, one in three pesticide users had head and arms unprotected while spraying, only one in ten wore face masks, and nine out of ten reported getting pesticides on their skin while spraying (on average 6 times per year) (Utsch, 1991). A survey in the West Indies indicated that 65 percent of respondents never used protective clothing when using pesticides (McDougall, 1993).

Agricultural fieldworkers rarely observe the re-entry period, the time required between spraying and other fieldwork. In one study, cultivators were exposed, on average, to 14 mg of parathion per day after disregarding the re-entry period and prematurely entering fields (Wolfe, 1975). In the Philippines, re-entry periods are not posted and farmers usually return to the fields the same day after spraying. "Thus, weeders as well as children and other household members in or near newly sprayed fields are also directly exposed to

pesticides" (Rola, 1993, 38). Especially in countries where pesticides are applied by aerial spraying, fieldworkers and households living near fields can be significantly exposed by winddrift (Richter, 1992). Fumigation workers are especially likely to inhale pesticides.

Organophosphate (OP) and carbamate pesticides work by inhibiting the activity of cholinesterase, an enzyme essential for normal neuromuscular functioning. As exposure levels increase, cholinesterase activity decreases. Plasma or red blood cell cholinesterase levels is a widely used biomarker of exposure to OPs. Despite inter-individual variability in baseline cholinesterase activity and inter-laboratory measurement variability, any substantial decrease in cholinesterase activity relative to a baseline period or to a control population indicates exposure (St. Omer, 1992).

Many studies demonstrate decreased cholinesterase activity among farmworkers in Latin America, where organophosphate insecticides and herbicides dominate. According to a WHO report, 10 to 30 percent of sampled farmworkers showed significant cholinesterase inhibition (WHO, 1990). Greenhouse and outdoor fumigation workers in Mexico showed significant cholinesterase depression (by 10 percent or more) after a one-day exposure to high levels of an organophosphate. Younger workers who were more likely to have engaged in more intense use of the pesticide suffered greater declines (Lopez-Carillo, 1993). In Nicaragua, a study using a 50 percent reduction relative to the mean of a control sample as a benchmark found that 19 percent of a sample of workers were occupationally exposed. The percentages ranged widely, from 37 percent of those who worked around the sprayplanes to 24 percent of fieldworkers and 8 percent of other agricultural workers in the sample. Fieldworkers, applicators, mixers, and loaders had the highest poisoning rates, and cotton was the crop associated with the most poisonings. By identifying 396 poisonings in a sample group that had reported only 7, this study also demonstrated the extreme underreporting of pesticide poisoning to health authorities (Cole, 1988). Other data from Nicaragua have also demonstrated lower cholinesterase levels in populations living next to regularly sprayed cotton fields (Rivas, 1991). In Indonesia as well, a study conducted by the Directorate of Hygiene and Sanitation showed that of 448 Balinese farmers examined more than 35 percent had cholinesterase depression of 25 percent or greater (Sim, 1985).

Pesticides that are acutely neurotoxic, such as some organophosphates, are still widely used in developing countries. Poisoning incidents provide a crude indicator of significant exposure but reflect only the upper tail of the exposure distribution, indicating a much larger number of sub-acute exposures. Even so, poisonings are grossly underreported (AID, 1990; Jeyaratnam, 1990). Poisoning surveillance systems are usually maintained only at large urban hospitals. Village health centers may be completely excluded from monitoring reports. Most less severe poisoning cases never reach the hospital and many of those that do are misdiagnosed as stroke or respiratory and cardiovascular disease (Loevinsohn, 1987).

Self-reported rates of pesticide intoxication from surveys in Latin America run from 13 percent of agricultural workers per year (among cotton farmers in Mexico) to 12 percent lifetime incidence (among diversified farmers in Brazil) (McConnell, 1993a). These rates are consistent with the lifetime self-reported rates in Indonesia, Malaysia, Sri Lanka, and Thailand which ranged from 11.9 to 19.4 percent (Jeyaratnam, 1987). However, directly observed poisoning rates are much higher than self-reported rates because farmers typically discount or ignore the symptoms.

A prospective study of pesticide exposure among farmers in Central Java observed that in 21 percent of the spray operations the sample of farmers averaged three or more neurological, intestinal, or respiratory symptoms of poisoning. If taken as a functional definition of poisoning, this attack rate is much higher than previously documented or recognized by the farmers themselves. Only 9 percent of farmers in the sample self-reported pesticide poisoning incidents over the year (Kishi, 1995).

Farmworker Families

In many developing countries, families share the farmwork. Men, women and children typically have different agricultural work roles. On southeast Asian rice farms, men prepare the paddies and irrigate while women and children transplant, weed, harvest, and tend domestic animals. Aerial drift can expose young children being tended by older siblings on field boundaries or herding animals near the fields. Women and children who help prepare or apply pesticides may also be exposed. For example, in the Benguet district of the Philippines, nearly one-third of all children and one half of all wives of farmworkers help apply pesticides (Rola, 1989).

Storing pesticides improperly in the home also creates risks for farm families. In Central Java, more than four-fifths of farmers stored pesticides in their homes within easy reach of children; three-fourths stored these chemicals within the living quarters (including the kitchen). Fewer than one in four pesticide containers were kept sealed and half were leaking (Kishi, 1995). Surveys in St. Lucia and Sri Lanka found similar problems in farmers' houses (McDougall, 1993; Utsch, 1991). A Kenyan study reported that 62 percent of farmers store pesticides in areas used for sleeping or cooking. Half used cooking pots or water containers to mix pesticides (Mwanthi, 1993b). Furthermore, many farm households use the same pesticides to control house and garden pests that they use on the fields. Agricultural pesticides have even been used to eliminate head lice and other bodily infestations.

Farmers routinely dump pesticide containers near the fields or leave them to corrode in sheds or houses. In Sri Lanka, pesticide bottles and cans holding toxic residues are basically thrown "in the field, in the jungle, into a canal, the road, behind the house or just anywhere" (Utsch, 1991, 306). In the Brazilian states of São Paulo and Santa Catarine, respectively 21 and 27 percent of rural residents left empty pesticide containers in the field without taking any safety measures (Almeida, 1991). In Penang Island and Province Wellesley in Malaysia, nearly one-half of all farmers disposed of pesticide containers by throwing them into the rivers, into the bushes, or by burying them in the ground (Shabat Alam Malaysia, 1984). Recycling pesticide containers for water storage, bathing, and cooking is also common—though even more risky.

Applicators commonly dump unused pesticide formulations and rinse used containers and equipment in irrigation canals. A PAHO review of several Latin American countries concludes that "it is common to find residues of organochlorine and organophosphorus compounds in drainage, wells, and river water" (Henao, 1993, 38). In many rural communities, people bathe in irrigation canals and streams into which such drainage waters flow. In the Philippines, 96 percent of farmers washed in the same irrigation canals where they cleaned their spray units (Castaneda, 1988). According to a survey in Sri Lanka, nearly 40 percent of pesticide mixing locations were within 50 meters of bathing sites and 20 percent were within 10 meters. More than one in four drinking water sources were within 50 meters of the sites of pesticide mixing, and nearly one in ten were within 10 meters (Utsch, 1991). These observations of typical practices in rural areas of developing countries show how widespread the risks of pesticide exposure are for rural households.

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Biomarkers of exposure in farmworker families confirm this conclusion. A study of farm children in Nicaragua demonstrated that nearly 40 percent of them had significantly depressed cholinesterase activity (McConnell, submitted). One in six Colombian teenagers who rotated

and region of Uzbekistan experienced inflammatory and infectious kidney diseases, 7.9 percent of rural residents living in pesticide application zones did. This rate increased to 12.5 percent among people living near pesticide storage facilities (Allazov, 1994, 1992). One study of people living in areas bordering sprayed cotton fields reported a 51 percent increase in respiratory tract disorders and a 28 percent increase in gastrointestinal tract diseases after 4 months of intensive aerial spraying (Babadzanov, 1988; Katsenovich, 1981a). Another study established a close correlation (R = 0.86–0.91) between use of pesticides on local cotton fields and diseases of the gastrointestinal tract in children living nearby (Faiziev, 1989). Pesticide exposure also exacerbated preexisting infections: tuberculosis patients with signs of pesticide intoxication were 4.4–7.0 more likely to have developed severe damage to fibrous lung tissues than patients who weren't exposed (Volkova, 1991).

Other infectious disorders were also more frequent in pesticide-contaminated areas (Saliev, 1990; Dzumatov, 1988; Nuritdinova, 1985; Atabaev, 1983). Evidence suggests that pesticides were responsible for direct damage to organ systems, leaving open the role of immunosuppression. However, Russian reviews of this literature conclude that decreased host "resistance under the influence of pesticides is one of the causes of increased disease incidence among the population living in zones with their increased utilization" (Kovtyukh, 1995b, 51; Nikolaev, 1988).

Cancer and Immunosuppression

People exposed to pesticides are at increased risk of contracting certain cancers known to be associated with immune suppression. Beyond doubt, patients whose immune systems are deliberately or fortuitously depressed experience strikingly higher rates of non-Hodgkin's lymphoma. Leukemias and stomach cancer are more common among persons with primary immunodeficiency syndromes than in the general population; soft-tissue sarcomas, melanomas, and squamous carcinomas of the skin and lip occur disproportionately in renal transplant recipients (who receive immunosuppressive drugs to avert tissue rejection); and brain and skin cancers occur frequently among bone-marrow transplant recipients (Blair, 1992). Transplant patients treated with cyclosporin A, an immunosuppressive drug, have a 100-fold increased risk of lymphatic tumors. Most tumors associated with immunosuppression have been leukemias and lymphomas, rather than the whole range of common malignancies (Holleb, 1991).

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Farmers, who as an occupational group experience lower risks of overall mortality, heart disease, and all cancers than other men of the same ages, experience elevated risk for many of the same cancers that immune-deficient patients develop (Maroni, 1993; Moses, 1993). An assessment of studies on farmers found significantly higher risks for Hodgkin's disease, melanoma, multiple myeloma, leukemia (all of which are cancers of the immune system) and cancers of the lip, stomach, and prostate (Blair, 1992). Higher risks were also found in this group of studies for non-Hodgkin's lymphoma and cancers of the brain and connective tissue, but the differences from general rates were not statistically significant. The same results have been found in epidemiological studies in the United States, Canada, Europe, Australia, China, and the Philippines (Blair, 1991; Shou-Zhen, 1987). Against a background of lower overall health and cancer incidence, these elevated risks suggest the presence of an occupational risk factor.

Since occupation is a weak proxy for exposure, studies based on occupation alone could seriously underestimate farmers' actual risks (Blair, 1990). Studies that improved the exposure measure by distinguishing farmers by age, amount of time spent in farming, or frequency of pesticide use found higher relative risks among more heavily exposed farmers (Figgs, 1995; Zahm, 1993). However, farmers are also exposed to other risk factors for cancer—organic dusts, fungal products, UV radiation, animal viruses, and diesel fuels and exhausts—complicating the matter.

Studies that specifically focussed on pesticide exposure have found that exposure to phenoxy acid herbicides and other pesticides is associated with non-Hodgkin's lymphoma and soft tissue sarcomas—two cancers associated with immunosuppression. Exposure to insecticides was found to be asociated with leukemia, multiple myeloma and brain cancer (Blair, 1991, 1985). A study of farmers in Kansas found that the relative risks for non-Hodgkin's lymphoma were systematically related to the frequency of pesticide use and the intensity of exposure (Hoar, 1986).

A number of cohort and case-control studies indicate elevated risks of the same cancers among those occupationally exposed outside of agriculture, including industrial workers, golf course maintenance workers, forest product workers, and veterinarians (Kross, 1994; Hoover, 1991; Blair, 1982). Finally, studies have found that non-occupational exposures to pesticides are also associated with higher risks of non-Hodgkin's lymphoma, childhood leukemia, and brain cancer (Leiss, 1995; Savitz, 1990; Shu, 1988; Hemminki, 1981; Infante, 1978).

Researchers at the U.S. National Cancer Institute (NCI) have concluded that "Exposure to pesticides has been associated with cancers of the lymphatic and hematopoietic system and brain. Associations between phenoxyacetic acid herbicides and non-Hodgkin's lymphoma in several countries from case-control and cohort designs and the existence of sharp exposure-response gradients build a strong case for a role for these herbicides in the development of non-Hodgkin's lymphomas in farmers. Organophosphate insecticides and fungicides may contribute to farmers' risks of non-Hodgkin's lymphoma, leukemia, soft-tissue sarcomas and brain cancer, but the evidence is not as strong..." (Blair, 1991, 348).

How pesticides increase these cancer risks is not thoroughly understood. Only about eight pesticides are judged likely to be direct carcinogens by the International Agency for Research on Cancer (IARC) (Vainio, 1994; IARC, 1991). However, some carcinogenic agents activate cancers indirectly by altering the genetic materials of cells, disrupting cell division. Since lymphocytes routinely undergo extremely quick cell division, genetic damage can accumulate rapidly. Some pesticides do induce chromosomal damage in lymphocytes and a number of researchers have hypothesized that this mechanism activates cancers (Cuneo, 1992; Garry, 1992). Among Indian cotton field workers, pesticide exposure has been associated with chromosome damage (Rupa, 1991). Other studies show similar effects, linking such pesticides as diazinon, dimethoate, Dursban, and Phosdrin to chromosomal damage (Desi, 1992; Rupa, 1988; Páldy, 1987; Rita, 1987; Ziemsen, 1987; Sobti, 1982; Yoder, 1973).

Pesticides may also reduce host resistance to cancer-initiating viruses, such as the Epstein-Barr virus (Stancek, 1995; Trichopoulos, 1994). Epidemiological studies of farmers with elevated rates of lymphomas and leukemias suggest a positive interaction between exposure to pesticides and to farm animals that transmit cancer-related viruses (Sharp, 1986).

Alternatively, pesticides can permit cancers to develop by causing a breakdown in immune surveillance (Purchase, 1994; Newcombe, 1992b). One responsibility of the immune system is to eliminate dysfunctional immune cells. Cancerous cells may express traits that differentiate them from normal cells, enabling the cell-mediated immune system to mount a reaction against them (Lotzova, 1993; Steen, 1993). Natural killer cells, cytotoxic-T cells, and macrophages are all involved in this process. Immunodeficiencies may weaken these natural defenses that eliminate

cancerous cells. Experimental studies using transplantable or virus-induced tumors in rats or mice can readily detect chemicals' immunosuppressive activity. "In fact, ample evidence demonstrates that exposure to immunotoxicants can diminish natural and/or acquired tumor resistance in well-defined tumor models" (Brooks, 1992, 196).

Thus, while some pesticides may activate cancers, others may act mainly as immunosuppressive cancer permitters (Newcombe, 1992b). An extensive review of laboratory studies concluded that pesticides may alter "functions of the immune system which may otherwise partially or completely abrogate the processes of tumorigenesis" (Exon, 1987, 77). In humans, pesticide exposure can heighten risks of non-Hodgkin's lymphomas and soft-tissue sarcomas, as can co-existing or pre-existing immune problems, such as immunosuppressive drug therapy, a family history of immune deficiency, rheumatoid arthritis, and mononucleosis (Woods, 1987).

In summary, "pesticides could affect a variety of cancers through an immunological mechanism" (Davis, Blair, & Hoel, 1992, 43). The fact that farmers and others exposed to pesticides experience higher risks for the same cancers that afflict patients with clear immune deficiencies suggests that pesticides suppress the immune system and its self-regulating capabilities and thus raise cancer risks.

Allergic Reactions

Allergic reactions provide obvious evidence that pesticides have some clinically observable effects on the human immune system. An extensive review confirms that pesticide exposure induces allergic contact dermatitis, an inflammatory response that produces a rash (Germolec and Luster, 1994). Among others, the pesticides atrazine, parathion, dinitrochlorobenzene, maneb, zineb, dichlorvos, naled, and dithianone have been shown to be extreme skin sensitizers (Abrams, 1991).

Acute hypersensitivity, also called pulmonary allergic response is an antibody-mediated (IgE) reaction with such manifestations as allergic rhinitis, asthma, and, in rare instances, extreme shock. Whether pesticides also cause pulmonary allergies is controversial, though the evidence cited below suggests that abnormally high IgE levels typically follow exposure to some pesticides. The fact that some pesticides produce allergic reactions does not imply that they are immunosuppressive, but does establish that they can sensitize the immune system.

Autoimmunity and Immune Disregulation

The human body can produce antibodies directed against itself—autoimmune antibodies—but a competent immune system normally weeds them out. However, a damaged one may not be able to prevent their development or may even stimulate them. Although the clinical consequences of autoimmunity differ markedly from those of immunosuppression, both disorders sometimes appear in the same individual since they can both arise from a poorly regulated immune system. For example, laboratory mice injected with low doses of the immunosuppressive drug, cyclosporin A, demonstrate symptoms of autoimmunity, including overproduction of autoimmune antibodies, even though they are clinically immunosuppressed (Majoor, 1991).

Some pesticides, especially metal-based ones (i.e. arsenic, copper and mercury), are well recognized agents of chemically-induced autoimmunity (Druet, 1995). "There is ample evidence to indicate that pesticides do perturb normal immune function and preliminary information suggesting that, at least in experimental animals, pesticides can induce [autoimmune] antibodies" (Rosenberg, 1995). The epidemiological literature on pesticide-induced autoimmunity in humans is limited, but studies of pesticide-exposed individuals have shown increases in autoimmune antibodies as well as changes in lymphocyte structure and function consistent with autoimmunity.

Patients chronically exposed to the organochlorine termiticide chlordane evaluated two to

four years after their last exposure demonstrated clinical and immunological symptoms "highly suggestive of immune pathology and probably a chlordane/heptachlor-induced autoimmune disorder" (Broughton, 1990, 68). These subjects showed significant increases in a class of lymphocytes that can respond to and damage human tissue, as well as increased rates of autoantibodies against human cells and tissues (Broughton, 1990). Nearly identical immunological results were found in patients exposed to the fungicide pentachlorophenol, the insecticide chlorpyrifos, and the fumigant formaldehyde (Thrasher, 1993, 1990; McConnachie, 1991; Madison, 1991).

Some pesticides conjugate with human cells, eliciting an immune response to the complex that is incidentally autoimmune. In the cotton, tobacco, and vegetable growing regions of Samarkand in Russia, rural workers and some urban residents exposed to organochlorine and organophosphate pesticides harbored antibodies against both pesticides and cells of the liver, lungs and brain (Krivoruchko, 1989). Similar results were observed in other groups, especially farm and factory workers exposed to pesticides elsewhere in the former Soviet Union (Nikolaev, 1988; Rakhmanov, 1975; Brusilovskii, 1973; Kozintseva, 1973; Katsenovich, 1970). Agricultural and vector control workers exposed to organochlorine pesticides for more than 7 to 10 years exhibited autoantibodies to immune system cells along with decreased leukocyte counts (Nikolaev, 1975).

Russian researchers found that autoimmune symptoms arose mainly from pesticides' disregulation of the immune system. Agricultural and factory workers with varying degrees of pesticide poisoning exhibited reduced effector-T cells counts and lymphoproliferative responses, but B cells and antibody levels increased (Nikolaev, 1988; Abdullayev, 1986; Ruzybakyev, 1983; Katsenovitch, 1981a, 1981b). Normally, effector-T cells (and their suppressor-T cells subsets) deactivate B cells. Pesticide-induced suppression of these effector-T cells could lead to concomitant overproduction of B cells and antibodies and generate an autoimmune response. While autoimmune disorders are less critical than immunosuppressive ones for people in developing countries, where the toll of infectious and parasitic diseases is so high, pesticide-induced autoimmunity and immunosuppression may be correlated.

Pesticides' Effects on the Immune System

During the 1970s and 1980s, most clinicians focussed on crude measures of immunotoxic potential, such as antibody ratios, complement levels, and white blood cell counts. Deviations in one or more of these immune components have been observed among a number of pesticide-exposed groups, including formulators in India, greenhouse workers in Argentina, factory workers in Poland and China, sprayers and greenhouse workers in Hungary and the former Soviet Union, and rural children in Cuba (Desi, 1992; Diez Córdova, 1991; Jingbo, 1991; Nikolaev, 1988; Albiano, 1986; Kashap, 1986; Wysocki, 1985). Bacteriocidal enzymes in saliva and blood and such external defenses as skin and mucous membrane immunity have also been found to be altered according to the duration and intensity of pesticide exposure (Bezrodnaya, 1990; Nikolaev, 1988; Kuzmenok, 1987; Dorofeyev, 1985). While these crude biomarkers do indicate immunotoxic potential, it is difficult to connect them with clinical symptoms and disorders.

More to the point, several clinical studies have examined the possibility that organophosphates and carbamates bind to and alter esterases, vital membrane-bound proteins that help immune system cells interact with and destroy foreign organisms. Among American and Eastern European factory workers, organophosphates were found to bind chemically to esterases on non-specific cells, such as monocytes, inactivating the esterases and suppressing the monocytes (Esa, 1988; Wysocki, 1987; Emmett, 1985). Neutrophils require esterases to move about by chemotaxis, which organophosphates suppress.

Among machine operators, packers, aerial spayers, and farm infants and children in the

former Soviet Union, pesticide exposure has been associated with dose-dependent reductions in the phagocytic activity of non-specific cells—a process that also requires esterases (Aristovskaya, 1989; Mogilnaya, 1989; Saidarimov, 1989; Nikolaev, 1988; Ladnova, 1984; Ivashina, 1980; Gronik, 1978). Greenhouse workers highly exposed to pesticides in enclosed spaces were found to be particularly vulnerable to the effects of pesticides on macrophage and neutrophil activity, including phagocytosis (Romash, 1987; Komarova, 1984; Zolotnikova, 1980a, 1980b).

Among factory workers in Poland, organophosphates were also found to inactivate esterases and to damage neutrophil function. These workers had symptoms indicative of neutrophil suppression, including recurrent respiratory tract infections that were correlated with the duration of pesticide exposure. Since neutrophils and macrophages protect the respiratory tract, the investigators concluded that the most likely explanation of the increased morbidity was the pesticides' localized immunosuppressive effects on pulmonary neutrophil function (Morgan, 1992; Hermanowicz, 1984, 1982).

Although infections of the upper respiratory tract are routinely associated with pesticide exposure, the pathology of the disorders are not completely known. Inhaling pesticides may also promote infections by directly damaging lung epithelial cells (Mushak, 1992). Chronic bronchitis, asthmas, and pneumonitis have been associated with exposure to agricultural and industrial chemicals with high volatility and small mass, including pesticides (Nordman, 1994; Zejda, 1993; Senthilselvan, 1992; Rastogi, 1989; Davidyan, 1986; Burge, 1985). Paraquat has been shown to disregulate macrophage activity, increasing secretion of damaging free oxygen radicals (Addo, 1986). In short, pesticides probably precipitate or exacerbate respiratory tract disorders through both immunosuppression and other mechanisms.

Most immunologists have by now adopted analytical techniques that can measure potential pesticide-induced immunosuppression more accurately. They can count the absolute numbers and ratios of various B cells and T cells (including helper-T cells and effector-T cells). These parameters are more sensitive indicators of potential problems in cell-mediated and humoral immunity. For example, AIDS-induced alterations in helper-T cells can be detected long before clinical symptoms appear.

Epidemiologists in the former Soviet Union have long observed that T cell counts and functions are suppressed after pesticide exposure.

Epidemiologists in the former Soviet Union have long observed that T cell counts and functions are suppressed after pesticide exposure (Kovtyukh, 1995b; Kaloyanova, 1991b; Nikolaev, 1988). For example, residents of agricultural districts of Karakalpakstan in southern Russia demonstrated reductions in T cell counts over control groups and higher rates of infectious diseases than the general population of the former Soviet Union (Eshanov, 1993).

A study among residents of cotton-growing districts exposed to butiphos recorded reductions in effector-T cell and helper-T cell counts coupled with significantly suppressed lymphocyte proliferative responses. Additionally, increased spontaneous B cell proliferative responses indicated that B cells were disregulated (Ruzybakyev, 1989a, 1989b). These immunoalterations were amplified among factory and agricultural workers exposed to a variety of pesticides (Maksudov, 1992; Madzhidov, 1990; Samedov, 1990; Saidarimov, 1989; Zinchenko, 1987). According to other Soviet studies, children appear to be particularly susceptible to the suppressive effects of pesticides on T cells (Kovalchuk, 1990; Zolotnikova, 1990; Aristovskaya, 1989; Jabtorov, 1987; Polchenko, 1987a, 1987b; Talankin, 1987; Fokina, 1985).

Studies conducted outside of the former Soviet Union have also recorded pesticide-induced changes in lymphocyte counts and function. Among Indian factory workers chronically exposed to several pesticides, blood lymphocyte levels decreased by as much as 66 percent in a maximally exposed group. In a group asked to take time off from work experimentally, immune parameters returned to normal within three months. The researchers concluded that the "exposure induced deviations...were time related and cessation of exposure or its withdrawal resulted in achieving normal levels" (Khan, 1993, 742).

American and Italian workers exposed to pentachlorophenol (PCP) had significantly diminished helper-T cell counts and lymphocyte proliferative response, and experienced flu-like illness and urinary tract infections (Colosio, 1993; McConnachie, 1991). Nearly identical results were obtained from individuals exposed to the organochlorine pesticide chlorpyrifos (Thrasher, 1993).

Germans exposed to PCP exhibited decreases in the ratio of helper-T cells to effector-T cells—an important indicator of possible immunosuppression—along with suppressed lymphocyte proliferative response. Bronchitis and colds were frequent among this group. In all, "these results indicate that increased levels of pentachlorophenol in blood can lead to severe T lymphocyte dysfunction" (Daniel, 1995, 287).

After consuming groundwater contaminated with the carbamate, aldicarb, healthy women in Wisconsin also showed significant decreases in the ratio of helper-T cells to effector-T cells. The women with lowest helper-T cells counts were rescreened a year later, with consistent results that indicated aldicarb's chronic effect on T cells (Hong, 1991; Mirkin, 1990; Fiore, 1986).

Dioxin-Like Compounds

Dioxin-like compounds are a subset of polycyclic halogenated aromatic hydrocarbons, similar in that they bind to a particular intracellular receptor. Though most organochlorine pesticides do not bind to this receptor, dioxins are found as contaminants in some pesticide products, such as pentachlorophenol. Some PCBs, widely used industrial compounds formerly also used in the United States as pesticide extenders, are dioxin-like compounds. So is hexachlorobenzene, an extensively used fungicide often found as a contaminant in other pesticides (Saboori, 1992). Such contaminants in pesticide formulations might sometimes produce immunotoxic effects. Ninety-nine percent pure pentachlorophenol (PCP) is not immunosuppressive in mice, but formulation quality PCP (86 percent pure) is; the dioxin contaminant is the likely culprit (Kerkvliet, 1982).

Since dioxin-like componds were first recognized as persistent organic pollutants, attempts to assess their risks—such as EPA's draft *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds*—have been controversial. Regardless, substantial evidence from experimental animal, wildlife, and human epidemiological studies suggests that dioxin-like compounds, including PCBs and the prototype dioxin, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) are immunosuppressive. According to researchers at the National Institute of Public Health and Environmental Protection in The Netherlands, "from...investigations in humans, it can be concluded that dioxin and related compounds cause immune alterations, particularly of the cell-mediated immunity. As a consequence, the resistance to infectious agents may be impaired as well. The findings in humans correlate with the findings in experimental animals" (Vos, 1991, 84).

The evidence of TCDD-induced immunotoxicity in humans stems from several incidents. In 1971, dioxin-contaminated wastes from a pesticides factory were sprayed on local roads in Missouri. Among exposed groups, including children, ratios of helper-T cells to effector-T cells and lymphoproliferative response were suppressed (Smoger, 1993; Hoffman, 1986). An explosion at a herbicide factory in Seveso, Italy in 1976 sent a large cloud of smoke and ash containing pesticides

and its dioxin-like compounds into nearby communities. One group of exposed children showed increased rates of childhood infectious diseases, while another group exhibited suppressed humoral immunity (Pocchiari, 1979). Some other epidemiological studies have shown similar immunological and clinical outcomes, though others have proved inconclusive (Institute of Medicine, 1994; Kerkvliet, 1994a, 1994b; Ray, 1992).

A review of polychlorinated biphenyls (PCBs) suggests "that PCBs are immunosuppressive" as well (IPCS, 1993, 41). During the spring of 1979, people in Taiwan consumed rice-bran oil contaminated with PCBs, and their symptoms—called Yu-Cheng (Oil Disease)—included rashes and increases in certain infections. Among consumers of the contaminated oil, effector-T cell counts and serum antibody levels were significantly suppressed, as were levels of neutrophils and monocyte subsets (Chang, 1982, 1981, 1980). A follow-up assessment of helper-T cell and effector-T cell counts three years after the accident revealed that "the chronic effect of PCB or its derivatives upon the immune system may last for more than three years, and the immunotoxicity affects both B and T lymphocyte functions, in addition to numbers" (Wu, 1984, 184). People exposed to PCB-contaminated rice oil in Japan in 1968, exhibited nearly identical symptoms: altered serum antibody levels, altered ratios of helper-T cells to effector-T cells, and secondary respiratory infections (Kuratsune, 1989).

More Comprehensive Studies

Two little-known groups of studies from central Moldova and northern Canada provide additional evidence of the risks of pesticide-induced immunosuppression. In both studies 1) exposure to pesticides is well established; 2) significant dose-related changes in immune biomarkers are reported; and 3) specific diseases and other clinical manifestations are reported and linked to exposure.

Retrospective studies conducted in the farming regions of central Moldova (in the former Soviet Union) have examined the human health effects of pesticide exposure. From the 1960s through the 1980s, agricultural districts in central and southern Moldova applied pesticides at rates as high as 40 kg per hectare per year, almost 20 times the world average. Copper-containing fungicides, organophosphates, organochlorines, carbamates, and pyrethroids predominated (Moldova, 1992a; Lupashku, 1984, 1980; Socolov, 1984).

Over the years, pesticide residues accumulated in soils, water, and agricultural products. In soils from one village in the Strasheny district, where an average of 22.73 kg/ha/yr of active ingredients were applied annually from 1983 to 1992, hexachlorane isomers, DDT and DDT metabolites exceeded accepted standards by up to twenty-fold. Peaches and other small fruit were heavily contaminated, averaging 2 mg of copper per kg of fruit (Moldova, 1992b). Surface waters and pit wells drawing from agricultural run-off were contaminated. In one survey, researchers detected pesticide residues above accepted standards in 10 to 15 percent of water samples (Kovtyukh, 1995a).

Epidemiological studies in Moldova have implicated pesticide exposure with increasing rates of infectious disease. In one study, teenagers in villages where pesticide application was greatest exhibited rates of infections of the respiratory tract and digestive tract two to five times and three times higher, respectively, than controls from areas of lower use (Vasilos, 1993, 1989, 1986). Based upon this association, researchers conducted a retrospective study of healthy children's immune systems in these villages. Nearly 80 percent of highly exposed infants and children showed significant deviations in more than five immunological parameters. T cell ratios and counts were significantly altered and subjects' lymphocyte proliferative responses were suppressed, indicating losses in cell-mediated immunity (Kozlyuk, 1989a, 1989b, 1987a, 1987b).

Among adults in Strasheny, a district of intensive pesticide use, the incidence of respiratory, reproductive, and sensory organ diseases, ulcers, and miscarriages was higher than in a less

exposed district. Complementary studies of the general adult population in these districts demonstrated that immune parameters changed significantly with increasing pesticide exposure. Nearly one third of adults in pesticide-exposed communities showed significant deviations in more than five immune system parameters, while more than two thirds showed similar changes in two to five parameters. Most of the alterations were observed in T cell counts and ratios, as well as in phagocytic activity (Kovtyukh, 1995a, 1994). The authors concluded that "individuals continuously exposed to pesticides and, living in areas with increased pesticide [use]...exhibit immunity disorders at the cell and humoral level" (Kovtyukh, 1995a, 31).

Among occupationally exposed farmers in particular, researchers found elevated rates of the infectious diseases of the following organ systems: gastrointestinal, urinary tract, female genital tract, and respiratory tract.

Among occupationally exposed farmers in particular, researchers found elevated rates of the infectious diseases of the following organ systems: gastrointestinal, urinary tract, female genital tract, and respiratory tract. Morbidity due to these infectious diseases increased with increasing occupational reliance on pesticides, an approximate measure of dose (Kovtyukh, 1995a; Vasilos, 1989). Researchers subsequently measured immune parameters in samples of agricultural and factory workers and found that T cell counts and ratios were altered and humoral responses were suppressed depending upon duration of pesticide exposure (Anisimova, 1990, 1989, 1987; Kozlyuk, 1989a, 1987a; Russu-Lupan, 1989, 1983). In all, "individuals with occupational long-term exposure to pesticides exhibit immunodysfunction," and "nearly all the deviations observed are enhanced with longer exposure to pesticides" (Kovtyukh, 1995a, 33).

In these studies from Moldova, confounding factors that were not completely controlled, such as smoking status and exposure to other pollutants, make it difficult to pin down the role of pesticide exposure on these diseases. These agricultural regions exhibit severe contamination from other pollutants—especially nitrates from chemical fertilizers and animal manures—that can affect health (Kozlyuk, 1989c). Yet, experimental animals exposed to the copper-based pesticides applied in Moldova undergo immunologic changes similar to those experienced by the Moldovans.

Ultimately, the major limitation of these Moldovan studies is their retrospective approach. The researcher had to test the immune status of healthy individuals exposed to pesticides, because illness itself influences the subject's immune status. Prospective studies allow researchers to observe exposure, immunological change, and health outcome together in the same sample group. Such a prospective study is under way in arctic Canada among the Inuit, whose isolation limits the possible sources of exposure.

The background levels of health of native populations in the Arctic is extremely poor. The Inuits "exhibit morbidity and mortality rates in some dimensions in excess of even the poorest Third World countries" (Drew, 1992, 163). Children are highly susceptible to infections. In the 1980s, Inuit children in Hudson's Bay were found to be 30 times more likely to suffer from meningitis than American children (Proulx, 1987). Chronic otitis (infection of the inner ear) was epidemic among Inuit children in Northern Quebec, resulting in high rates of hearing impairments (Julien, 1987). During the same period, other researchers measured immune parameters in healthy Inuit children in the Northwest Territories. In comparison to healthy children from southern Canada, the healthy Inuit children had lower T cell percentages, helper-T cell counts and lymphocyte proliferative responses, as well as altered antibody levels. Altogether, "significant

differences in both cellular and humoral immunity are found in both normal and recurrently ill Inuit infants" (Reece, 1987, 62). The immune system changes are similar to those found in the Moldovan studies.

Transported by atmospheric winds, ocean currents, and rivers from as far away as Mexico, persistent contaminants have been found to accumulate in arctic Canadian ecosystems in extremely high levels (Pearce, 1995; Barrie, 1992; Lockart, 1992; Muir, 1992; Thomas, 1992). Because fish, whale, seal, walrus, and bear meat are mainstays of their diet, some Inuits consume relatively large amounts of polycyclic halogenated organochlorine compounds, including PCBs, dioxins, and organochlorine pesticides, and bioaccumulate these agents in fatty tissues over years of exposure (Kinloch, 1992). In the early 1990s, PCB, DDE, and mirex concentrations in Inuit breast milk were four, four, and ten times higher, respectively, than for women from control groups (Dewailly, 1993a, 1992, 1991, 1989). PCB concentrations in Inuit breast milk fat equalled and in some cases, surpassed that in beluga whale blubber. Because these organochlorine compounds can cross the placental barrier and bioccumulate, these findings aroused concerns over adverse health effects on Inuit infants including increased susceptibility to infections (Dewailly, 1993b).

This motivated a prospective cohort study of Inuit infants born in 1989–90, which revealed that breast-fed Inuit babies that had accumulated higher doses of organochlorines were significantly more likely to have experienced acute otitis media attacks. As breast-feeding normally confers protection against infectious diseases and as Inuit breast milk contains high levels of organochlorines, researchers hypothesized that these residues had altered the children's immune status. In comparison to bottle-fed babies, these breast milk-fed babies demonstrated decreased ratios of helper-T cells to effector-T cells that were correlated with duration of breast-feeding and organochlorine levels in breast milk (Dewailly, 1993c). In addition, Inuit babies are hard to vaccinate, since many fail to produce a primary antibody response to the usual vaccines. The infectious disease incidence among the Inuit children "appears to be associated with immune dysfunction as measured by a low immunization take rate, and raises issues of altered host resistance" (Birnbaum, 1995, 158; Lindstrom, 1995). However, since levels of pesticide and non-pesticide organochlorine compounds correlate closely in the babies examined, researchers can't disentangle whether one or the other, or both, are suppressing immune responses.

Conclusion

The results from human studies presented here are consistent with the evidence from experimental, animal, and wildlife studies. Exposure to many pesticides produces significant changes in immune system structure and function, including reduced and altered T cell populations, reduced lymphocyte proliferative response, reduced cell-killing activity, and altered antibody levels in circulation. There is evidence that these changes can be accompanied by increased risks of infectious diseases and cancers associated with immunosuppression, even in otherwise healthy populations. Though not conclusive, the weight of evidence gives grounds for concern. Clinicians agree that susceptible groups are more likely to suffer adverse health consequences from any immune suppression. The majority of people in developing countries, including children, the sick and the malnourished fall into this category.

VII. Conclusions and Recommendations

The preceding chapters establish that there are substantial grounds for concern about the public health risks from pesticide-induced suppression of the immune system, especially in less developed countries and countries in transition. The tonnage of pesticides used in these countries will continue to increase as agricultural production intensifies. Chemicals with known acute and chronic toxicity are still widely used, including many that have been banned, severely restricted, or withdrawn from agricultural uses in the United States and Europe.

Controls over pesticide use in developing country agriculture are generally lax. Typically, government regulations over marketing and use are weakly enforced. Distribution networks provide for less product stewardship and support than in more advanced markets. Many pesticides in use in developing country markets no longer have patent protection and are produced and sold on a commodity basis. Pesticides are often used in applications and in ways for which they are not intended, creating safety and health risks.

Though systematic estimates of overall exposure are not available, evidence indicates that hundreds of millions of farmworkers, farm households, and consumers are probably exposed to dangerous levels of pesticides. Direct observations of pesticide handling, spray operations, and disposal confirm significant occupational exposure. Observations of household practices in pesticide storage and disposal, proximity to pesticide applications, and washing and food preparation establish that rural household members can be exposed through various routes. These observations are confirmed by biological measurements of pesticide residues in the body and of acetylcholinesterase depletion. The presence of persistent bioaccumulative pesticide residues in foods, body tissues and human breast milk indicate that consumers far removed from agricultural operations can also be significantly exposed.

A large body of experimental evidence based on *in vitro* and *in vivo* models suggests that many of the pesticides to which such populations are exposed damage the immune system. Established testing protocols for use with experimental animals show that many organochlorine, organophosphate, carbamate and metallic pesticides are immunotoxic. They alter the normal structure of the immune system, disregulate and disturb immune responses, and reduce the exposed animals' resistance to antigens and infectious agents. This assessment of the experimental evidence is widely shared by immunotoxicologists working in this field.

Studies in the wild of fish, birds, and mammals exposed to pesticides and other organochlorine compounds through their diet also provide evidence that these compounds are immunosuppressive. In particular, a carefully controlled prospective study of harbor seals in captivity provided conclusive evidence that dietary exposure to pesticides and other polyhalogenated aromatic hydrocarbon compounds resulted in significant alteration and suppression of immune functioning.

There is direct and indirect evidence that these findings carry over to human populations exposed to pesticides. The indirect evidence stems largely from studies of cancer risks in populations occupationally exposed to pesticides. Farmers and other exposed workers are at significantly elevated risks of cancers that are typically found in people who are immunosuppressed because they have AIDS, because they are taking immunosuppressive drugs to safeguard organ transplants, or because they suffer from genetic immunological deficiencies. The same cancers of the immune system occur at elevated rates in people known to be immunosuppressed and in groups exposed to pesticides.

Clinical and epidemiological studies of humans who are occupationally or accidentally exposed to pesticides provide direct evidence that normal immune system structure and functions are thereby altered. In general, these findings are consistent with the experimental evidence, showing reductions or disruptions in cell-mediated and non-specific immunity. Many of these studies have not assessed or have not found concomitant evidence of reduced host resistance to infectious disease or other significant clinical consequences. Other epidemiological studies show an association between pesticide exposure and increased risks of chronic health disorders, including infectious diseases, but without assessing or documenting alterations in the immune system.

For several reasons, few epidemiological studies on human populations have been designed to investigate pesticide exposure, immunological change and immunosuppression, and resulting increased health risks from infectious or other diseases. Until recently, concern over pesticide toxicity centered on cancer risks and acute poisonings, rather than on immunotoxicity or other chronic effects. In addition, environmental immunotoxicology is a relatively young discipline and there are few such scientists working in developing countries, where risks are highest. Finally, such studies are difficult to design and implement: the problems in measuring exposure and immunological changes, controlling for confounding risk factors, and detecting elevated risks from high background levels are substantial. Because research funding has also been inadequate, no such studies have been carried out in the developing countries.

However, considerable research of this kind has been carried out in the former Soviet Union in regions of heavy pesticide use. Studies have shown dose-dependent effects of pesticide exposure on cell-mediated, non-specific, and autoimmunity. Associated with these changes, researchers have demonstrated elevated risks to exposed populations from infectious and other chronic diseases.

Important epidemiological research focussed on an isolated Canadian Inuit population that eats mainly fish and marine mammal flesh contaminated with bioaccumulative pesticides and other organochlorine compounds is reaching similar conclusions. Infants who ingest these compounds through contaminated breast milk show pronounced immunological deficiencies and elevated risks of infections, including meningitis and inner ear infections.

There are reasons to be especially concerned about the immunosuppressive effects of pesticides on exposed populations in developing countries. In those countries, infectious and parasitic diseases are by far the most important causes of illness and death and are largely responsible for the reduced overall life expectancy. Case mortality rates for such diseases as measles, which often leads to secondary bacterial infections, are much higher than in richer countries. Unsanitary living conditions, unprotected water supplies, crowded settlements, and inadequate housing mean that children and adults are inevitably highly exposed to infectious and parasitic diseases. Lack of access to curative health services and lack of money to purchase medicines imply that people must rely largely on their own natural defenses to survive and recover. However, children, malnourished people in general, and the chronically ill have weakened immunological defenses. To a far greater extent than healthy farmers in the American Midwest, they are clinically

vulnerable to further immunosuppression due to chemical exposures.

Consequently, the evidence presented in this study points to a serious but unrecognized public health concern, especially in developing countries and other regions where vulnerable populations are heavily exposed. At a minimum, an appropriate response would include an expanded program of epidemiological research sited in such regions and specifically designed to investigate the immunosuppressive effects of pesticide exposure and consequent health impacts on vulnerable populations. This research would seek to confirm whether pesticides now in use have immunosuppressive effects under actual exposure conditions, and if so, whether this results in elevated health risks to susceptible groups.

These investigations warrant a very high priority according to criteria set by a WHO expert group established to set research priorities in environmental epidemiology (WHO, 1994). These criteria include:

- the size and wide distribution of the population exposed;
- the increasing extent and intensity of exposure;
- the biological plausibility of and experimental evidence for adverse health effects;
- the lack of adequate epidemiological evidence in humans;
- the potential synergism with other risk factors;
- the likelihood of impacts on sensitive subgroups; and
- the potentially high morbidity and mortality costs.

Indeed, this expert committee has already concluded that epidemiological research on pesticide health effects, particularly on the immune system, deserves high priority.

To our knowledge, even though leading immunotoxicologists around the world recognize the need, almost no such research is under way. Nor is any to be found in the current workplans of major health research or funding agencies. The World Health Organization and its affiliates are currently constrained by severe funding shortages, and despite interest, have not been able to mount a research program on this subject. Neither are other specialized UN agencies supporting such research: not UNICEF, despite its strong interest in maternal and child health, nor the ILO, despite its responsibilities for worker health and safety around the world. *Agenda 21*, which contains the commitments made by governments at the UN Conference on Environment and Development to work for sustainability, puts priority on controlling communicable diseases and reducing health risks from environmental pollution and hazards. It sets ambitious targets to reduce deaths from measles, childhood diarrhea and other communicable diseases by the end of the century and it charges international organizations with the responsibility of supporting national efforts to achieve these goals.

The World Health Organization should take the lead in designing and organizing an appropriate program of epidemiological and other research to address this risk. The major pesticide companies also have a responsibility to ensure that the products they sell do not pose a threat to the human immune system.

In view of its central responsibility among the UN agencies in protecting the health of people around the world from environmental assaults, the World Health Organization should take the lead in designing and organizing an appropriate

program of epidemiological and other research to address this risk. Member governments should provide the necessary financial support for this program.

Little or no funding has been allocated from national health research or foreign assistance budgets for such research. The health research budgets of countries of the former Soviet Union, in which considerable epidemiological work was previously undertaken, have all but collapsed. In the United States, the Environmental Protection Agency, the National Cancer Institute, and the National Institutes of Health have funded research on pesticides' health risks, including experimental studies of immunotoxicology, but little or no epidemiological research focussed on immunotoxic effects, and none in developing countries. Government health research budgets, especially for environmental epidemiology, are being drastically cut in 1996. The United States Agency for International Development (USAID) has also financed some health effects research on pesticides through cooperative arrangements with the Centers for Disease Control and Prevention (CDC), but none directed toward these risks. Its funding is also being cut. Agricultural sustainability and the protection of maternal and child health have been among USAID's highest program priorities, and have led to efforts to reduce pesticide risks in developing countries by promoting Integrated Pest Management programs. Through its cooperation with CDC, USAID should also support epidemiologic research on pesticides' health risks to immunologically vulnerable populations in developing countries.

Multilateral development banks—the World Bank, in particular—should also support such investigations. The World Bank has invested enormous resources in water supply and sanitation systems in developing countries to reduce exposures to infectious and parasitic agents. The Bank has also invested heavily in primary health care systems to deal with the heavy burden of morbidity from infectious and parasitic diseases. Yet, billions of people are still without adequate water and sanitation or adequate health care. It may well prove highly complementary and cost-effective to reduce environmental threats to the immune system, thereby helping developing country populations resist and recover from infectious diseases that take such a deadly toll among children and other vulnerable groups in developing countries.

The major pesticide companies also have a responsibility to ensure that the products they sell do not pose a threat to the human immune system. Many of these companies, including Ciba-Geigy, DuPont, and Monsanto, have made strong corporate policy commitments to product safety. They have joined Responsible Care, a voluntary chemical industry organization devoted to environmentally sound production methods and life-cycle product stewardship. In that spirit, they should join and support health research programs to ensure that the products they—or their subsidiaries and affiliates—make and sell do not pose immunotoxic health risks.

Regulatory agencies should substantially strengthen their surveillance and control over the use of potentially immunotoxic pesticides.

Finally, of course, government regulatory agencies should substantially strengthen their surveillance and control over the use of potentially immunotoxic pesticides. The use of banned and restricted pesticides, the sale of pesticides without proper labels, and the improper disposal of pesticide containers should be prevented. Thorough immunotoxic testing should be required as a condition of continued registration of products for sale. Government agricultural ministries should substantially expand programs of training and extension in safe pesticide use. In most developing and transitional economies, these programs are badly handicapped by a lack of personnel and operating funds. Budgets for these programs should be substantially increased.

A good way for governments to do this would be to authorize the agricultural ministry to levy a moderate flat fee per kilogram of active ingredients on all pesticides sold, with the resulting revenues dedicated to health research, training, extension, and development of IPM programs. Since the current pesticide market in developing and transitional markets exceeds $2 billion per year, a relatively modest fee could raise enough revenues to expand these regulatory, research and training programs substantially.

A flat fee per kilogram of active ingredients would also help shift pesticide use away from the more dangerous compounds. It would fall more heavily on pesticides that are cheap on a per kilogram basis and are used at relatively high application rates in terms of kilograms per hectare. These include the older organochlorine, organophosphate, and carbamate compounds that pose some of the most serious health risks, including immunotoxicity. The relative cost of using such compounds would rise, compared to compounds that cost more per kilogram but are applied sparingly. Farmers would be encouraged to substitute newer pest control products, many of which are safer. Such a fee would also encourage the adoption of Integrated Pest Management systems and other practices to reduce overall pesticide use. Market as well as regulatory mechanisms can be used to reduce health risks and encourage efficient pest management practices.

The overriding point, however, is that this public health concern should not be neglected. If it is true that pesticides in widespread, increasing, and largely uncontrolled use are immunosuppressive, then mortality rates from common infectious diseases that already account for most deaths in developing countries may be much higher than need be. People may continue to die from respiratory and gastrointestinal infections in large numbers, as they always have, and the added risk to their natural defenses from chemical exposure might remain undetected. Already, the evidence of pesticide-induced immunosuppression warrants a conclusive research program and precautionary actions.

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Glossary

Acquired Immunity
Immunity that develops following initial exposure to an antigen, usually involving T cells and B cells.

Allergy
Hypersensitivity to an antigen resulting in inflammation and tissue damage.

Antibody
Proteins also called immunoglobulins (Ig) produced by B cells in response to an immune challenge and capable of binding to a specific antigen. There are four types of antibodies, IgA, IgE, IgG, IgM, each having distinct functions.

Anticholinesterase
Any compound capable of binding to and inhibiting the enzymatic activities of cholinesterase. Anticholinesterase compounds include organophosphate and carbamate pesticides.

Antigen
A foreign component that reacts specifically with antibodies or T cells. Antigens are usually protein or carbohydrate constituents on or in bacteria, viruses, parasites, or tumor cells.

Antigen Presentation
The process by which macrophages, B cells, and virally infected cells display antigens from foreign organisms on their surface. T cells inspect these antigens presented to them and kill the infected host cell or foreign cell or induce macrophages and B cells to do so.

Antigen Presenting Cell
Cells that are capable of processing and presenting antigens to T cells. Antigen presenting cells are usually macrophages or B cells.

Autoimmunity
An immune response directed against an organism's own cells or components.

B cells
Cells, also called B lymphocytes, that produce antibodies.

Cell-Mediated Immunity
An immune response requiring interactions between T cells and other host cells during an immune challenge. Include delayed-type hypersensitivity and cytotoxic-T cell responses.

Chemotaxis
Directed movement of cells in response to a foreign agent. Non-specific immune cells such as neutrophils undergo chemotaxis.

Cholinesterase
An enzyme needed for proper neuro-muscular function. Without cholinesterase, an important neurotransmitter (acetylcholine) is not broken down, which leads to overstimulation of nerve endings.

Complement
The set of blood proteins that, when activated, form a cascade of interactions leading to the death of a foreign cell.

Cyclosporin A
A potent immunosuppressive drug widely used to prevent rejection of transplanted organs.

Cytokines
Chemical messengers usually secreted by macrophages in response to an immune challenge that affect growth and differentiation of other cells.

Cytotoxic
Able to kill cells.

Cytotoxic-T Cell
A kind of T cell able to destroy virally infected cells when presented with a viral antigen by the infected cell. Cytotoxic-T cells, like suppressor-T cells, contain a membrane-bound protein called CD8.

Delayed-Type Hypersensitivity
A cell-mediated immune response involving T cells, macrophages, and chemical messengers in response to a stimulus.

Effector-T Cell
A class of T cell containing CD8 that includes cytotoxic-T cells and suppressor-T cells.

Esterases
Enzymes essential for proper energy exchange and chemical transformation. Some chemicals that bind to and inhibit esterases block normal cellular functions.

Helper-T Cell
A class of T cells containing CD4 that releases growth and differentiation factors when presented with an antigen. Helper-T cells instruct B cells and macrophages to kill foreign organisms.

Host Challenge
The deliberate exposure of a laboratory animal to bacteria, viruses, parasites, or tumor cells in order to test whether the animal has a healthy immune system.

Humoral Immunity
Immune responses mediated by antibody and complement (in contrast to cell-mediated immunity).

Hypersensitivity
A state of heightened responsiveness to an antigen. There are several types of hypersensitivity reactions, including delayed-type hypersensitivity.

Immune Surveillance
Process by which the immune system destroys cancerous and other abnormal cells by recognizing specific antigens on these cells that distinguish them from healthy cells.

In Vitro
Experiments with tissue, cells, or cell components performed outside the body.

In Vivo
Experiments performed in a living organism.

Leukemia
A cancer of the blood characterized by increased numbers of abnormal white blood cells in circulating blood.

Leukocyte
Any blood cell that is not a red blood cell, including lymphocytes, natural killer cells, monocytes, macrophages, and neutrophils. Also called white blood cells.

Lipophilic Compound
Any compound that is chemically similar to oil and is repelled by water. Since fatty tissues are themselves chemically similar to oil, lipophilic compounds accumulate in fatty tissues.

Lymphocyte
A class of immune cells including T cells and B cells derived from a common precursor cell and involved in acquired immunity.

Lymphocyte Proliferative Response
The process of lymphocyte growth, differentiation and multiplication in response to a stimulus.

Lymphokines
Chemical messengers that are secreted by T cells in response to an immune challenge and that affect growth and differentiation of other cells.

Lymphoma
A cancer of lymphoid tissue, such as Hodgkin's lymphoma and non-Hodgkin's lymphoma.

Macrophage
A large non-specific cell capable of phagocytosis and able to present antigens to helper-T cells.

Monocyte
A macrophage precursor cell similar to macrophages but incapable of phagocytosis or antigen presentation.

Natural Killer (NK) Cell
A non-specific cell that can recognize and destroy some types of tumor cells in the process of immune surveillance.

Neutrophil
A non-specific cell that can respond to and destroy foreign organisms through phagocytosis. Neutrophils are similar to macrophages but are incapable of antigen presentation.

Non-Specific Immunity
Host defenses usually involving natural killer cells, neutrophils, and macrophages that function on initial exposure to a specific antigen independently of T cells and B cells.

Phagocytosis
A process by which cells ingest and destroy foreign cellular and particulate matter. Macrophages and neutrophils are capable of phagocytosis.

Primary Immune Response
The cellular and humoral immune response to an initial exposure to antigen. This response has a longer lag phase, shorter duration, and smaller effect than the secondary response.

Secondary Immune Response
The heightened, more rapid immune response, usually requiring a cell-mediated mechanism, that follows a second or subsequent exposure to a foreign agent.

Spleen
A small, secondary immune system organ located near the liver where macrophages mature and T cells, B cells, and macrophages interact.

Suppressor-T Cell
A kind of T cell that can inhibit or down-regulate immune responses. Suppressor-T cells, like cytotoxic-T cells, contain a membrane-bound protein called CD8.

T Cells
Lymphocytes defined by the presence of a T cell receptor protein (CD4 or CD8). Three known subsets of T cells are helper-T cells, which contain CD4 proteins, cytotoxic-T cells, and suppressor-T cells, both of which contain CD8 proteins.

Thymus
A small, primary immune system organ located near the sternum where T cells mature.

White Blood Cells
Immune cells, such as lymphocytes, natural killer cells, monocytes, macrophages, and neutrophils that are also known as leukocytes.