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PESTICIDES AND THE IMMUNE SYSTEM:

The Public Health Risks

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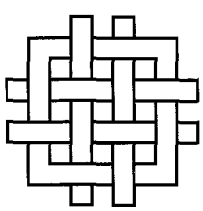

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R.R.
S.S.B.

Foreword

This report about the effects of pesticides on the human immune system makes one thing abundantly clear: we need to know more about these linkages, but we already know more than enough to take preventive action.

Hundreds of millions of farmworkers, farm households, and consumers are probably exposed to dangerous levels of pesticides. Most of these people live in the developing world and the countries of the former Soviet Union. In many cases, they are using chemicals with known acute and chronic toxicity and applying them without adequate safeguards.

The scientific evidence suggesting that many pesticides damage the immune system is impressive. Animal studies have found that pesticides alter the immune system's normal structure, disturb immune responses, and reduce animals' resistance to antigens and infectious agents. There is convincing direct and indirect evidence that these findings carry over to human populations exposed to pesticides.

Even a conservative guess about the years of productive life that are being lost around the world as a result of this problem would suggest that a small investment to minimize the risks will almost certainly provide benefits that far outweigh the costs.

Pesticides and the Immune System: The Public Health Risks continues an effort that dates back over many years at WRI to examine the health effects of environmental pollution and policies that will move us toward more sustainable agricultural practices. In *Field Duty,* Robert Wasserstrom and Richard Wiles assessed both the scientific and policy issues surrounding pesticide use and farmworker safety. In *A Better Mousetrap,* Michael J. Dover examined the strategies embodied in Integrated Pest Management that could reduce the health risks associated with pesticides. *Paying the Price,* by Robert Repetto, described how government subsidies for pesticides in developing countries encouraged wasteful use and needlessly increased health risks. More recently, Paul Faeth's *Growing Green* systematically examined the economic and environmental effects of changes in U.S. farm policy.

This study typifies WRI's team approach to research. The WRI team included Robert Repetto, WRI vice president and a former professor at the Harvard School of Public Health, and Sanjay Baliga, who graduated from Stanford University and acquired an M.P.H. degree at the University of Michigan. The team was aided by an advisory panel with extensive experience in this field.

Pesticide-induced immunosuppression is one of several emerging, imperfectly understood health risks associated with chemical exposures. The evidence assembled in this report underscores the need to continue improving our understanding of such risks.

For our part, WRI plans to aggressively expand its work in this area in the coming years. In 1995 we began a new program on health, environment, and development headed by Dr. Devra Davis. This program is intended to fully inform policy-makers about the environmental determinants of threats to public health and about the opportunities to reduce the risks of disease through sound environmental stewardship.

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I. Introduction

This report addresses a potentially serious risk to public health, the risk that many pesticides affect the human immune system in ways that suppress normal immune responses to invading viruses, bacteria, parasites and tumors. Based on accepted tests for immunotoxicity, evidence has accumulated from many laboratory experiments on various mammals and human cells exposed to widely used categories of pesticides. Unfortunately, these tests were not required when regulatory authorities screened most pesticides now on the market for potential health hazards.

Although extrapolating from laboratory test results to human health effects under actual exposure conditions is difficult, the experimental findings are supported by studies of mammals exposed to pesticides in the wild or in captivity and by epidemiological studies of people exposed to pesticides at work or through their diet. These epidemiological studies link pesticide exposure to immune system changes similar to those observed in laboratory experiments. Some also find elevated risks of infectious diseases or of certain cancers typical of immunosuppressed patients. Unfortunately, few epidemiological studies have been conducted (except in the former Soviet Union, where these concerns apparently arose decades ago). Difficult and expensive to carry out, such studies have not been a priority among the small community of environmental immunotoxicologists. But the need for more epidemiological studies, especially in the populations most at risk, is obvious.

The risks are greatest in many parts of the developing world and in countries of the former Soviet Union, where, compared to the industrialized world, much larger fractions of the populations still live in the countryside and work on farms. In developing regions, pesticide use is still growing rapidly, and compounds that have long been banned or restricted on health grounds in the United States are still in use. Moreover, pesticide regulations are weak and farmers lack the training and equipment to handle pesticides safely.

In developing regions, pesticide use is still growing rapidly, and compounds that have long been banned or restricted on health grounds in the United States are still in use.

People in these countries are at high risk from any chemical exposure that weakens their immune defenses. Few people have adequate housing, water supplies, and sanitation. Infectious and parasitic diseases are rampant: respiratory infections and gastro-intestinal diseases are the leading causes of death. Health care is inadequate, especially for low-income households, so people are forced to rely on their own defenses to recover from diseases. Widespread malnutrition has already weakened those immune responses.

Fatality rates are high from common diseases—measles and whooping cough, for example—from which patients almost always recover in wealthy countries. On top of these other health risks, pesticide-induced immunosuppression might be substantially increasing the burden of common diseases. The consequences could remain undetected because people would die not from acute pesticide poisoning (although many do), but from such diseases as pneumonia or gastro-enteritis or the complications of measles. The fact that pesticide exposure weakened their immune responses and increased their vulnerability would remain unrecognized.

This report makes the case that existing evidence of a significant worldwide public health risk justifies both greater efforts to reduce pesticide exposures and much-expanded research into pesticide-induced immunosuppression and its health consequences. Chapter II describes patterns and trends in pesticide use in various parts of the world. Chapter III presents evidence that farmers, farm households, and households exposed to persistent pesticides through their diet represent large populations potentially at risk. Chapter IV summarizes a large amount of experimental research on pesticide immunotoxicity, citing the conclusions of immunologists and toxicologists who have reviewed this evidence. It also describes some important studies of immune deficiencies in marine mammals exposed to pesticides that bioaccumulate up the food chain. Chapter V summarizes epidemiological research on human populations, focussing especially on key studies carried out in Canada and the former Soviet Union. Chapter VI explains the compounding risk factors that make this issue especially critical in developing nations and countries in transition from socialism. The final chapter summarizes the entire report and presents our conclusions and recommendations.

II. Trends and Patterns of Pesticide Use

The World Pesticide Market

Data on worldwide pesticide sales and use are remarkably difficult to find. Few other $30-billion-a-year industries are as reticent about the products they sell. Few are as concentrated, either. The top ten multinational pesticide companies (Ciba-Geigy, DuPont, Monsanto, Zeneca, Bayer, DowElanco, Rhone-Poulenc, Hoechst, American Cyanamid, and BASF) account for about two-thirds of world sales. The United Nations Food and Agriculture Organization (FAO) surveys agricultural ministries in each country regarding pesticide use every year, but responses are not always reliable (Curti, 1994). A few market research firms sell data on pesticide sales in important national markets but the prices they charge puts the information out of reach for the general public.

In dollar terms, about 62 percent of the $30 billion pesticide market in 1995 was in the United States, Western Europe and Japan, where intensive farming systems encouraged by internal price supports and external trade protection result in heavy applications per hectare. For example, average application rates in Western Europe are 7.3 kilograms of active ingredients per hectare, almost four times the world average of 1.9 kilograms. In weight of active ingredients, only 55 percent of the market was in developed regions. The difference arises because the advanced countries tend to buy more sophisticated and expensive products that operate more selectively at lower application rates. Most such products are still under patent protection and sell at considerably higher prices per kilogram than older broad-spectrum pesticides, many of which have gone off patent protection and have been banned or withdrawn from developed markets.

However, many of these older products are still produced and sold in developing country markets, either by domestic companies or by some multinationals acting through subsidiaries or joint ventures. These include DDT and other persistent organochlorine insecticides, which represent about 15 percent of the value of insecticide sales in regions outside of the United States, Western Europe and Japan (Wood MacKenzie, 1994a). Organochlorine pesticides' tonnage share is even greater, though it has been declining substantially. Approximately 70,000 to 80,000 tons of these compounds were applied in developing and formerly socialist countries in 1995, including public health and veterinary uses. The older and more toxic organophosphate and carbamate insecticides and herbicides also have very significant sales. Such products are sold in developing countries on a commodity basis with relatively little product support.

The key point from a public health perspective is that pesticides of toxicological concern, many long banned in the U.S. and elsewhere, are sold in large volumes in developing country markets. Although different information sources on country-by-country usage don't always agree, products under strict regulatory restriction, bans, or voluntary withdrawal in advanced countries but

still widely sold and used in the Third World include alachlor, aldicarb, benomyl, captan, carbofuran, chlordane, cyanazine, DDT, dimethoate, endosulfan, EPN, mancozeb, lindane, monocrotophos, paraquat, parathion, toxaphene, and zineb. Many other widely used pesticides are under special regulatory review on health grounds in the United States, including the carbamates aldicarb (Temik), and carbaryl (Sevin), the herbicides alachlor (Lasso), atrazine, glyphosate (Roundup), and 2,4-D, and the organophosphate insecticides dichlorvos, malathion, and phorate. Although these pesticides have been reviewed for a range of acute and chronic toxicities, including possible risks of cancer and birth defects, they have not been reviewed in regulatory proceedings for potential toxicity to the immune system.

Although many pesticides have been reviewed for a range of acute and chronic toxicities, including possible risks of cancer and birth defects, they have not been reviewed in regulatory proceedings for potential toxicity to the immune system.

Global Patterns

In dollar terms, global pesticide sales increased by 11.2 percent annually between 1960 and 1992 but part of this increase represents inflation and a shift toward more expensive products. Sales growth decelerated during the 1980s and stagnated in the early 1990s because of recession or slow growth in OECD countries and the collapse of markets in Central Europe and the former Soviet Union. Although markets in these transitional economies will recover, sales volume is expected at best to stagnate in the United States, Japan, and Western Europe, and will decline substantially if agricultural protectionism is phased out. Sales value may still grow as older products are replaced with more sophisticated, expensive, and sometimes less toxic ones.

Most of the growth in the world pesticide market is in the developing countries. In value terms, growth between 1987 and 1993 in Latin America and Asia (outside Japan) was more than twice the world average. Corrected for inflation and exchange rate changes, growth in large developing country markets, including China, Brazil, Mexico, and India, is expected to range from 2.5 to 3.5 percent per year through 1998, two to three times the world average (Wood MacKenzie, 1994b). The commercialization and intensification of agriculture, the difficulty in expanding cropped acreage, the growth in demand for agricultural products as consumer incomes rise, and the shift to cash crops for domestic and export sales will all stimulate pesticide use. Growth is fastest in South and East Asia, followed by Latin America. Local production has increased substantially in the larger developing countries, such as Brazil, Mexico, China, and India. Major multinationals are increasing their presence in these expanding markets as barriers to direct foreign investment fall, and are introducing higher valued products in competition or partnership with domestic firms.

In densely populated Asian and Central American developing countries, insecticides account for a much greater share of the total pesticide market than in developed markets and transitional economies, where herbicides are equally important. Where typical farms are small and labor costs are low, weeding is done by hand. In the United States and Europe, by contrast, hand weeding is unheard of and rising energy costs have prompted a shift from mechanical tillage to chemical weed control.

Globally, organophosphates account for nearly 40 percent of total insecticide sales by value, followed by carbamates (20.4 percent), pyrethroids (18.4 percent), and organochlorines (6.1 percent). However, organochlorines are used almost en-

tirely in developing and transitional economies, partly for public health vector control and animal health programs. However, these compounds also have agricultural uses on cotton, maize, and other crops—either alone or in mixtures (Wood MacKenzie, 1994a). Fruits and vegetables, cotton, and rice are the crops that are sprayed most intensively.

Latin America

Pesticide use in Latin America is expected to nearly triple by the year 2000, compared to use in 1980. Most of the increase is occurring in Brazil, the region's largest country, although the intensity of pesticide use is far greater in smaller countries, including Costa Rica, Belize, and Panama (Dinham, 1994; McConnell, 1993a). Testifying before a U.S. Senate panel, a researcher at the Pesticides Program at the National University School of Environmental Sciences in Costa Rica, called pesticide use in Central America "intensive, extensive, and thoroughly out of control" (Wesseling, 1991).

From 1984 to 1994, the U.S. Food and Drug Administration (FDA) detained shipments of fruits and vegetables from Guatemala worth nearly $18 million because of excessive pesticide residue levels.

The Pan American Health Organization (PAHO) uses figures for pesticide consumption (in kg) per agricultural worker as an indicator of the intensity of pesticide use in nine Latin American countries. By this measure, intensity was highest in Costa Rica, which used 14.0 kg/worker/year. Next, in order, were Panama (10.0), Colombia (6.0), Mexico (4.5), Ecuador (2.5), El Salvador (2.5), Brazil (2.3), Honduras (2.1), and Guatemala (1.7) (McConnell, 1993a). Though Guatemala was the least intensive user in this group, other evidence nonetheless suggests serious overuse and exposure problems. From 1984 to 1994, the U.S. Food and Drug Administration (FDA) detained shipments of fruits and vegetables from Guatemala worth nearly $18 million because of excessive pesticide residue levels. In 1993 alone, these detentions were eight times those that Mexican produce—the next highest—incurred for that year, even though Mexican exports of fruits and vegetables to the United States are far greater than Guatemala's (Thrupp, 1995).

The Brazilian agrochemical market has been growing at an average of 5 percent per year since 1983, despite macroeconomic difficulties. Structural adjustment is expected to increase agricultural exports and pesticide use in future years. At this point, most of the acreage of major crops (soybeans, maize, coffee, and wheat) is still not treated. There are already at least 50 pesticide manufacturers and formulators operating in Brazil, including most of the major multinationals. According to one information source, "The major insecticides used are commodities, such as toxaphene, DDT, carbaryl, malathion, monocrotophos, etc., although the pyrethroids are making substantial inroads.... Organophosphorus compounds still dominate with over 40% share" (Wood MacKenzie, 1994b, 47). Other common insecticides are endosulfan, chlorpyrifos, carbofuran, aldicarb, parathion and other organophosphates. Herbicides include atrazine, 2,4-D, glysophate, trifuralin, and others.

In Mexico, the major crop uses are on fruits and vegetables for export, followed by maize, sugarcane, cotton, and potatoes. NAFTA will increase agrichemical use on export crops. Organophosphates such as methamidophos and methyl parathion dominate the insecticide market, though DDT, endrin and BHC are still produced, carbofuran and other carbamates are important and use of pyrethroids has increased. Herbicides used include atrazine, 2,4-D, glysophate and paraquat. All the major multinationals have market share.

Table 1. Pesticide Use Per Cropped Hectare

Country	Year	Metric Tons (MT)	Hectares ('000 Ha)	Intensity (Kg/Ha)
Latin America				
Belize	1992	993	57	17.40
Brazil	1990	67,000	61,350	1.10
Chile	1991	8,300	4,384	1.90
Colombia	1989	19,967	5,430	3.70
Costa Rica	1991	9,560	529	18.00
Ecuador	1990	6,200	2,750	2.30
Honduras	1992	8,147	1,855	4.40
Mexico	1989	48,000	24,720	1.90
Paraguay	1992	15,887	2,270	7.00
Suriname	1991	557	68	8.10
Trinidad & Tobago	1989	1,601	120	13.30
Asia				
Bangladesh	1989	4,500	9,137	0.50
China	1991	300,000	96,554	3.10
Hong Kong	1992	80	7	11.40
India	1991	72,094	169,500	0.40
Iran	1991	25,915	18,170	1.40
Jordan	1989	1,195	391	3.10
Malaysia	1992	44,721	4,880	9.20
Mongolia	1989	48	1,375	0.03
Myanmar	1992	357	10,039	0.04
Pakistan	1992	5,517	21,110	0.26
Papua New Guinea	1988	1,367	388	3.50
South Korea	1989	20,000	2,010	10.00
Sri Lanka	1992	4,633	1,903	2.40

Asia

Most of the major agrochemical companies have targeted the fast-growing Asian pesticide market for their expansion plans. Together, the Asian nations produce 90 percent of the world's rice crop, which alone uses about 14 percent of the world's pesticide output (Dinham, 1994). Farming is intensive and typical farm sizes are tiny because agricultural land is extremely scarce in most Asian countries. Land is cropped two or three times per year wherever water conditions allow. Chemicals and other inputs are applied heavily to push up yields. After Japan, China and India are the largest users. Despite substantial research in China on biological pest control methods, over 100 million hectares of Chinese cropland—mostly planted to rice, fruits and vegetables, cotton, and wheat—are sprayed, typically with hand sprayers (Landell Mills, 1994a). China's production of pesticides more than doubled over the past decade to nearly 300,000 tons per year of active ingredients, including a range of organophosphate and pyrethroid insecticides.

Country	Year	Metric Tons (MT)	Hectares ('000 Ha)	Intensity (Kg/Ha)
Thailand	1990	23,160	29,000	0.80
Turkey	1990	17,618	27,689	0.60
Africa				
Angola	1987	518	3,450	0.01
Benin	1989	85	1,860	0.05
Botswana	1992	17	1,164	0.01
Burundi	1992	4,047	1,350	3.00
Cameroon	1992	1,700	7,020	0.24
Chad	1992	724	3,256	0.22
Congo	1989	5	168	0.03
Cote d'Ivoire	1992	5,330	3,690	1.40
Egypt	1992	5,548	2,600	2.10
Gambia	1993	100	180	0.56
Kenya	1992	2,032	2,440	0.83
Madagascar	1992	500	3,102	0.16
Mali	1992	295	2,203	0.13
Mauritius	1990	1	106	0.01
Morocco	1990	93,940	9,503	9.90
Mozambique	1988	262	3,130	0.08
Rwanda	1992	221	1,170	0.19
Seychelles	1991	9	7	1.30
Tanzania	1989	14,100	3,370	4.20
Togo	1987	1,700	669	2.50
Zaire	1991	1,075	7,880	0.14
Zambia	1989	1,700	5,268	0.32
Zimbabwe	1992	2,424	2,814	0.86

India has more than 20 local producers, including joint ventures with leading multinationals. Insecticides comprise two-thirds of the total pesticide market, and more than half of the total volume is used on rice and cotton. Installed production capacity in India is greatest for the organochlorines lindane and other BHC isomers (45,000 tons/yr), DDT (9,000 tons/yr), endosulfan (4,000 tons/yr), the organophosphates monocrotophos (2,500 tons/yr), malathion (10,000 tons/yr), parathion (2,700 tons/yr), dimethoate (2,000 tons/yr) and a carbamate product, carbaryl (2,000 tons/yr). Pyrethroids expanded their market share rapidly until resistance problems emerged some years ago. Major herbicide products include butachlor, 2,4-D, paraquat, and atrazine.

Central Europe and the Former Soviet Union

Economic disruption and decline during the 1990s has depressed pesticide use considerably in this region. The collapse of intra-regional trade,

the break-up of state farms, and sharp reductions in consumer purchasing power reduced agricultural demand. At the same time, state-owned pesticide plants, which dominated production, faced marketing and financial constraints and imports were curtailed by foreign exchange shortages. Thus, pesticide use in the states of the former Soviet Union in 1994 was only one-third as much as in the USSR in 1990. Sharp declines were also experienced in Eastern Europe, especially in Hungary, Rumania and Bulgaria.

Nonetheless, even in 1994, the region was a major consumer of pesticides. Roughly 80,000 tons of active ingredients were applied, about evenly divided between the countries of Central Europe and those of the former Soviet Union. Herbicides—used mostly on cereals—represent the largest share of the pesticide market (Landell Mills, 1994b). Phenoxy herbicides (2,4-D), triazine herbicides (atrazine) and acetanilide products (alachlor, metolachlor) are widely used. Copper compounds and sulfur are used in large volumes to control fungi and mites. Organophosphate and carbamate insecticides such as dimethoate and carbofuran predominate. In the former Soviet Union, over two-thirds of all pesticides are used on the cotton crop, which occupies less than 3 percent of total cultivated acreage.

Africa

Pesticide use in Africa is the lowest overall of all continents because poverty, instability, unreliable rains, and indifferent soils have kept smallholder agriculture from modernizing in much of the region. However, there are areas of intensive pesticide use—across North Africa, for example. The cotton-growing regions of Sudan, Egypt, and Cote d'Ivoire are also heavy pesticide users. Large-scale commercial farms and plantations producing coffee and other export crops in South Africa, Zimbabwe, and Kenya are also chemical-intensive. Structural adjustment in response to the debt problems of the 1980s has markedly increased export crop production, the major pesticide user. Cotton acreage in Africa doubled between 1983 and 1993, for example. According to one report, "many of the organochloride pesticides, such as DDT, toxaphene, lindane, chlordane, and heptachlor, which have been banned or whose use has been severely restricted in Europe and North America, are still marketed and used in Africa and much of the developing world" (Szmedra, 1994, 7). Data for Egypt suggest that organophosphates and carbamates dominate insecticide use there, primarily on cotton. In South Africa, another major consumer, such herbicides as atrazine, glyphosate, alachlor, and 2,4-D have relatively large sales volume.

Pesticide Application Rates

Aggregate consumption data are presented in Table 1 for 57 countries, collected from FAO and other sources (Dinham, 1994, 1993; FAO, 1994; Szmedra, 1994; WRI, 1994; PAN, 1989).

Costa Rica (18.0 MT/1,000 Ha), Belize (17.4), South Korea (10.0), Morocco (9.9), and Malaysia (9.2) are among the most intensive pesticide users but, even in countries where per hectare application rates are lower, persistent or hazardous pesticides, unsafe practices, or geographically concentrated patterns of use can create significant exposure risks for large populations. The overall picture emerges of heavy and growing use of highly risky pesticide products in large parts of the developing world.

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.

Hundreds of millions of people are exposed significantly to pesticides each year.

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.

A study of farm children in Nicaragua demonstrated that nearly 40 percent of them had significantly depressed cholinesterase activity.

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

between school and farmwork exhibited cholinesterase levels reduced by 20 percent or more (Henao, 1990). Similar cholinesterase reductions were identified for 33 percent of Nicaraguan farm children and 10 percent of Honduran neighbors of rice fields that were sprayed from the air (McConnell, 1990; Honduras, 1982). In Bolivia, nearly 10 percent of workers who demonstrated reduced cholinesterase activity were under 18 years of age (Bolivia, 1990). In Costa Rica, it was one in five, although it is illegal for people under 18 to handle pesticides (Wesseling, 1990).

A PAHO review found that occupational pesticide poisonings among children under 18 years of age accounted for roughly 10 to 20 percent of all poisonings (Henao, 1993). In the Philippines, children accounted for nearly one in eight poisonings (Rola, 1993). In Sri Lanka, children less than 10 years of age are predominant in accidental poisoning cases (Utsch, 1991). In the Department of Antioquia in Colombia, nearly one in five poisonings were recorded in children under 14 years of age (Nieto, 1990). Similar conditions were found in Nicaragua (McConnell, 1993b). Thus, biological indicators and symptoms show that not only farmworkers but also their families and children are exposed.

In California, children of migrant farmworkers living near sprayed fields experienced depressed cholinesterase activity and symptoms of acute pesticide exposure. Nearly one in five of these children had below-normal cholinesterase levels, even though they had not worked in the fields. Of the children who did fieldwork, 40 percent had abnormally low levels. "Observations indicated that toxic effects were associated with residential exposures to residues in drift" (Richter, 1992, 627).

Bioaccumulated Pesticide Products

The general population tends to have only low-dose, chronic exposures to pesticides but nonetheless may receive much larger doses if exposed to pesticides that are persistent and bioaccumulate. Groups within the general population that can be exposed to high levels of bioaccumulated pesticides include 1) habitual consumers of fish, livestock, and dairy products, 2) fetuses and nursing infants whose mothers' bodies have accumulated substantial levels of persistent pesticides, and 3) sick people who metabolize pesticide-bioaccumulated fatty tissues while ill.

The general population can be exposed to pesticides in three general ways: 1) vector control for public health and other non-agricultural purposes, 2) environmental residues, and 3) food residues. People are often exposed through spraying for vector control. Organochlorines, such as DDT, are still used in malaria control and other public health programs in many countries. A study in KwaZulu, South Africa found significantly elevated levels of DDT and metabolites in blood serum of people living in DDT-treated households. In small children the primary route seemed to be through breast milk (Bouwman, 1994). In Brazil, households sprayed with HCH against Chagas Disease had an order of magnitude higher serum content than did controls (Lara, 1987).

Roughly 85–90 percent of pesticides applied agriculturally never reach target organisms, but disperse through the air, soil and water.

Persistent pesticides move through air, soil, and water, finding their way into living tissues where they can bioaccumulate up the food chain into human diets. Roughly 85–90 percent of pesticides applied agriculturally never reach target organisms, but disperse through the air, soil and water (Moses, 1993). Although many organic pesticides quickly degrade in the environment, most organochlorine and metal-containing pesticides do not. The half-life of toxaphene in soil, for

example, is up to 29 years (PAN, 1993). From soils, persistent pesticide residues can be taken up by plants and then by herbivores. High levels of persistent pesticide contaminants have been found in animal dairy products—in Kazakstan, for example, where pesticides have been heavily misused, and in the La Laguna Region of Mexico, where DDT residues in cows milk averaged 2.56 ug/g, well above standard tolerances (Lederman, 1993; Albert, 1990). In the Soconusco region of the State of Chiapas, Mexico and the Argentine cities of Santa Fe and Rosario, most butter and cheese samples contained pesticide residues (Lenardon, 1994; Albert, 1988).

Pesticides that are not bound in soils or taken up into plants and animals can drain into rivers and lakes and move into the aquatic food chain. Chlorinated pesticides have been detected in rivers in Tanzania, Colombia, Indonesia, Malaysia, China, and Thailand at levels suggesting "potentially severe damage" (Egboka, 1989; Meybeck, 1989, 189.) In Asia's densely populated rice growing areas, ecological bioaccumulation can be quite rapid since farmers commonly stock their flooded paddies with small fish and harvest them when the paddies are drained. In Malaysia, where this combined fish/rice culture is common, fish exposed to organochlorine pesticides in the paddies for only six months contained high levels of these bioaccumulated compounds (Meier, 1983).

Some volatile pesticides also reach the upper atmosphere and are carried hundreds or thousands of miles by the wind, only to fall into bodies of water and enter the aquatic food chain. Reports of this long range atmospheric transport come from North America, Asia, Africa, Oceania, Europe, and Siberia and the levels of organochlorines in the aquatic environment correlate strongly with levels of use in neighboring lands (Iwata, 1995, 1993).

In Michigan, people historically consuming more than 24 pounds of fish annually from the highly polluted Great Lakes showed DDT blood levels nearly 2.3 times that of a control group, even though the pesticide was banned in the United States decades ago (Hovinga, 1993). Other studies from the Great Lakes region corroborate these findings (Asplund, 1994; Fiore, 1989; Davies, 1988; Hallet, 1988).

A PAHO review of studies in Latin American countries concludes that "the pattern of the residues found [in human body tissues] is similar: high frequencies and levels of DDT and its metabolites, followed by BHCH, dieldrin, heptachlor epoxide and hexachlorobenzene" (Henao, 1993, 46). Another review found high concentrations of these organochlorines in people's body tissues in 22 Third World and formerly socialist countries (Kaloyanova, 1991a).

Many organic and metal-based pesticides can also pass from mother to unborn child through the placenta, potentially leading to birth defects, abnormal development of the immune system, and fetal death.

People bioaccumulate most organochlorine and metal-containing pesticides in their fat, where they tend to stay unless the fat is metabolized for energy—during bouts of illness, for example. Then, the contaminants may become bioavailable. Many organic and metal-based pesticides can also pass from mother to unborn child through the placenta, potentially leading to birth defects, abnormal development of the immune system, and fetal death (Sesline, 1994; Slikker, 1994).

Since dermal exposure is the main exposure route for farmworkers, pregnant women who continue to work in fields sprayed with pesticides may run an increased risk of exposing their unborn children. In developing countries, most pregnant women work until the onset of labor. Prenatal exposure via the mother is measurable

in newborn infants. Blood serum DDT levels of newborn babies in São Paulo, Brazil averaged 14 ug/l, nearly half the average concentration in their mothers' bodies (Procianoy, 1981).

Infants are at great risk from pesticides in breast milk because their intake relative to bodyweight is so high.

Infants are at great risk from pesticides in breast milk because their intake relative to bodyweight is so high. Infants and children also metabolize many of these chemicals more slowly than adults do. Consequently, strong positive correlations are found between organochlorine levels in breast milk and in the blood of infants who breastfeed (Bouwman, 1993).

A 1991 study in Delhi, India found DDT and HCH residues in urban water, soil, and fauna. Even though DDT use had been banned for agricultural uses earlier, human breast milk samples showed DDT and HCH levels had not declined substantially over the past decade, and were comparable to levels found in the Punjab, an area of intensive farming. Infants ingesting such breast milk received roughly 12 times the allowable daily intake of DDT (Nair, 1992).

After a systematic review of data from Latin America, PAHO's Center for Human Ecology and Health concluded that "levels of organochlorine compounds, particularly DDT, in mother's milk are high, and frequently above appropriate guideline limits" (Henao, 1993, 45). Another thorough review of the global literature concluded that "the levels of these pesticides are now mostly much higher in human milk from developing countries than in that from industrialized countries" and "the persistent organohalogens seem to constitute the largest potential health problem" (Jensen, 1991, 184).

Studies of mothers' milk in Thailand, India, Turkey, and Kenya also demonstrated pesticide residues above recommended levels (Prapamontol, 1992; Jani, 1988; Karakaya, 1987; Kanja, 1986). More recent studies have detected high levels of DDT, dieldrin, and other organochlorines in human milk studies of Mexico, Colombia, Uruguay, and to a lesser extent in Costa Rica (Vargas, 1990; Viveros, 1990; Wesseling, 1990; Burger, 1987). Children continue to be exposed to organochlorine pesticides in developing countries, where these compounds are still produced and used. Fortunately, declines in use lead to decreased breast milk residues. In Guatemala, after DDT use was prohibited in 1979, breast milk residues decreased four-fold from 12.2 ppm in 1971 to 3.37 ppm in 1982 (De Campos, 1987).

Pesticide residues on foods create an important—though under-reported—exposure route for the general population in most developing countries. Episodes of mass pesticide poisonings often point to ingredients, such as seeds, flour, sugar, oils and wheat contaminated with pesticides in storage or transport (WHO, 1990). These dramatic incidents suggest that less extreme contamination of foodstuffs with pesticides is a more widespread risk.

Food standards in developing countries are typically neither as stringent nor as well enforced as those in the industrialized world, and pesticide residues are often found on agricultural products. Residues of DDT, endrin, lindane, and others were found on 25 to 88 percent of the food samples from the cities of Alexandria, Behera, Gharbia, Dakahlia, and others (Abdel-Gawaad, 1990). In Brazil, 13.6 percent of fruits and 3.7 percent of vegetables exceeded tolerance limits (Henao, 1993). Vegetables in town and city markets in the Philippines in 1985 showed the presence of DDT, aldrin, dieldrin, chlordane, heptachlor and other organochlorines, even though these compounds were sanctioned only for use against termites and not on food crops (Rola, 1989). Significant food residues have been found in many other countries, including Tunisia, Venezuela, and India (Dinham, 1993).

Conclusion

Taken as a whole the wide range and variety of evidence compiled here shows that exposure to pesticides with known human toxicity continues to be widespread and heavy in many countries around the world, among farmworkers and their families and the general population. Direct observations and biological measurements bear this out. Infants and children are among those subject to significant exposure.

IV. The Experimental and Wildlife Evidence

Experimental Studies

Experimental studies on human cell cultures and laboratory animals provide strong evidence that many pesticides are immunotoxic. Such studies form part of all recommended batteries of tests used to evaluate chemicals for immunotoxicity. Test-tube (*in vitro*) studies employ tissues, cells, or cell components outside the body, making experiments easy to control and carry out. Researchers can isolate cells of interest (such as human immune cells), control exposures to the chemicals being studied, and analyze any effects carefully. However, *in vitro* experiments act on cell materials that are far simpler than living organisms, and so may give results that differ from those of actual exposures.

Experimental animal (*in vivo*) studies are also used extensively in toxicological research, because chemicals that are toxic to humans are usually toxic to other mammalian species. All mammalial (and avian and fish) immune systems are structurally similar (Turner, 1994). Humoral, cell-mediated, and non-specific immune responses are remarkably similar in humans and the rodent species used experimentally, and considerable evidence shows that animal models are valid for testing human immunotoxicity. For example, the immunosuppressive drug cyclosporin A, used in graft surgery and organ transplantation, has been found to have similar toxicological and immunosuppressive properties in a wide variety of mammalian species, including rats, mice, monkeys and humans (Dean, 1987). Canadian studies of the effects of heavy metals (including metal-based pesticides) on immune systems in several species, including earthworm, trout, mouse, rat, beluga whales, swine, calf, and humans, found that the effects were the same in all species; only the sensitivities differed (Fournier, 1995a, 1995b). The U.S. National Research Council Committee on Immunotoxicology has "accepted that the immune systems of many animals and humans are comparable; that animal models are available to assess immune dysfunction objectively; that positive immunosuppressants, such as cyclophosphamide and cyclosporin A, are used to validate assays; and that data obtained from animal studies can sometimes be verified in humans" (NRC, 1992, 3).

Nonetheless, the usefulness of tests on lab animals to predict human health impacts is still debated. Skeptics claim that the high doses administered to lab animals to detect effects in relatively small samples lead to many false positive results, and that extrapolating toxicity from these high doses to the much smaller doses to which humans are exposed is unreliable. To be sure, the high doses often administered to experimental animals can suppress immune parameters simply through toxic stress, and even if laboratory studies do measure some immune suppression, humans subject to similar exposures may not show clinical symptoms, since normal immune systems have overlapping defenses against attack (Botham, 1990).

On the other hand, the laboratory evidence of pesticide-induced immunotoxicity may underestimate actual risks precisely because the test

Box 1. How the Immune System Defends the Body

The immune system is essential to health and survival. It defends the body against pathogens and cancers through a complex interaction of white blood cells and blood serum molecules. Three distinct immunity mechanisms work in concert to recognize and eliminate bacteria, fungi, viruses, parasites, and cancer cells. These three branches generate a quick **primary response** to an invader as well as a more vigorous **secondary response**, should the invader reappear even months or years later.

One mechanism, **non-specific immunity,** involves *macrophages, neutrophils* and *natural killer cells* that roam the body on the lookout for new intruders. When encountering foreign or cancerous cells, macrophages and neutrophils ingest and destroy them in a process called phagocytosis; natural killer cells punch holes in them.

Another mechanism, **humoral immunity**, involves *B cells, antibody* proteins, and *complement* proteins. Produced by B cells, antibodies can bind to portions of foreign cells called *antigens*. Because B cells genes are readily rearranged, billions of distinct antibodies are present at any time in the body to protect against the almost infinite variety of antigens on invaders. When bound to antigens, antibodies neutralize foreign cells by activating scavenger cells or complement proteins that kill the foreign cells.

The third mechanism, **cell-mediated immunity**, involves another class of white blood cells called *T cells*, which also have receptors that can bind to antigens. Macrophages and B cells encounter and attack foreign invaders, process antigens from these invaders and present them for inspection to T cell receptors in a process called *antigen presentation*. After T cell receptors bind to the antigen, specialized *helper-T cells* secrete *lymphokines*, chemical messengers that travel to the foreign organism and induce nearby macrophages to kill it through a process called *delayed-type hypersensitivity*. In addition to cell-mediated immunity, these lymphokines affect humoral immunity by inducing B cells to produce large numbers of antibodies directed against the foreign organism. Helper-T cells assist B cells and macrophages in killing bacteria, fungi, and parasites.

Another cell-mediated immunity mechanism that works against viruses involves *cytotoxic-T cells*, another kind of T cell. Viruses typically penetrate inside human cells and can use the cell's own genetic mechanisms to reproduce. Fortunately, human cells can present viral antigens to T cell receptors. When this happens, cytotoxic-T cells kill the virally infected cell, keeping the infection from spreading. *Suppressor-T cells*, another class of T cell structurally similar to cytotoxic-T cells, help prevent excessive processes of cell-mediated immunity, which could kill off too many of the body's own cells. Cytotoxic and suppressor-T cells are also known as *effector-T cells*, because they directly bring about the destruction of compromised cells.

animals used are typically healthy young male adults fed carefully selected and nutritious diets (Olson, 1986a). In real populations, whether animal or human, the individuals most likely to suffer health consequences are those whose immune systems are weak because they are very young, aged, pregnant, sick, or malnourished (Luster, 1993a; NRC, 1993; IPCS, 1986).

Experimental animal and test tube studies have generated much evidence of pesticide-induced immunotoxicity. Hundreds of studies have found that pesticides can induce changes in immune system structure and function, and these changes correlate closely in experimental animals with altered host resistance to pathogens (Vos, 1994).

The laboratory evidence of pesticide-induced immunotoxicity may underestimate actual risks precisely because the test animals used are typically healthy young male adults fed carefully selected and nutritious diets.

Recently, the well recognized textbook, *Immunotoxicology and Immunopharmacology*, reviewed and summarized over 100 primary experimental studies of the immunosuppressive nature of many classes of pesticides, including organochlorines, organophosphates, carbamates, and metal-based pesticides. Some studies show activation of particular immune system mechanisms, but the large majority shows various immunosuppressive effects (Barnett, 1994).

The review concludes that, among the organochlorines, aldrin and dieldrin reduce mouse resistance to viral infection through effects on macrophages, possibly including both their ability to kill infected cells and their ability to present viral antigen for specific humoral and cell-mediated immune responses. Chlordane and heptachlor have been found to affect the developing immune system, depressing the proliferation of immune system parent cells. They also retard the activation of macrophages and reduce humoral and cell-mediated immune functions *in vitro*. Lindane, BHC, and similar compounds also affect macrophage activity *in vitro*. In experiments *in vivo*, animals fed lindane-spiked diets were unable to resist a giardia infection while all control animals eliminated it. Some evidence of a non-monotonic immunotoxic effect at low and high exposure levels was found, though the evidence is ambiguous. There have been fewer studies of DDT's immunotoxic effects, because in OECD countries DDT has been banned from most uses for other reasons, but dose-dependent reductions in antibody production have been found in tested mammals and bird species (Barnett, 1994).

Among the organophosphorus and carbamate pesticides, malathion disregulates the immune system, especially affecting non-specific immune mechanisms. Chronic exposure at low doses over prolonged periods can also depress humoral immune responses. Parathion, a more acutely toxic compound, suppresses T-cell proliferative response and blocks both humoral and cell-mediated immune responses *in vitro*. It has also been shown to reduce host resistance to viral and bacterial infection in live animals (Barnett, 1994).

According to another recent review of organophosphate and carbamate immunotoxicity in *Clinical Immunotoxicology*, "there is increasing evidence that organophosphorus compounds exert immunosuppressive effects on human as well as animal cell systems" (Newcombe, 1992a, 359). Parathion has been found to reduce and delay production of antibodies to a previously unrecognized antigen. Other organophosphates also impair antigen presentation by macrophages. Other organophosphate pesticides, such as triphenylphosphate, suppress natural killer cell activity. OOS-TMP, an impurity formed in OP pesticides, has several immunotoxic effects, including suppression of antibody and cytotoxic-T cell production and a reduction in antigen presentation by macrophages. Research suggests that reduced antigen presentation and cytotoxic-T cell activity occur because organophosphates bind to essential enzymes on the immune cell, inhibiting their activity (Newcombe, 1992a).

Other reviews of the experimental literature from North America, Western Europe, and the former Soviet Union conclude that pesticides of many chemical classes are immunosuppressive in most laboratory animals (Rodgers, 1995, 1992; Holliday, 1994; Burrell, 1992a; Murray, 1992; Pruett, 1992a; Saboori, 1992; Sharma, 1992, 1978; Dayan, 1990; Descotes, 1988; Nikolaev, 1988; Thomas, 1988; Exon, 1987; Olson, 1986a; Smialowicz, 1984; Street, 1981; Dandliker, 1979; Ercegovich, 1973). Besides the pesticides mentioned above, many pesticide solvents, inert ingredients, and contaminants cause

measurable immunosuppression in several species (Kerkvliet, 1994a, 1994b; Synder, 1994; Tryphonas, 1994; Vos, 1991).

Researchers in developing countries have also conducted and reviewed experimental studies of pesticide immunotoxicity. A group of toxicologists in India concluded that pesticides may render "people more prone to new or existing diseases by causing immunosuppression" (Bhatia, 1993, 61). Nearly identical observations were made by researchers in other developing countries, including Brazil and China (Gao, 1990; Queiroz, 1986).

Two-Tiered Immunotoxicological Testing

These review articles, based on hundreds of primary studies, state clearly that many pesticides have statistically significant effects on the immune system, but interpreting these effects is more difficult. It is unclear whether any single immunological change has potential health consequences in humans. To help resolve this issue, the U.S. National Institute of Environmental Health Sciences recommended that immunotoxicologists use a two-tiered battery of experimental tests (Luster, 1995, 1993b, 1992, 1988). Tier 1 tests assess changes in sensitive immune parameters. If such changes are found—or if other evidence suggests immunotoxicity, Tier 2 tests can be used to measure functional changes more fully. Tests in each Tier examine humoral, cellular, and nonspecific components of immunity.

This tiered testing system provides a cascade of evidence. Substances that show immunotoxicity in tests from the second tier are almost always toxic in some tests from the first tier. Of course, exposure conditions, such as the level, duration, timing, frequency, and the pathway of the dose, may influence test outcomes. For example, baby mice fed hexachlorohexane showed heightened cell-mediated immunity, but adult mice fed the equivalent dose had diminished cell-mediated immunity (Meera, 1992). Live mice and mouse

Table 2. Two Tiered Testing Protocol

	Immune Parameter	Test
T	• Immunopathology	• Pathology of Immune Organs
I		• Complete Blood Counts
E	• Humoral Immunity	• B Lymphoproliferative Response
R		• Antibody Levels
	• Cell-Mediated Immunity	• T Lymphoproliferative Response
1	• Non-Specific Immunity	• Macrophage Activity
T	• Immunopathology	• Differential Blood Counts
I	• Humoral Immunity	• Secondary Antibody Responses
E	• Cell-Mediated Immunity	• Delayed Hypersensitivity
R		• T Cell Cytosis
	• Non-Specific Immunity	• Phagocytosis
2	• Host Resistance Models	• Bacterial Challenge
		• Parasite Challenge
		• Viral Challenge
		• Tumor Challenge

cells *in vitro* showed increased and decreased cell-mediated immunity respectively when exposed to chlordane (Johnson, 1987, 1986). Nonetheless, as Table 3 and Table 4 make clear, many experimental studies provide substantial evidence that many pesticides induce immunosuppression, according to each set of tests in both Tier 1 and Tier 2 of the protocol.

The first screen measures pathological changes in immune system organs, including the thymus, where most lymphocytes mature. Baby mice whose thymuses are surgically removed have fewer circulating mature T cells and weakened immunity. Although its importance declines with age, abnormalities in thymic weight or structure suggest pesticide immunotoxicity (Kendall, 1991). Another immune organ, the spleen, serves as a biological sieve where macrophages mature and interact with T and B cells. Tests for pesticide-induced abnormalities in spleen weight indicate effects on macrophage development, antibody presentation, and cell-mediated immunity.

Pesticides can also undermine immunity by disrupting the process by which B cells produce antibodies. Normally, specific B cells proliferate in response to an antigen, but tests to measure this response show that pesticide exposure can reduce B cell proliferation and primary antibody response.

Cell-mediated responses are normally based on interactions between T cells, B cells, and macrophages. The Tier 1 tests for cell-mediated immunity measures the critical capacity of T cells to proliferate in response to a foreign agent (called T cell proliferative response). Experiments have shown that pesticide exposure can reduce T cell proliferative response and cell-mediated immunity.

Non-specific immunity, dependent on natural killer cells, neutrophils and macrophages, can respond to and destroy foreign organisms. Various tests measure non-specific immune cell activity, including their ability to mobilize in response to a foreign agent in a process called chemotaxis. Macrophages normally ingest and destroy bacteria, viruses, tumor cells and harmful particles through a process called phagocytosis. Tier 2 tests have also recorded decreases in chemotaxis and phagocytosis after pesticide exposure.

Tier 2 tests have also found that pesticides alter the absolute numbers and proportions of white blood cells and lymphocytes. Key tests in this battery also measure the secondary antibody response by first injecting a foreign agent into a live creature, allowing the immune response to develop, and then re-injecting the same agent to see how quickly antibodies are generated. This is analogous to testing whether vaccination would effectively protect a human subject. Pesticides can reduce the production of antibodies necessary for this secondary response.

Tier 2 tests also measure hypersensitivity, a process in which various immune system components, including macrophages, and T and B cells, work together to destroy invading agents and create an immunologic memory to ward off future attacks. Pesticides have been found to suppress hypersensitivity reactions.

Studies have shown that pesticide exposure significantly reduces resistance to bacterial, viral, and parasitic infections and promotes tumor growth in many animal species.

In host resistance tests, in experimental research, laboratory animals are injected with bacteria, viruses, parasites or tumor cells to see if chemical exposures alter the animals' ability to ward off infections (Bradley, 1995). In a sense the bottom line in experimental research, "host resistance models...offer endpoints that are clinically most relevant, and therefore useful for estimation of risk to man" (Van Loveren, 1995, 137). Such studies have shown that pesticide exposure significantly reduces resistance to bacterial, viral, and parasitic infections and promotes tumor growth in many animal species.

Table 3. Tier 1 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
IMMUNOPATHOLOGY				
Thymus Weight				
Organochlorines				
Chlordecone	Rat	Oral	↓	Smialowicz, 1985a
DDT	Rabbit	Oral	↓	Street, 1975
DDT	Chicken	Oral	↓	Rao, 1977
Pentachlorophenol	Cow	Oral	↓	McConnell, 1980
Organophosphates				
Diazinon	Rat	Oral	↓	Moon, 1986a
Dichlorvos	Rat	Oral	↑	Institoris, 1995a
Dimethoate	Mouse	Under Skin	↓	Tiefenbach, 1980
Dimethoate	Rat	Oral	↑	Institoris, 1995b
EPN	Rat	Oral	↓	Moon, 1986a
Fenitrothion	Rat	Oral	↓	Moon, 1986a
Fenthion	Rat	Oral	↓	Moon, 1986a
Methyl Parathion	Rat, Rabbit	Oral	↓	Institoris, 1995b; Street, 1975
Carbamates and Thiocarbamates				
Carbaryl	Fish	Oral, Dermal	↓	Walsh, 1975
Methyldithiocarbamate	Mouse	Oral	↓	Pruett, 1992b
Zineb	Rat	Oral	↓	Vos, 1983a
Metals and Minerals				
Mercuric Chloride	Mouse	Oral	↓	Dieter, 1983
Tributyltin	Chicken	Oral	↓	Socacio, 1985
Tributyltin Chloride	Rat	Oral	↓	Bress, 1991
Tributyltin Oxide	Rat	Oral	↓	Bress, 1991; Smialowicz, 1989
Tributyltin Oxide	Rat	Oral	↓ *	Krajnc, 1984
Other				
Atrazin	Rat	Oral	↓	Vos, 1983a
Atrazine	Fish	Oral, Dermal	↓	Walsh, 1975
Captan	Rat	Oral	↓	Vos, 1983a
Cycloheximide	Mouse	Under Skin	↓ *	Olson, 1983
Maleic Hydrazide	Mouse	Under Skin	↓	Olson, 1983

Table 3. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Spleen Weight				
Organochlorines				
Chlordecone	Rat	Oral	↓	Smialowicz, 1985a
DDT	Chicken	Oral	↓	Rao, 1977
DDT	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Dieldrin	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974; King, 1962
Endosulfan	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Trichloroethylene	Mouse, Rat	Oral	↓	Wright, 1991
Organophosphates				
Azinphos-Methyl	Rat	Oral	↓	Vos, 1983a
Dichlorvos	Mouse	Oral	↓	Casale, 1983
Dimethoate	Mouse	Under Skin	↓	Tiefenbach, 1980
Malathion	Mouse	Oral	↓	Casale, 1983
Parathion	Mouse	Oral	↓	Casale, 1983
Carbamates and Thiocarbamates				
Carbaryl	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Chlorpropham	Rat	Oral	↑	Vos, 1983a
Methyldithiocarbamate	Mouse	Oral	↑	Pruett, 1992b
Molinate	Mouse	Oral	↑	Smialowicz, 1985b
Metals and Minerals				
Mercuric Chloride	Mouse	Oral	↓	Dieter, 1983
Tributyltin Oxide	Rat	Oral	↓	Krajnc, 1984
Triphenyltin Chloride	Mouse	Oral	↓	Hiroyuki, 1990
Triphenyltin Hydroxide	Rat	Oral	↓	Vos, 1984a
Other				
2,4-D	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Atrazine	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Diuron	Rat	Oral	↑	Vos, 1983a
HUMORAL IMMUNITY				
B Cell Proliferative Response				
Organochlorines				
Trichloroethylene	Rat	In Vitro	↓	Wright, 1991
Organophosphates				
Malathion	Mouse	Oral	↑	Rodgers, 1986

Table 3. Tier 1 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Metals and Minerals				
Mercuric Chloride	Mouse	In Vitro	↓ *	Nakatsuru, 1985
Mercuric Chloride	Mouse	Oral	↑ *	Dieter, 1983
Tributyltin Oxide	Rat	Oral	↑	Vos, 1984b
Triphenyltin Hydroxide	Rat	Oral	↓	Vos, 1984a
Pyrethroids				
Allethrin	Mouse	In Vitro	↓	Stelzer, 1984
Cypermethrin	Mouse	In Vitro	↓	Stelzer, 1984
Fenpropathrin	Mouse	In Vitro	↓	Stelzer, 1984
Permethrin	Mouse	In Vitro	↓	Stelzer, 1984
Other				
2,4-D	Mouse	Dermal	↑	Blakely, 1986
Captan	Mouse	Oral	↓ *	Lafarge-Frayssinet, 1982
CELL-MEDIATED IMMUNITY				
T Cell Proliferative Response				
Organochlorines				
Chlordane	Mouse	In Vitro	↓	Johnson, 1987
Chlordane	Mouse	Oral	↑ *	Johnson, 1986
Chlordane	Mouse	Prenatal	↑	Barnett, 1985
Chlordecone	Rat	Oral	↓	Smialowicz, 1985a
Dieldrin	Mouse	Oral	↓	Loose, 1982
Endrin	Human	In Vitro	↓	Park, 1978
Hexachlorobenzene	Mouse	Oral	↓	Silkworth, 1980; Loose, 1978a
Hexachlorobenzene	Mouse	Prenatal	↓	Barnett, 1987
Lindane	Mouse	Oral	↓	Cornacoff, 1988
Lindane	Human	In Vitro	↓	Roux, 1979; Fisher, 1970
Pentachlorophenol	Mouse	Oral	↓	Kerkvliet, 1985
Pentachlorophenol	Chicken	In Vitro	↓	Prescott, 1982
Pentachlorophenol	Cow	Oral	↑	McConnell, 1980
Organophosphates				
Carbophenothion	Human	In Vitro	↓	Park, 1978
Crufomate	Human	In Vitro	↓	Park, 1978

Table 3. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Dichlorvos	Mouse, Carp	In Vitro	↓	Casale, 1993; Cossarini-Dunier, 1991
Malathion	Mouse	In Vitro	↑	Rodgers, 1990, 1986
Malathion	Human	In Vitro	↓	Lee, 1979
Methyl Parathion	Human	In Vitro	↓	Park, 1978
Mevinphos	Mouse	In Vitro	↓	Casale, 1993
Trichlorfon	Carp	In Vitro	↓	Cossarini-Dunier, 1991
Carbamates and Thiocarbamates				
Aldicarb	Mouse	Oral	↓	Shirazi, 1990; Olson 1987
Carbaryl	Mouse, Human	In Vitro Lee, 1979	↓	Casale, 1993;
Carbofuran	Mouse	In Vitro	↓	Casale, 1993
Methiocarb	Mouse	In Vitro	↓	Casale, 1993
Propham	Human	In Vitro	↓	Park, 1978
Metals and Minerals				
Arsenic	Human, Cow	In Vitro	↑ ↓	McCabe, 1983
Mercuric Chloride	Mouse	Oral	↓	Dieter, 1983; Gaworski, 1978
Mercuric Chloride	Mouse	In Vitro	↓	Nakatsuru, 1985
Tributyltin Oxide	Rat	Oral	↑ ↓	Vos, 1984b
Tributyltin Oxide	Rat	Oral	↓	Smialowicz, 1989
Triphenyltin Hydroxide	Rat	Oral	↓ *	Vos, 1984a
Pyrethroids				
Allethrin	Mouse	In Vitro	↓	Stelzer,1984
Cypermethrin	Mouse, Rabbit	In Vitro	↓	Stelzer,1984; Desi, 1986
Fenpropathrin	Mouse	In Vitro	↓	Stelzer, 1984
Permethrin	Mouse	In Vitro	↓	Stelzer, 1984
Other				
2,4-D	Mouse	Dermal	↑	Blakely, 1986
Atrazine	Mouse	Oral	↓	Fournier, 1992
Captan	Mouse	Oral	↓	Lafarge-Fraysinnet-1982
Piperonyl Butoxide	Human	In Vitro	↓	Lee, 1979

Table 3. Tier 1 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
NON-SPECIFIC IMMUNITY				
Macrophage/Neutrophil/Natural Killer Cell Activity				
Organochlorines				
Chlordane	Mouse	Prenatal	↓	Theus, 1992a, 1992b, 1991
Chlordane	Guinea Pig	In Vitro	↑	Suzaki, 1988
Chlordecone	Rat	Oral	↓	Smialowicz, 1985a
Chlorfenethol	Goat	Oral	↓	Aripdzhanov, 1973a, 1973b
Dieldrin	Rat	Oral	↑	Hewett, 1988
Dieldrin	Mouse	Oral	↓	Bernier, 1988; Fournier, 1988 Jolicoeur, 1988; Hugo, 1988a, 1988b; Krzystyniak, 1987, 1986
Lindane	Mouse	In Vitro	↑	Meade, 1984
Endrin	Rat	Oral	↑	Akubue, 1992
Hexachlorobenzene	Rat	Oral	↓	Ziprin, 1977
Pentachlorophenol	Fish	Oral, Dermal	↓	Anderson, 1992
Organophosphates				
Dichlorvos	Human	In Vitro	↓	Lee, 1977
Dichlorvos	Carp	Oral, Dermal	↓	Cossarini-Dunier, 1991
Naled	Human	In Vitro	↓	Lee, 1977
Tetrachlorvinphos	Human	In Vitro	↓	Lee, 1977
Trichlorfon	Carp	Oral, Dermal	↓	Cossarini-Dunier, 1991
Carbamates and Thiocarbamates				
Aldicarb	Mouse	Under Skin	↓	Dean, 1990a, 1990b
Aldicarb	Mouse	Oral	↓	Selvan, 1989
Barban	Rat	Oral	↓	Olefir, 1973b
Carbaryl	Rat, Rabbit	Oral	↓	Shtenberg, 1972
Carbaryl	Mouse	In Vitro	↓	Forgue, 1990
EPTC	Rat	Oral	↓	Olefir, 1973b
Methyldithiocarbamate	Mouse	Oral	↓	Pruett, 1992b

Table 3. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Metals and Minerals				
Tributyltin	Fish	Oral, Dermal	↓	Wishkovsky, 1989; Rice, 1980
Tributyltin Oxide	Rat	Oral	↓	Vos, 1984b
Other				
Diquat	Rat, Mouse	Oral	↓	Styles, 1974
Paraquat	Rat	Oral	↓	Styles, 1974
Neutrophil Chemotaxis				
Organochlorines				
DDT	Human	In Vitro	↓	Lee, 1979
Endrin	Human	In Vitro	↓	Lee, 1979
Lindane	Human	In Vitro	↓	Lee, 1979
Organophosphates				
Crufomate	Human	In Vitro	↓	Lee, 1979
Methyl Parathion	Human	In Vitro	↓	Lee, 1979
Carbamates and Thiocarbamates				
Propham	Human	In Vitro	↓	Lee, 1979
Metals and Minerals				
Copper	Rabbit	In Vitro	↓	Ward, 1975
Mercuric Chloride		In Vitro	↓	Nordlind, 1990
Tributyltin Chloride	Rabbit	In Vitro	↓	Arakawa, 1984
Other				
Piperonyl Butoxide	Human	In Vitro	↓	Lee, 1979
Triisopropylphosphate	Rabbit	In Vitro	↓	Woodin, 1973

Notes;
↓ Indicates a Decrease
↑ Indicates an Increase
* Indicates a Graduated Dose-Response

Table 4. Tier 2 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
IMMUNOPATHOLOGY				
Leukocyte Count				
Organochlorines				
Chlordane	Mouse	Oral	↑	Johnson, 1986
DDT			↓	Evdokimov, 1974
Endrin	Fish	Oral, Dermal	↓	Mount, 1966
Mirex	Catfish	Oral, Dermal	↑ ↓	Rogillio, 1974
Pentachlorophenol	Chicken	Oral	↓	Prescott, 1982
Organophosphates				
Dichlorvos	Rat	Oral	↓	Institoris, 1995a
Malathion	Fish	Oral, Dermal	↑	Areechon, 1990
Monocrotofos	Mouse	Oral	↓	Gupta, 1982
Phorate	Fish	Oral, Dermal	↑	Chakrabarty, 1988
Phosalone	Fish	Oral, Dermal	↑	Reddy, 1991
Trichlorfon	Fish	Oral, Dermal	↓	Siwicki, 1990
Carbamates and Thiocarbamates				
Maneb	Rat	Oral	↓	Shtenberg, 1972
Other				
Atrazine	Fish	Oral, Dermal	↓	Prasad, 1991;
Chlormequat Chloride	Mouse	Oral	↓	Fairbrother, 1986
Chlormequat Chloride	Mouse	Oral	↓	Olson, 1984
Glyphosine	Mouse	Oral	↓	Fairbrother, 1986
Phenthoate	Fish	Oral, Dermal	↑	Chakrabarty, 1988
				Walsh, 1975
Lymphocyte Count				
Organochlorines				
Chlordane	Mouse	Oral	↑	Johnson, 1986
Dieldrin	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
DDT	Chicken	Oral	↓	Glick, 1974
Endosulfan	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Mirex	Chicken	Oral	↓	Glick, 1974
PCNB	Rat	Oral	↓	Vos, 1983a
Organophosphates				
Dimethoate	Mouse	Under Skin	↓	Tiefenbach, 1980

Table 4. *Continued*

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Malathion	Fish	Oral, Dermal	↓	Walsh, 1975
Phorate	Fish	Oral, Dermal	↓	Chakrabarty, 1988
Carbamates and Thiocarbamates				
Aldicarb	Fish	Oral, Dermal	↑ ↓	Gill, 1991
Carbaryl	Fish	Oral, Dermal	↓	Walsh, 1975, 1974
Carbofuran	Mouse	Oral	↓	Gupta, 1982
Chlorpropham	Rat	Oral	↑	Vos, 1983a
Molinate	Fish	Oral, Dermal	↑ ↓	Kawatsu, 1977
Metals and Minerals				
Tributyltin Oxide	Rat	Oral	↓	Krajnc, 1984
Mercuric Chloride	Mouse	Oral	↑ ↓	Dieter, 1983
Other				
2,4-D	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Phenthoate	Fish	Oral, Dermal	↓	Chakrabarty, 1988
Atrazine	Rat	Oral	↓	Vos, 1983a
Atrazine	Salmonid	Oral, Dermal	↓	Walsh, 1975, 1974
Captan	Rat	Oral	↓	Vos, 1983a
Diquat	Fish	Oral, Dermal	↓	Berry, 1975
Endothall	Fish	Oral, Dermal	↓	Berry, 1975 Thaxton, 1973
Mercuric Chloride	Mouse	In Vitro	↓ *	Lawrence, 1981
Pyrethroids				
Cypermethrin	Rabbit, Rat	Oral	↓	Desi, 1986, 1985
HUMORAL IMMUNITY				
Secondary Antibody Response				
Organochlorines				
Chlorofenethol	Goat	Oral	↓	Aripdzhanov, 1973a, 1973b
Chlorobenzilate	Rat	Oral	↑ ↓	Nikolaev, 1972
Dieldrin	Mouse	Under Skin	↓	Bernier, 1987
Dieldrin	Rabbit	Oral	↓	Wassermann, 1972
DDT	Chicken	Oral	↓	Glick, 1974; Lukic, 1973
DDT	Goldfish	Oral, Dermal	↓	Zeeman, 1975

Table 4. Tier 2 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Organochlorines (continued)				
DDT	Rabbit	Oral	↓	Perelygin, 1971; Wassermann, 1971
DDT	Rat	Oral	↓	Perelygin, 1971; Olefir, 1971
DDT	Rat	Oral	↑ ↓	Wassermann, 1969
Hexachlorobenzene	Mouse	Oral	↓	Loose, 1979
Hexachlorobenzene	Rat	Prenatal	↑	Vos, 1979a
Hexachlorobenzene	Rat	Oral	↑	Vos, 1983b, 1979b
Lindane	Rabbit	Oral	↓	Desi, 1978
Pentachlorophenol	Rat, Chicken	Oral	↓	Exon, 1983; Prescott, 1982
Toxaphene	Mouse	Oral	↓	Allen, 1983
Toxaphene	Mouse	Prenatal	↓	Allen, 1983
Trichloroethane	Mouse	Oral	↓	Sanders, 1985
Organophosphates				
Diazinon	Mouse	Oral	↓	Moon, 1986a
Dichlorvos	Rabbit, Rat	Oral	↓	Desi, 1980, 1978; Institoris, 1995a
Dimethoate	Mouse	Under Skin	↓	Tiefenbach, 1980
Dimethoate	Mouse, Rat	Oral	↑ ↓	Nikolaev, 1972
Dimethoate	Rat	Oral	↓ *	Institoris, 1995b
EPN	Mouse	Oral	↓	Moon, 1986a
Fenitrothion	Mouse	Oral	↓	Moon, 1986a
Fenthion	Mouse, Rat	Oral	↓	Moon, 1986a; Nikolaev, 1972
Fenthion	Mouse	Oral	↑ ↓	Nikolaev, 1972
Glyphosine	Mouse	Oral	↓	Fairbrother, 1986
Malathion	Catfish	Oral, Dermal	↓	Plumb, 1990
Malathion	Rodent	Oral	↓	Desi, 1978
Methyl Parathion	Rat	Oral	↓	Institoris, 1995b
Parathion	Mouse	Oral	↓	Pruett, 1992c
Carbamates and Thiocarbamates				
Aldicarb	Mouse	Oral	↓	Olson, 1987
Aldicarb	Mouse	Oral	↓	Hajoui, 1992
Aldicarb	Mouse	Oral	↑ ↓	Shirazi, 1990
Carbaryl	Rat	Oral	↓	Shtenberg, 1972; Bolkhovitianova, 1969

Table 4. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Carbaryl	Mouse	Oral	↓	Olson, 1986b; Wiltrout, 1978
Carbofuran	Mouse	Oral	↓	Fan, 1978
Maneb	Rat	Oral	↓	Shtenberg, 1972
Zineb	Rat	Oral	↓	Shtenberg, 1972
Ziram	Rat	Oral	↓	Shtenberg, 1972
Metals and Minerals				
Copper	Mouse	In Vitro	↓ *	Lawrence, 1981
Nickel Sulfate	Mouse	Oral	↓ *	Graham, 1978
Sodium Arsenite	Mouse	Oral	↓	Blakely, 1980
Tributyltin Oxide	Rat	Oral	↓	Vos, 1984b
Tributyltin Oxide	Rat	Oral	↑	Smialowicz, 1989
Triphenyltin Chloride	Mouse	Oral	↓	Hiroyuki, 1990
Mercuric Chloride	Chicken, Mouse	Oral	↓	Bridger, 1983; Dieter, 1983;
Other				
2,4-D	Mouse	Dermal	↓ *	Blakely, 1986
Captan	Mouse, Rat	Oral	↓	Lafarge-Frayssinet, 1982
Captan	Rat	Prenatal	↓	Vos, 1983a
Chlordimeform	Mouse	Under Skin	↓	Shopp, 1985
Chloromequat Chloride	Mouse	Oral	↓	Fairbrother, 1986, Olson, 1984
Cycloheximide	Mouse	Under Skin	↓ *	Olson, 1983
Fluometuron	Rat	Oral	↓	Nikolaev, 1972
Maleic Hydrazide	Mouse	Under Skin	↑	Olson, 1983
CELL-MEDIATED IMMUNITY				
Hypersensitivity				
Organochlorines				
Chlordane	Mouse	Prenatal	↓	Barnett, 1985; Spyker-Cranmer, 1982
Chlordane	Mouse	Oral	↓	Johnson, 1986
DDT	Rat, Rabbit	Oral	↑	Andre, 1983; Lukic, 1973; Wassermann, 1969

Table 4. Tier 2 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
DDT	Rabbit	Oral	↓	Street, 1975
Hexachlorobenzene	Rat	Oral	↑	Vos, 1983b
Hexachlorobenzene	Mouse	Prenatal	↓	Barnett, 1987
Lindane	Mouse	Prenatal	↑ ↓	Das, 1990
Pentachlorophenol	Rat	Oral	↓ *	Exon, 1983
DDT	Rabbit	Oral	↓	Street, 1975
Hexachlorobenzene	Rat	Oral	↑	Vos, 1983b
Hexachlorobenzene	Mouse	Prenatal	↓	Barnett, 1987
Lindane	Mouse	Prenatal	↑ ↓	Das, 1990
Pentachlorophenol	Rat	Oral	↓ *	Exon, 1983
Organophosphates				
Diazinon	Rat	Oral	↓	Moon, 1986b
EPN	Rat	Oral	↓	Moon, 1986b
Fenitrothion	Rat	Oral	↓	Moon, 1986b
Fenthion	Rat	Oral	↓	Moon, 1986b
Carbamates and Thiocarbamates				
Carbofuran	Rabbit	Oral	↓	Street, 1975
Metals and Minerals				
Copper	Mouse	Oral	↓	Pocino, 1991, 1990
Tributyltin Oxide	Rat	Oral	↓ *	Vos, 1984b
Triphenyltin Hydroxide	Rat	Oral	↓	Vos, 1984a
NON-SPECIFIC IMMUNITY				
Macrophage Phagocytosis				
Organochlorines				
Dieldrin	Rat	Under Skin	↓	Kaminski, 1982
DDT	Rat	Under Skin	↓	Kaminski, 1982
DDT	Rabbit	Oral	↓	Perelygin, 1971
Lindane	Rabbit	Oral	↓	Grabarczyk, 1990
Pentachlorophenol	Rat	Oral	↑ *	Exon, 1983
Toxaphene	Mouse	Oral	↓ *	Allen, 1983
Organophosphates				
Diazinon	Mouse	Oral	↓	Moon, 1986b
EPN	Mouse	Oral	↓	Moon, 1986b
Fenitrothion	Mouse	Oral	↓	Moon, 1986b
Fenthion	Mouse	Oral	↓	Moon, 1986b

Table 4. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Trichlorfon	Carp	Oral, Dermal	↓	Siwicki, 1990
Carbamates and Thiocarbamates				
Carbaryl	Rat	Oral	↓	Shtenberg, 1972; Bolkhovitianova, 1969
Carbaryl	Rat, Mouse	Oral	↓	Olefir, 1973b
				Peppy, 1983
Thiram	Rat, Rabbit	Oral	↓	Perelygin, 1971; Olefir, 1973b
Zineb	Rat, Rabbit	Oral	↓	Perelygin, 1971
Metals and Minerals				
Nickel Sulfate Hydrate	Mouse	Inhalation	↓	Haley, 1990
Tributyltin Chloride	Rabbit	In Vitro	↓	Elferink, 1986
Other				
Atrazine	Mouse	Oral	↓	Fournier, 1992
HOST RESISTANCE				
Bacteria and Fungi				
Organochlorines				
DDT	Fish	Oral, Dermal	↓	Schoenthal, 1963
Hexachlorobenzene	Rat	Prenatal	↓	Vos, 1979a
Hexachlorobenzene	Mouse	Oral	↓	Loose, 1979, 1978b, 1977
Lindane	Mouse	Oral	↓	Andre, 1983
Organophosphates				
Methyl Parathion	Mouse	Oral	↓	Fan, 1978
Carbamates and Thiocarbamates				
Barban	Rat	Oral	↓	Olefir, 1973a
Carbaryl	Mouse, Rat	Oral	↓	Andre, 1983; Olefir, 1973a, 1973b
Carbofuran	Mouse	Oral	↓	Fan, 1978
EPTC	Rat	Oral	↓	Olefir, 1973a
Maneb	Rat	Oral	↓	Olefir, 1973a
Molinate	Rat	Oral	↓	Olefir, 1973a

Table 4. Tier 2 Tests for Pesticide Immunotoxicity

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Thiram	Rat	Oral	↓	Olefir, 1973a
Metals and Minerals				
Arsenic Trioxide	Mouse	Inhalation	↓	Aranyi, 1985
Tributyltin Oxide	Rat	Oral	↓	Vos, 1984b
Triphenyltin Hydroxide	Rat	Oral	↓	Vos, 1984a
Other				
Dinitrocresol	Rat	Oral	↓	Olefir, 1973a
Formaldehyde	Mouse	Oral	↓	Dean, 1984
Viruses				
Organochlorines				
Chlordane	Mouse	Prenatal	↑ ↓	Menna, 1985
DDT	Mouse	Under Skin	↓	Crocker, 1976
Dieldrin	Mouse	Under Skin	↓	Krzystyniak, 1985
Dieldrin	Duck	Oral	↓	Friend, 1974
Organophosphates				
Glyphosine	Mouse	Oral	↓	Fairbrother, 1986
Parathion	Mouse	Oral	↓	Selgrade, 1984
Metals and Minerals				
Sodium Arsenite	Mouse	Oral	↓	Gainer, 1972
Other				
Chlormaquat Chloride	Mouse	Oral	↓	Fairbrother, 1986
Parasites				
Organochlorines				
DDT	Chicken	Oral	↓	Radhakrishnan, 1972
DDT	Fish	Oral, Dermal	↓	Schoenthal, 1963

Table 4. Continued

Pesticide	Animal Used	Exposure Route	Direction of Change	Reference
Hexachlorobenzene	Mouse	Oral	↓	Loose, 1978b, 1977
Carbamates and Thiocarbamates				
Carbaryl	Quail	Oral	↓	Zeakes, 1981
Tumors				
Organochlorines				
Pentachlorophenol	Mouse	Oral	↓	Kerkvliet, 1982
Organophosphates				
Diazinon	Mouse	Oral	↓	Moon, 1986b
EPN	Mouse	Oral	↓	Moon, 1986b
Fenitrothion	Mouse	Oral	↓	Moon, 1986b
Fenthion	Mouse	Oral	↓	Moon, 1986b
Metals and Minerals				
Sodium Arsenate	Mouse	Oral	↓	Kerkvliet, 1980, 1978
Other				
Formaldehyde	Mouse		↑	Dean, 1984
Overall Host Resistance				
Organophosphates				
Methyl Parathion	Mouse, Rabbit	Oral	↓	Raise, 1983; Fan, 1984, 1981

Notes;
↓ Indicates a Decrease
↑ Indicates an Increase
* Indicates a Graduated Dose-Response

Assessing this research and its implications for human health risks, an often-cited review concluded that "a large body of evidence has accumulated over the past 20 years that exposure to environmental chemicals, many of which are pesticides or contaminants of pesticide formulations, can produce immune dysfunction (i.e., altered immune function and altered host resistance) in experimental animals following acute and subchronic exposure" (Thomas, 1988, 266). The authors note that translating these findings into demonstrable health risks to humans has been difficult, since humans are usually exposed to pesticides in chronic low doses and for other reasons, but that this caveat should not be interpreted to mean that people are not at risk.

Wildlife Studies

A major limitation of experimental studies involves dose-response extrapolation. Since exposure to the foreign chemical in animal experiments is purposely high and usually short-lived, the extrapolation of toxic effects to human exposures can be questioned. Wildlife studies can partially overcome these limitations by taking animals in their natural environments and studying the effects of pesticides under actual exposure conditions. Of course, the price researchers must pay when studying birds, fish, and mammals in the wild is that they usually can't control for other factors that might be implicated in the disease, including exposure to other potentially immunotoxic chemicals such as polychlorinated biphenyls (PCBs) and dioxins that act through different mechanisms.

The laboratory and field evidence of pesticide-induced immunotoxicity in fish is ample (Zelikoff, 1994; Dunier, 1993; Zeeman, 1981). For example, young chinook salmon chronically exposed to pesticides in the Duwamish Waterway in Washington showed drastic reductions in humoral response (Arkoosh, 1994). So did fish from Visakhapatnam Harbor in India (Rao, 1990). The organophosphate pesticides trichlorfon and dichlorvos, frequently used to ward off ectoparasites and plankton in fishponds in Eastern Europe, reduced non-specific immune response in carp (Siwicki, 1990).

Rachel Carson's *Silent Spring* did much to warn the world's people of the subtle effects of the pesticide DDT on birds' ability to reproduce. Pesticides also weaken their ability to resist disease. Birds that feed on fish accumulate persistent organochlorine compounds, including pesticides and PCBs. Compared with non-exposed birds, herring gull and caspian tern chicks in the Great Lakes region had smaller thymuses and less T cell activity, the greater their exposure to these compounds (Grasman, 1995, 1994).

Like fish and birds, marine mammals are chronically exposed to organochlorine pesticides and PCBs from eating contaminated foods. Autopsies on dead whales from the highly contaminated St. Lawrence Seaway found high tissue concentrations of organochlorine pesticides and PCBs and severe bacterial infections, suggesting immunosuppression. Autopsies also demonstrated more frequent and severe tumors than found in whale populations elsewhere (De Guise, 1994). The authors concluded that "two factors could have contributed to such a high prevalence of [cancers] in that single population: exposure to carcinogenic compounds and decreased resistance to the development of tumors" (De Guise, 1995, 75).

A recent plague affecting dolphins in the Mediterranean, the North Sea and the North Atlantic gave rise to more research. In the early 1990s, dead dolphins were washing up on beaches in the Mediterranean with infections of normally tolerated viruses. According to one researcher of the British Government's Veterinary Science Laboratory, "We have gone back over the literature for more than a hundred years and we found nothing like it, no other cluster of virulent epidemics like we have now" (Simons, 1992, 10). Scientists hypothesized that organochlorine pesticides, PCBs and other chemical pollutants made these marine mammals more susceptible to the virus (Aguilar, 1993).

Researchers who assayed blood samples from live bottlenose dolphins captured off the Florida

coast determined that immune function had been compromised by high levels of organochlorine contaminants. In these dolphins, decreased T cell lymphocyte proliferative response was highly correlated with increased levels of bioaccumulated organochlorines (Lahvis, 1995). The dolphins exhibited "infections suggestive of immune dysfunction" (Lahvis, 1993, 115). The organochlorine contaminants stored in the blubber may have been mobilized during periods of sickness and reduced dietary intake, causing further immunosuppression.

Harbor seals have also suffered unusual die-offs from morbillivirus infections in the Baltic and North Seas in the last decade, with mortality rates reaching 60 percent in some areas. Researchers at the Netherlands National Institute of Public Health and Environmental Protection conducted a prospective immunologic study on harbor seals. Seal pups captured off the relatively unpolluted Northwest coast of Scotland were fed uncontaminated fish for a one-year acclimatization period in holding tanks. Then, the seals were put into two tanks; one group was fed herring taken from the polluted Baltic Sea, while the other group was fed herring from Iceland as a control. Herring from both sources were purchased directly from fish markets and were intended for *human* consumption. After an initial three-week period, during which the young seals *refused to eat* the contaminated diet, both groups gained weight at about the same pace. The dietary intake of pesticides and PCBs of seals fed Baltic fish was several-fold higher than that of controls, and led to a ten-fold higher concentration of organochlorines in their blubber. Both groups were tested at intervals for various immune system parameters. Seals that ate the organochlorine-rich diet showed significantly reduced natural killer cell activity, reduced T-cell proliferative response, antibody response, and neutrophil levels. In all, the authors concluded that the seals fed the contaminated herring had immune responses three times weaker than those of the control group and increases in opportunistic infections indicative of this weakened immune response (De Swart, 1995a, 1995b, 1994, 1993; Ross, 1995a, 1995b, 1994a). Though the specific role of pesticides remains undefined, it was "the first demonstration of immunosuppression in mammals as a result of exposure to environmental contaminants at ambient levels found in the environment" (Osterhaus, 1995).

Conclusion

This experimental and wildlife research literature provides substantial evidence that many pesticides are immunosuppressive. Although many health regulations have been based on such evidence alone, additional evidence from epidemiological studies of human populations also points toward the same conclusion.

V. The Human Evidence

Introduction

Few epidemiological studies have been carried out to assess changes in the human immune system from pesticide exposure or the health impacts of pesticide-induced immunosuppression, except in the former Soviet Union. Elsewhere, research into pesticides' health impacts has until recently concentrated on their damage to the nervous system and their potential role in cancer. Environmental immunotoxicology, a science that has developed rapidly in recent years, is concentrated in developed countries, where industrial chemicals have been a bigger worry than pesticides. Resources for epidemiological research on pesticide immunotoxicity have been extremely limited in developing countries, where pesticide-related risks are prominent. For these reasons, epidemiologists emphasize that scanty epidemiological evidence on pesticide immunotoxicity does not imply that there is no potential problem (Rose, 1992).

Most studies conducted so far suffer from various limitations. Measuring pesticide exposure accurately is virtually impossible in retrospective studies, which must rely on participants' incomplete or biased recollections. Imperfect proxies for exposure, such as the average intensity of pesticide use in a geographic area or the occupation of the subjects of the study must sometimes be used, although doing so may bias the results.

Finding appropriate ways to measure a pesticide's impacts on the immune system also poses problems. Even the guidelines proposed by the U.S. Centers for Disease Control, which include detailed immunotoxicology testing protocols for use in epidemiological research, may not always predict changes in susceptibility to infectious disease or other clinical disorders accurately (CDC, 1990). Absent any chemical disruption, the immune system parameters tested in these protocols still vary substantially among normal individuals and over time for each person.

Moreover, although pesticide-induced immunosuppression may increase people's susceptibility to infectious and parasitic diseases, these diseases are so prevalent among low-income populations, and malnutrition and unsanitary living conditions are so widespread that distinguishing any greater susceptibility due to immune deficiencies is difficult. This is particularly problematic because it is difficult to measure differences among groups in their exposure to pathogens, let alone their exposure to pesticides. Given these limitations, the epidemiological evidence discussed below is far from definitive but should be considered together with the results of experimental and animal studies.

General Health Effects

One line of evidence stems from health studies linking pesticide exposure to increases in illness and death from infectious disease. Most such studies have not assessed immunological changes directly nor have they controlled for factors other

Box 2. How is the Human Evidence Assessed?

Scientists can use epidemiological and clinical studies to assess the health impacts of chemical exposure. *Epidemiology* is the statistical and biological analysis of the determinants, distribution and frequency of diseases. Epidemiologists can use descriptive, case-control, retrospective cohort, and prospective cohort studies in their analysis. *Descriptive studies* characterize causes of disease and provide a foundation for more thorough examination. *Case control studies* examine two similar groups of patients, one with a disease and one without, and then assess whether those with the disease were more exposed to a suggested risk factor than those without the disease. *Retrospective cohort studies* examine two populations, one that was exposed to a risk factor and another that was not, to determine whether the exposed population is more likely to suffer from a particular disease. *Prospective cohort studies* follow two groups over time, one exposed and another not exposed to a suspected health risk, and then ascertain whether the two groups differ in disease outcomes. For this reason, prospective studies are the most conclusive, but are expensive and time-consuming. *Clinical studies* consist of detailed reports on individuals who have been physically examined and subjected to a battery of laboratory tests after having been exposed to a suspected health risk.

than pesticide exposure that may also contribute to illness or immune system alteration. They can at most suggest a link between pesticide exposure and resistance to disease.

A good example of this material is a study of mortality trends and pesticide use in Central Luzon in the Philippines, where pesticide use had risen dramatically over the five-year period studied. Researchers found a clear association between pesticide exposure and mortality rates: mortality rates rose among adult male farmers exposed to pesticides in smallholder rice farming while falling for adult females in the same villages and for adult males living in nearby towns. Seasonal peaks in mortality among farmers coincided with periods of intensive pesticide application. Confounding factors, such as socio-economic status and smoking, were reported but not assessed statistically. Mortality from infectious diseases was not reported separately in all cases, so distinguishing between the effects of immunosuppression and those of acute pesticide poisoning was impossible (Loevinsohn, 1987).

Studies carried out in the cotton-growing regions of Uzbekistan in the former Soviet Union documented serious health consequences from indiscriminate pesticide use, including increased incidence and severity of infectious diseases.

Studies carried out in the cotton-growing regions of Uzbekistan in the former Soviet Union, documented serious health consequences from indiscriminate pesticide use, including increased incidence and severity of infectious diseases. Heavy spraying of numerous compounds, including organochlorine and highly toxic organophosphorus insecticides, exposed workers and populations living amid the fields to high chronic doses in water, air, and food (Bakhritdinov, 1991; Faiziev, 1989; Isakanderov, 1986).

These exposed populations in cotton-growing districts suffered markedly higher rates of respiratory, gastrointestinal, and acute inflammatory kidney infections than did residents of other districts where pesticide use was lower but other conditions were similar (Kovtyukh 1995c; Chugunikhina, 1994; Palvanova, 1987; Ubaydulayev, 1984). Whereas only 1.6 percent of non-exposed individuals living in urban areas in the Samark-

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).

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.

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.

VI. Compounding Risk Factors

Introduction

In healthy people, some immunosuppression may occur without discernible effects, because the immune system has overlapping and redundant capacity to deal with challenges. Perhaps for this reason, many studies that measured changes in the immune system after chemical exposure detected no health consequences. But many people are immunologically vulnerable, because they are very young or very old, malnourished, or already chronically ill. All these conditions weaken immune defenses. For such people, who make up a large fraction of the population in developing and formerly socialist countries, further immunosuppression from pesticide exposures can raise markedly the risks of serious illness or death.

Many people are immunologically vulnerable because they are very young or very old, malnourished, or already chronically ill. All these conditions weaken immune defenses.

Immunologists recognize such threshold effects. According to one authority, "The immune system contains many redundancies and backups, so that any given abnormality may be compensated for by other functional pathways. Thus, it is possible that an abnormality may be present but not clinically manifest unless a pathway of compensation becomes compromised or a severe challenge occurs" (Rose, 1992, 14). However, should this redundant capacity be depleted, further immunosuppression could significantly reduce resistance to infections. A well-known textbook of immunotoxicology states, "Although the concept is controversial, data suggest that there is tremendous functional reserve in the immune system in individual animals and humans. Biologically relevant effects occur only after the functional reserve capacity has been exceeded" (Burrell, 1992b, 227). In developing countries alone, there are billions of people—infants and children, the malnourished, and the sick—who are immunologically stressed, and many of these people are also regularly exposed to pesticides.

Demographic Factors

The human immune system is not fully developed at birth and remains immature in early childhood. The fetus depends mainly on the placental barrier to protect it from its mother's infections and on her antibodies that pass across the placenta (Lewis, 1995). The mother's uterine tissue also produces prostaglandin and other substances that keep her immune system from attacking the fetus, which contains the father's genetic material and might otherwise be rejected as foreign (Chaouat,

1993; Sargent, 1993; Starkey, 1993). Although pregnant women are not severely immunocompromised in this way, they are more likely to get reproductive and urinary tract infections and such parasitic blood infestations as malaria.

In surviving infants, colostrum and breast milk provide antibodies and allow their own immune defenses time to develop (Hanson, 1993; Stephens, 1993). During gestation and infancy, the thymus develops slowly. Children under two, especially those exposed to infections in the womb, still have relatively few mature circulating T cells and low cytokine levels, so they are deficient in those T cells involved in immunologic memory (Sigal, 1994; English, 1992). Non-specific immunity, especially in the respiratory tract, is also undeveloped. Alveolar macrophages, non-specific cells involved in eliminating aerosol particles in the lung, are not present at birth and only work imperfectly in the early weeks of life. Infants are prone to acute respiratory infections, therefore, mainly because they have difficulty generating non-specific immune responses at the site of primary bacterial invasion (Yoder, 1994). Also, antibody levels reach normal adult levels only by the time children reach age 10. For all these reasons, a population containing large numbers of infants and children is at particularly high risk from immune suppression.

Worldwide, malnutrition is the most common cause of secondary immunodeficiency.

Malnutrition

The immunosuppressive effects of malnutrition are well known. Worldwide, malnutrition is the most common cause of secondary immunodeficiency. Malnutrition and infection typically interact in childhood sickness and death. The sick child typically eats less and, in cases of diarrhea, cannot absorb nutrients effectively. The sick, malnourished child cannot resist infection, in part because of specific effects that nutritional deficiencies have on the immune system.

Protein-energy malnutrition atrophies the thymus, reduces the number of mature lymphocytes (especially helper-T cells), and impairs cell-mediated immune responses (Keusch, 1993; Chandra, 1992). Protein-energy malnutrition also impairs natural killer cell activity, depresses blood levels of interleukin-1 (a protein that stimulates the immune system), and elevates production of prostaglandins and cortisol, hormones that suppress the immune system (Salimonu, 1993; Simpson, 1993; Hoffman-Goetz, 1988).

Some vitamin and mineral deficiencies also lead to immunosuppression. Vitamin A deficiencies are associated with reduced lymphocyte counts and proliferative responses, indicating reductions in cell-mediated immunity. Macrophage functions and natural killer cell counts are also suppressed in Vitamin A deficient patients and can be restored with vitamin supplements. Vitamin A deficiency in children can also alter the differentiation and maturation of B cells, reducing antibody response (Ross, 1994b; Watson, 1993). Vitamin A deficiency coupled with measles ranks among the most widespread causes of child morbidity and mortality in the world today, mainly because the syndrome depletes natural defenses against secondary infections. In fact, vitamin A supplemented diets have decreased childhood mortality in developing countries (Keusch, 1994).

The B vitamins, water-soluble enzyme helpers and building blocks of DNA, are also essential for proper immune response. B vitamin deficiencies suppress T cell proliferative response, hypersensitivity reactions, and some T cell subsets (Carver, 1994; Van Buren, 1994). B vitamin malnutrition also reduces antibody production and immune surveillance by natural killer cells (Jyonouchi, 1994; Kulkarni, 1994).

Vitamin E deficiencies have been implicated in suppressed T cell proliferative response, cytokine

production, and macrophage function. Vitamin E protects cytotoxic lymphocytes, macrophages, and neutrophils from the damaging effects of oxidation. Deficiencies in the antioxidant B-carotene can also lead to oxidative damage of white blood cells. Vitamin E also plays a key role in reducing the synthesis of natural immunosuppressive agents, such as prostaglandin (Meydani, 1993).

Vitamin C deficiencies suppress non-specific immune mechanisms, such as neutrophil chemotaxis, respiratory burst function, and macrophage phagocytosis. Vitamin C malnutrition can reduce cytokine production, reducing the activation of monocytes into macrophages that can destroy bacteria and viruses (Cunningham-Rundles, 1993; Muggli, 1993).

Small amounts of minerals, including iron and zinc, are also needed for normal immune functioning. Iron is vital to respiration, by which cells generate energy, and mitosis, by which cells divide. Because lymphocytes undergo rapid cell division for proliferative responses, these immune cells can be limited by iron deficiencies. Anaemia reduces T cell proliferative responses, delayed hypersensitivity reactions, and cell-mediated immunity (Bryan, 1993). Phagocytic mechanisms are suppressed in anaemic patients because the enzymatic reactions that destroy foreign organisms require iron. Hence, anaemia increases infectious morbidity and mortality (Bhaskaram, 1988).

Zinc deficiencies are a well-known cause of immunosuppression, affecting both lymphoctyes and macrophages and resulting in increased rates of infections in children (Dardenne, 1993). Because zinc is required for the enzymatic synthesis of DNA and in hormone functions, deficiencies of this mineral can limit lymphocyte proliferative response. Thus, zinc deficiency causes reductions in circulating T cells and delayed hypersensitivity reactions. Moreover, zinc appears to be vital to enzymatic activity in respiratory burst, a process by which phagocytic cells destroy foreign bacteria in the respiratory passages (Cook-Mills, 1993; Prasad, 1993). For all these reasons, malnutrition in its various guises is a potent additional risk factor compounding chemical-induced immunosuppression.

Sickness and Infectious/Parasitic Disease

Besides causing the stress and weight loss that accompany illness, infectious agents can alter the immune system directly. Viruses—the intracellular parasites that commandeer a host cell's biochemical machinery to reproduce themselves—can infect immune system cells, taking over essential cell functions and causing premature cell death. Since proper defenses require interaction among immune cells, viral infection of a subset of immune cells can lead to a broader immune dysfunction and an acute infection (McChesney, 1987).

The measles virus suppresses T cell and B cell proliferative responses and cytotoxic-T cell activity. It also locks its host (predominantly lymphocytes) into an early stage of growth before cell division, differentiation, and proliferation can occur. Cytomegalovirus also suppresses T cell proliferation and cytotoxic activity, as well as natural killer cell activity and antibody production. Herpes virus predominantly infects T cells, arresting cell division and differentiation. The hepatitis B virus can produce severe immunosuppression by infecting both monocytes and lymphocytes, especially in the liver and kidneys (Alp, 1994; McChesney, 1987). Secondary bacterial infection—a normal consequence of viral diseases—is responsible for most measles-related fatalities in developing countries, and bacterial pneumonia usually follows lung infections caused by influenza virus and cytomegalovirus (Coovadia, 1988).

Although bacteria don't typically penetrate host cells, some bacteria do secrete protein components that suppress host defense mechanisms. The common Staphylococcus and Pseudomonas bacteria make their hosts more susceptible to secondary infections by secreting proteins aptly termed leukocidins, which can kill macrophages and neutrophils (Noda, 1995). Toxins produced by the Diphtheria bacterium can destroy

leukocytes by inhibiting their protein synthesis (McConkey, 1994).

Some microorganisms such as the Pertussis (whooping cough) bacterium and its toxins penetrate and damage mucous tissues in the gut and lungs, impairing local host defense mechanisms (Relman, 1995). The Cholera, Shigella, and Salmonella toxins alter the permeability of gut tissues, causing tissue damage, severe fluid loss and weakening barriers against infectious agents (DuPont, 1995). Recovery from the damage is slow and concurrent secondary infection is likely. Because of similar mechanisms of tissue damage in the lung, "if the lung is exposed to another infection before it has fully recovered from an earlier insult, the damage is likely to be considerably more extensive" (Berman, 1991, 326). Thus, viral and bacterial agents can directly suppress both immunological and non-immunological host defense mechanisms.

In addition, the immune response to pathogens sometimes causes more damage than the invading agent. Immune cells located near injured tissue often secrete Tumor Necrosis Factor (TNF) which at low levels assists in host defenses, but at higher levels "evidently has some means of inducing immunosuppression" (Clark, 1992, 318). Overproduction of this chemical especially during parasitic infestation can lead to septic shock or cachexia, a chronic persistent wasting syndrome (Tracey, 1992). Similarly, though cytokines assist in host defenses, they can actually suppress immune functions if they are chronically stimulated. As "immunosuppression is a frequently encountered feature of chronic infection," cytokines could be involved in down-regulating the immune response, especially to parasitic agents, such as malaria, leishmania, trypanosoma, and schistosomiasis (Sher, 1992, 181).

In short, viral, bacterial, fungal and parasitic diseases contribute to weakened immunity in several ways. Populations in which such communicable diseases are widespread are highly vulnerable to the effects of further suppression of the immune system, and, of course, are at risk of higher mortality from common infectious diseases.

Other Immunologic Risk Factors

Immunosuppressive fungal metabolites known as mycotoxins are ubiquitous in rice, corn, and soybean fields and grain storage facilities. Occuring worldwide in the global food supply, the most immunotoxic of these fungal products is aflatoxin, which can induce clinically significant immunosuppression in humans, swine, cows, and turkeys (Honstead, 1992). Besides reducing resistance to infections, these mycotoxins alter antibody and lymphocyte proliferative responses, complement and natural killer cell activities, and neutrophil chemotaxis (Pestka, 1994; Sorenson, 1993; Richard, 1992).

Farmwork and other outdoor activities may expose people to high doses of UV light that compound other risks of immunosuppression.

According to the World Health Organization, "evidence has accumulated in studies of animal models that exposure to high doses of UV-B radiation produces selective alterations in the immune function that are mainly seen in the form of suppression of the normal delayed type cutaneous immune responses" (WHO, 1990, 22). In humans, synergistic interactions between sunlight-induced immunosuppression and viral agents may increase the frequency of skin cancer (Bouwes Bavinck, 1995; Rivas, 1994). Farmwork and other outdoor activities may expose people to high doses of UV light that compound other risks of immunosuppression.

The Prevalence of Compounding Risk Factors

Widespread in developing countries, the compounding risk factors described above interact to

produce high rates of illness and premature death. The demographic structure of developing countries makes them immunologically vulnerable. Of the approximately 250 million pregnant or lactating women and two billion children under the age of 15 in the world, about 90 percent live in the developing countries. The number of live births a typical African woman will have during her lifetime—six—is three times that of the average American woman. The percentage of the population under age 15 in India—35 percent—is twice as large as it is in Germany.

Immune function also declines among the aged. This is a particular risk factor for high-income countries in which populations—including farm populations—are aging. In some developing countries where the demographic transition is virtually complete, such as China, life expectancy is already comparable to that in the United States and the fraction of elderly people in the population is also high. Although developing country populations generally contain a much smaller fraction of elderly people, this does not offset the heightened vulnerability of the young to infectious diseases.

Malnutrition is widespread in the Third World. Nearly a billion people, mostly women and children, are chronically hungry. They don't eat enough to satisfy basic protein and calorie needs, let alone other nutritional requirements. Largely because of maternal malnutrition, a quarter of the babies born in the developing world (and more than a third in South Asia) have low birthweight (UNICEF, 1995). Low birthweight babies have much poorer chances of surviving neonatal diseases, but for those who do, nutritional deficits continue. Thirty-seven percent of children under five are moderately or severely underweight for their heights, and 43 percent are stunted (i.e., quite short for their ages) (UNICEF, 1995).

Deficiencies in vitamins and essential minerals are equally widespread. Only half the developing world's half-billion children under five consume enough vitamin A, for example; more than 13 million are sufficiently deficient in this critical nutrient that they suffer night blindness or worse (UNICEF, 1995). These nutritional deficiencies are enough to weaken immune defenses among large fractions of the developing country population.

Iron deficiency anaemia affects more than one out of three people—roughly 1.4 billion—in developing countries. Pregnant women, infants, children, adolescents, and those infested with certain parasites are prone to be anaemic. Nearly two thirds of pregnant women in South Asia and more than two fifths of young children globally are (DeMaeyer, 1989). "Because iron deficiency is the most prevalent nutritional disorder in the world and because it is most common in women of reproductive age and their children, the implications of dysfunctional immunity resulting from iron deficiency are vast" (Sherman, 1992, 607).

The burden of parasitic and infectious disease compounds this assault on the body's defenses. The World Health Organization estimates that on average, each child under five in the developing world undergoes three or four severe attacks of diarrhea or dysentery each year. More than three million succumb, making this the fourth most common cause of death worldwide. Each child is likely to suffer five to eight bouts of pneumonia or other acute lower respiratory infections annually before reaching the age of five, assuming the child manages to survive. Each year four million do not (WHO, 1995a).

Communicable diseases are responsible for nearly half of all deaths in the developing world.

Respiratory and diarrheal infections, tuberculosis, malaria, and measles are all among the ten leading causes of death worldwide. Communicable diseases are responsible for nearly half of all deaths in the developing world, but less than 10

percent of mortality in developed countries. Communicable diseases are far more prevalent in developing countries, largely because living conditions are typically so unsanitary and unhealthy, and people who contract these diseases are far more likely to die from them because their natural defenses are weak and medical care is often unavailable.

Some infectious diseases are resurgent. Tuberculosis, once considered a disease of the past, was declared a global emergency in 1993. Nine million new cases are expected in 1995, mostly in developing countries. Almost three million people will die from it. Approximately two billion people carry the tuberculosis mycobacterium, but those whose immune systems are fully competent keep it in check. When the immune system weakens, an active disease emerges. Tuberculosis commonly afflicts AIDs patients, but WHO estimates that only 4 percent of the active tuberculosis cases worldwide are associated with HIV. Tuberculosis has grown dramatically in Central Europe and the former Soviet Union, where chemical pollution is widespread (WHO, 1995b; Dolin, 1993).

Many opportunistic infections that typically appear among immunocompromised patients, such as AIDs sufferers, are also resurgent in broader populations among those who do not carry the HIV virus.

Many such opportunistic infections that typically appear among immunocompromised patients, such as AIDs sufferers, are also resurgent in broader populations among those who do not carry the HIV virus. The infectious agents are widespread but typically contained by functioning immune mechanisms. Along with the tuberculosis mycobacterium, they include streptococcus pneumonia (pneumonia and otitis media), listeria monocytogenes (listeriosis), cryptococcis neoformans (cryptococcosis), pseudomonas aeroginosa (lower respiratory tract infection), candida albicans (candidiasis, thrush), and herpes simplex virus (Lederberg, 1992). This increase in opportunistic infections suggests that the immune competence of large populations may be impaired.

Synergies Among Pesticides and Compounding Risk Factors

Developing country populations, which contain relatively large proportions of children, pregnant and lactating women, malnourished and sick people, are immunologically stressed to begin with. Pesticide exposure exacerbates an already precarious situation. "A large proportion of the populace, being under stress from malnourishment and disease, is exquisitely sensitive to further insult from environmental toxicants. Malnourishment, infectious disease, and toxic chemicals interact with each other and with the immune system" (Jamall, 1991, 372). Consequently, pesticides' immunosuppressive effects could have more pronounced health consequences in developing countries than elsewhere, and pesticides could significantly affect immune responses at lower doses.

Despite advice from the U.S. National Research Council's Committee on Immunotoxicology, few experimental or epidemiological studies have actually examined either the additive or synergistic interactions of chemically-induced immunotoxicity and other immunological risk factors (NRC, 1992). Yet, nutritional deficiencies can magnify pesticide toxicity. Malnourished animals are less able to detoxify and excrete pesticides. For example, protein-deficient laboratory rats are more susceptible to liver damage from malathion exposure than well-fed rats. Extrapolating from experimental studies, researchers conclude: "Malnutrition prevalent in many developing country populations could therefore bring about an increased susceptibility to [pesticide] intoxication, espe-

cially in women and children" (Forget, 1991, 16). Studies of children exposed to pesticides in the cotton-growing regions of Uzbekistan confirm this risk: pesticide-induced T and B cell immunodeficiencies were especially striking among children with pre-existing iron deficiency anaemia (Sadikova, 1990).

Researchers rarely conduct immunotoxicity experiments on sick animals because any immunoalteration could be attributed to either the sickness or to pesticide exposure and controlling for each is painstaking. Yet, previous or concurrent sickness is known to make pesticides more toxic. In humans exposed to pesticides, T and B cell deficiencies are more noticeable among people with pre-existing liver disease, GI tract disorders, and chemical sensitivities (Rea, 1994, 1991; Umarova, 1985; Fedorina, 1981). Sickness may also make pesticides more toxic or bioavailable. To meet the increasing energy demands of illness, the sick individual normally metabolizes fatty tissues, where some pesticides accumulate. In particular, pesticide stored in fatty bone marrow tissue where lymphocytes regenerate may become bioavailable during disease episodes (Fleming, 1993; McConnachie, 1992; Rea, 1992).

In short, developing country populations and many people elsewhere in the world probably have little immunological redundancy and their ability to repel common infectious agents is diminished. Many of them—the half of the world's population who live in rural areas in farm households—are increasingly exposed to pesticides known from experimental studies to be immunosuppressive. Such exposures constitute a potentially large public health risk that is almost completely hidden from view.

Pesticide-Induced Immunosuppression and Global Change

The increasing use of potentially immunosuppressive pesticides is only one aspect of the worldwide threat to the immune system. Many countries are industrializing rapidly with few environmental controls. Consequently, exposure to immunotoxic industrial chemicals, such as PCBs, dioxins, and heavy metals is increasing. Meanwhile, global emissions of CFCs and other substances that deplete stratospheric ozone have exposed people living in temperate and higher latitudes to increasing doses of potentially immunosuppressive ultraviolet B radiation.

At the same time, vector-borne diseases are spreading rapidly as worldwide transport and human migration carry the disease vectors across borders and continents, exposing populations to diseases to which they have little natural or acquired immunity. For example, a mosquito carrier of dengue hemorrhagic fever has become well-established in the southern United States. Similarly, large-scale population movements, deforestation, and other land use changes are bringing people into contact with new infections, including those like the Ebola virus that has apparently crossed from an animal reservoir to humans. These current trends could be amplified by climate alterations that either change the range of disease vectors or force people to move out of habitats subject to increased flooding or drought (Patz, 1996).

Multiple assaults on the immune system, spreading disease vectors, and a diminishing range of control options surely are causes for concern.

Many disease vectors and infectious agents have developed resistance to the chemicals that previously controlled them. Malaria has again spread worldwide mainly because the mosquito carrier is now resistant to DDT and other insecticides used for vector control. The tuberculosis mycobacterium is now resistant to many antibiotics. Antibiotic-resistant Staphylococcus infections are posing a growing health risk in many

hospitals around the world. This combination of multiple assaults on the immune system, spreading disease vectors, and a diminishing range of control options surely is cause for concern. These trends are especially threatening in the developing countries, where they compound the problems of malnutrition, demographic vulnerability, inadequate preventive and curative health services, and elevated rates of infectious disease.

Conclusion

In all, the human health threats of pesticide-induced immunosuppression are potentially severe, especially in developing countries where compounding risk factors are common. The effects of global change can only amplify these threats. Unfortunately, little is being done to address these concerns.

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.

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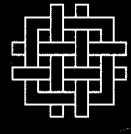

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