# Human Health Effects of Agrichemical Use

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**The use of pesticides and nitrogen fertilizers in agriculture has grown dramatically over the past 30 years. Currently, approximately 600 active pesticide ingredients are used, but adequate toxicologic data are available for only approximately 100 of these. Environmental exposure of humans to agrichemicals is common and results in both acute and chronic health effects, including acute and chronic neurotoxicity (insecticides, fungicides, fumigants), lung damage (paraquat), chemical burns (anhydrous ammonia), and infant methemoglobinemia (nitrate in groundwater). A variety of cancers also have been linked to exposure to various pesticides, particularly hematopoietic cancers. Immunologic abnormalities and adverse reproductive and developmental effects due to pesticides also have been reported. The health effects associated with pesticides do not appear to be restricted to only a few chemical classes. Therefore, enhanced efforts are needed to control or eliminate human exposures wherever possible. Research also is needed to better characterize and quantitate the adverse effects of agrichemicals on human health. HUM PATHOL 24:571-576. Copyright © 1993 by W.B. Saunders Company**

Prior to the 1940s, farmers relied on a combination of mechanical, chemical, and biologic methods to limit pest damage to crops. The discovery of DDT, however, ushered in an era of increasing dependence on chemicals for pest control. In the United States pesticide use in agriculture nearly tripled between 1965 and 1985. In 1987 four to five billion pounds of active pesticide ingredients were used around the world, including approximately one billion pounds in the United States.[1] Currently, approximately 600 active pesticide ingredients are marketed in some 45,000 to 50,000 formulations, amounting to worldwide sales of over $20 billion. Of the pesticides used in the United States, approximately 60% to 70% are herbicides, 25% to 30% are insecticides, and 10% to 15% are fungicides. In the United States approximately 75% of all cropland and 70% of livestock are treated with pesticides, with almost 100% of some crops (corn, soybeans, cotton) treated with herbicides. However, adequate toxicologic data obtained according to current standards are available for only approximately 100 of the 600 active pesticide ingredients on the market.[1]

The use of pesticides has resulted in increased availability, improved quality, and lower prices of a large number of agricultural products. Without pesticide use agricultural production of fresh produce and field crops would drop by 30% to 50%.[1,2] However, the benefits of pesticide use must be considered in light of increasing concerns regarding environmental degradation, worker safety, and public health. In this article I have attempted to summarize the current level of knowledge regarding the human health effects of agrichemical use, with much of the information taken from current reviews and a recent book on this subject.[1]

## HUMAN EXPOSURE TO AGRICHEMICALS

In the United States approximately two million farmers, three million hired farm workers, and six million farm family members have potential contact with agrichemicals. In addition, persons employed in the manufacturing and formulation of agrichemicals, as well as other plant growers and harvesters, aerial applicators, fumigators, professional ground and structural applicators, and their support personnel, are likely to have a significant exposure to agrichemicals. During pesticide application most exposure is via dermal absorption. In workers who are occupationally exposed to organophosphate insecticides, one can estimate the biologic exposure by measuring red blood cell or plasma cholinesterase levels before and after the application. In such studies approximately 20% to 40% of farm applicators have a significant reduction in their plasma cholinesterase level, some with symptoms of toxicity, whereas even higher percentages are reported in migrant farm workers, factory workers and formulators, and third-world farm laborers.[3-6]

Nonoccupational pesticide exposures among the general population appear to be low relative to occupational exposures. A major source of pesticide exposure for the general population results from the use of pesticides in and around the home, since approximately 90% of all United States households use pesticides. In California alone, an estimated 30 million kilograms of pesticides were sold for home and garden use in 1980.[1] From 1976 to 1977 the Environmental Protection Agency estimated that exposure to pesticides in and around the home resulted in 2.5 million reported symptomatic incidents.[7] Of particular concern are pesticides that persist in the home environment for long periods of time, particularly termiticides such as chlordane. House dust and lawn residues are thought to represent important means of exposure for small children. However, little is known regarding the chronic health effects of low-level home exposures.

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Contrary to widespread public belief, pesticide residues in fresh and processed foods are typically absent or well below the legal tolerance levels.[1] However, in rural areas contamination of drinking water by pesticides and nitrates from fertilizers is a concern, since water is a major part of the diet and significant exposures may occur over a lifetime.[8] However, few scientific studies of the health effects of such exposures have been done and little is known.

**TABLE 1.** Acute and Subacute Effects of Organophosphate Insecticide Poisoning

| | |
|---|---|
| Acute intoxication: | systemic symptoms, including muscle tremors, twitching and weakness, anorexia, nausea, vomiting, bronchoconstriction, hypersecretion, miosis, blurred vision, headache, impaired cognition, seizures, coma |
| Intermediate syndrome (1 to 4 days later): | respiratory paralysis and failure, proximal muscle weakness. |
| Delayed distal polyneuropathy (2 to 5 weeks later): | irreversible weakness, ataxia, paralysis. |

## ACUTE HEALTH EFFECTS OF AGRICHEMICALS

Due to lack of a national database, no accurate or current statistics are available regarding the incidence of acute pesticide poisoning in the United States. Approximately 20,000 persons are taken to emergency rooms each year for actual or suspected pesticide poisoning, and approximately 10% are admitted to the hospital. Each year 30 to 40 persons die of acute pesticide poisoning in the United States.[1] In California, where pesticide poisoning is a reportable illness, there were approximately 17,000 human pesticide exposure incidents in 1987, approximately 30% to 60% of which were symptomatic. Of these, only 1,507 cases were occupational, with 744 cases demonstrating systemic toxic symptoms.[9] However, many affected workers probably never see a doctor and therefore go undiagnosed and unreported. Occupational deaths in California over the past 10 years have averaged about one per year.[9] In contrast, acute pesticide poisoning is thought to be a major global health problem, with approximately 25 million occupational poisonings per year.[10] Most of these occur in third-world countries, where pesticide education and monitoring and the use of safety equipment are largely nonexistent.

In the United States most cases of occupational acute pesticide poisoning result in neurotoxicity and are due to exposure to organophosphate or carbamate insecticides. Organochlorine insecticides also are neurotoxic, but are no longer commonly used in the United States. Some of the acute and subacute neurotoxic effects of the organophosphate insecticides are listed in Table 1. Their principle toxic effect is the inhibition of cholinesterases in the blood and nervous system, which prevents degradation of acetylcholine at the neuronal synapses and results in overactivity of the cholinergic neurons. The carbamates and organochlorine insecticides can cause a similar picture of acute intoxication,[11,12] and these effects are usually reversible. However, a delayed, progressive, and irreversible distal polyneuropathy may occur as a result of organophosphate exposure and is due to Wallerian degeneration in large myelinated nerve fibers that leads to axonal death.[12] In contrast, the pyrethroid insecticides induce only cutaneous paresthesias, which last 12 to 18 hours.[11] The herbicides are generally not thought to be neurotoxic in humans, although a variety of fungicides and fumigants may cause acute and chronic neurotoxic effects.[11]

Paraquat is a contact herbicide that causes severe and progressive lung damage resulting in anoxia and death.[12] The initial phase of lung damage is an extensive alveolitis with neutrophil infiltration and progressive pulmonary edema. The second phase follows shortly thereafter and consists of rapidly progressive and extensive intraalveolar and interalveolar fibrosis, which destroys the alveolar architecture. Acute renal failure due to tubular necrosis and liver dysfunction also may be seen in paraquat poisoning.[12]

Anhydrous ammonia is a colorless gas that is used as a fertilizer. It is usually handled as a pressurized liquid for ease of transportation and storage. Because of high pressure and a temperature of −28°F, a stream of vaporizing anhydrous ammonia will penetrate and freeze any tissue that it strikes, resulting in chemical burns of the skin and eyes.[13] Inhalation of the gas will result in laryngospasm, tracheitis, bronchitis, and chemical pneumonitis with pulmonary edema. Eye injury may result in permanent damage, whereas lung injury is usually reversible.[13]

An acute health effect of groundwater contamination by nitrate is the occurrence of methemoglobinemia, either clinical or subclinical, in infants under 6 months of age.[14] The current drinking water standard for nitrate-nitrogen of 10 ppm was set primarily to prevent this occurrence. However, cases of infant methemoglobinemia, some resulting in death, continue to occur in rural areas.[15]

## CHRONIC HEALTH EFFECTS OF AGRICHEMICALS

### Neurologic Effects

It has become increasingly apparent from recent studies that acute and chronic occupational exposure to a variety of pesticides can result in mild to severe deterioration in neurologic function that may be irreversible.[11] Chronic neurologic effects have been associated with exposures to the organophosphate, organochlorine, and carbamate insecticides, as well as a variety of fungicides (mercurials, diphenyl, hexachlorobenzene, hexachlorophene) and fumigants (methyl bromide, carbon disulfide, sulfuryl fluoride).[11,16-20] A list of commonly reported chronic neurologic effects is given in Table 2. In a recent case-control epidemiologic study Rosenstock et al[21] found convincing evidence of chronic central nervous system effects in workers with a history of an episode of acute organophosphate insecticide intoxication. These investigators found that the poisoned group did significantly less well than the control group

**TABLE 2.** Chronic Neurologic Effects of Pesticide Poisoning

| |
|---|
| Lethargy, fatigue, headache, hyperirritability, dizziness |
| Muscle tremor, twitching, jerks, weakness, paralysis |
| Paresthesias, polyneuropathy, incoordination, ataxia |
| Visual disturbances, abnormal electroencephalograph |
| Central nervous system impairment, cognitive deficits, loss of memory, forgetfulness, confusion, altered sleep, slurred speech, impaired motor skills, altered behavior, nervousness, agitation |
| Psychiatric symptoms, depression, anxiety |
| Parkinsonian-like syndrome (carbon disulfide) |

in tests assessing a wide array of neuropsychologic functions, including auditory attention, visual memory, visuomotor speed, sequencing and problem solving, and motor steadiness, reaction, and dexterity. Rosenstock et al[21] concluded that even single episodes of clinically significant acute organophosphate intoxication may be associated with a persistent decline in neuropsychologic function.

A characteristic feature of carbon disulfide poisoning is the presence of a parkinsonian-like syndrome.[16] Interestingly, recent epidemiologic studies of Parkinson's disease have found that rural living, exposures to pesticides, and drinking well water are associated with the disease.[22,23] However, further studies are needed to clarify these relationships. Also of note is the report by Sterman and Varma[24] that as many as 19% of individuals exposed to well water containing a carbamate insecticide (aldicarb) had neurologic complaints, including paresthesias, locomotor difficulties, visual problems, and dizziness.

## Carcinogenic Effects

In recent years there has been increasing public concern that exposure to pesticides may pose a potentially serious cancer risk to the general population. Currently, the available data are insufficient to estimate a pesticide-related cancer rate for the general population, but it must be small when compared with other factors, such as smoking. However, excesses of certain types of cancer, particularly those of the hematopoietic system, have been observed in occupational groups with significant pesticide exposures.[25-29] These findings should not be surprising since a variety of pesticides are known to cause cancer in laboratory animals, even though many older pesticides have not been adequately tested.[27,29] In a recent survey of 47 pesticides evaluated for carcinogenicity by the National Toxicology Program, Hoover and Blair[29] found that six pesticides (13%) were positive in both sexes in mice and rats, 10 pesticides (21%) were positive in both sexes of one species, and six pesticides (13%) were positive in one sex of at least one species. For six other pesticides (13%) there was inadequate or equivocal evidence for carcinogenicity, whereas 19 pesticides (40%) tested negative. The 16 chemicals that were positive in both sexes of at least one species included organochlorine and organophosphate insecticides, herbicides, fungicides, and fumigants, suggesting that no chemical class of pesticides can be considered problem free. Similarly, the International Agency for Research on Cancer recently concluded that 43% of a wide variety of pesticides they reviewed were or probably were carcinogenic in humans.[27] With pesticides of all the various types showing some evidence of carcinogenicity in these studies, the concern about human exposure seems to be well founded. With regard to mechanisms of carcinogenesis, a survey of the genotoxic activities of 65 pesticides by Garrett et al[30] found that 35 of the pesticides (54%) tested positive, including organophosphate and thiocarbamate insecticides, pyrethroid insecticides, and a variety of herbicides and fungicides. However, some nongenotoxic pesticides also may be involved in carcinogenesis via their epigenetic properties, such as tumor promotion, inhibition of intercellular communication, or induction of peroxisome proliferation.[27]

Much of the epidemiologic data available on the carcinogenicity of pesticides come from studies of persons employed in agricultural or related occupations. Although farmers have a lower overall mortality for cancer in general, consistent excesses for certain types of cancer (Table 3) suggest a role for work-related factors.[28] The excesses of lip and skin cancer are thought to be due to ultraviolet light. Note that the risks for most of the other cancers are relatively low, in the range of 1.5-fold to threefold, although such studies are likely to underestimate the true risk. Although farmers typically perform many tasks resulting in a variety of exposures,[28] pesticides have received the most attention. However, few studies have attempted to assess the cancer risks of exposure to specific pesticides. Table 4 shows the cancers that have been associated with occupational exposures to specific pesticides or classes of pesticides.[28,29] The epidemiologic data linking specific pesticide exposures to hematopoietic cancer (ie, non-Hodgkin's lymphoma, leukemia, and multiple myeloma) are the strongest, whereas the data on soft tissue sarcoma are mixed and for Hodgkin's disease it is weak.[25-29] However, two recent studies have strengthened the association between soft tissue sarcoma and exposure to the phenoxyacetic acid and chlorophenol pesticides.[31,32] Little is known about specific pesticides and cancer of the brain, although ovarian carcinoma has been associated with exposure to triazine herbicides in one

**TABLE 3.** High-Risk Cancers in Mortality Surveys of Farmers

| Types of Cancer | No. of Studies | No. of Studies With RR > 1.0 | No. of Significant Studies | Range of RRs |
|---|---|---|---|---|
| Lip | 9 | 9 | 5 | 1.3-3.1 |
| Melanoma | 12 | 8 | 3 | 0.5-6.3 |
| Leukemia | 21 | 12 | 3 | 0.3-2.0 |
| Non-Hodgkin's lymphoma | 21 | 11 | 3 | 0.6-2.6 |
| Multiple myeloma | 16 | 12 | 4 | 0.4-3.1 |
| Hodgkin's disease | 13 | 10 | 1 | 0.6-1.5 |
| Soft tissue sarcoma | 9 | 6 | 0 | 0.9-1.5 |
| Brain | 20 | 15 | 2 | 0.7-6.5 |
| Stomach | 23 | 12 | 8 | 0.5-1.7 |
| Prostate | 24 | 17 | 10 | 0.9-2.0 |

Abbreviation: RR, risk ratio.

**TABLE 4.** Types of Cancer Associated With Specific Pesticide Exposures

| Cancer | Pesticides |
|---|---|
| Soft tissue sarcoma and lymphoma | Phenoxyacetic acid herbicides (2,4-D, 2,4,5-T), DDT |
| Non-Hodgkin's lymphoma | Organophosphate and organochloride insecticides, fumigants |
| Soft tissue sarcoma | Chlorophenols, animal insecticides |
| Leukemia | Dichlorvos, crotoxyphos, famphur, methoxychlor, pyrethrins, DDT, chlordane, heptachlor, lindane, ethylene oxide |
| Lung carcinoma | Organochlorine insecticides (DDT), arsenicals |
| Ovarian carcinoma | Triazines |

study.[33] Recent case-control studies in Kansas[34] and Nebraska[35] have demonstrated a significantly increased risk of non-Hodgkin's lymphoma (risk ratios, 1.3 to 2.2) among farmers using the phenoxyacetic acid herbicide 2,4-D, with the risks increasing threefold to sevenfold among those reporting use for 21 or more days per year. The use of organophosphate insecticides by Nebraska farmers also resulted in a significant 2.4-fold increased risk for non-Hodgkin's lymphoma, independent of the effects of 2,4-D, with the risk being over threefold for those using these insecticides 21 or more days per year.[35] Recently, a case-control study of canine non-Hodgkin's lymphoma revealed a positive association (risk ratio, 1.3) with the dog owner's use of 2,4-D, with the risk rising to a twofold excess with four or more yearly lawn applications.[36] Although mutagenesis tests and animal experiments provide only weak support for the role of 2,4-D as a carcinogen, 2,4-D has been shown to have multiple epigenetic properties, acting both as an inhibitor of intercellular communication and a stimulator of peroxisome proliferation.[27]

Leukemia and brain cancer in children have been associated with parental employment in agriculture and exposure to pesticides,[37-41] as has non-Hodgkin's lymphoma in recent, yet unpublished, studies. Brain cancer in children[42] and stomach cancer in adults[43] also have been linked to N-nitroso compounds, which could result from drinking groundwater contaminated by nitrate.[8] Increased rates of non-Hodgkin's lymphoma also have been found in communities and counties where nitrate contamination of groundwater is a problem.[8] Although nitrate per se does not appear to present a cancer risk, it acts as a precursor to nitrite which forms via bacterial reduction in saliva. Nitrite then reacts with other nitrosatable dietary substrates in an acid-catalyzed reaction in the stomach to produce N-nitroso compounds, which are potent carcinogens in experimental animals. It is intriguing that several of the cancers associated with farming (non-Hodgkin's lymphoma, multiple myeloma, brain cancer, and stomach carcinoma) are reportedly increasing in several countries around the world.[44-46]

## Immunologic Effects

Ample and convincing evidence that pesticides or pesticide contaminants can modulate or alter the immune response in experimental animals has been reported, but there is little evidence to suggest that pesticide exposures compromise human health through interference with the immune system.[47] However, contact dermatitis due to pesticides appears to be more common than previously thought,[48] and asthma-type reactions can be triggered by pesticide exposures.[47] Although altered immunoglobulin and complement levels and changes in T-cell populations have been reported in humans exposed to pesticides,[47] no adverse health effects have been noted. However, impaired neutrophil chemotaxis accompanied by an increase in respiratory tract infections was correlated with the length of occupational exposure to organophosphate pesticides in one study.[49] Further studies of the immune effects of pesticides in humans are needed since depressed immunity is known to predispose humans to a variety of cancers, including non-Hodgkin's lymphoma.

## Pulmonary Effects

Chronic respiratory impairment has been found in workers with many years of exposure to organochlorine and organophosphate insecticides.[50] Persistent pulmonary fibrosis has been reported in survivors of paraquat poisoning,[51] and chronic cough, bronchiolitis obliterans, and bronchiectasis have been described as sequelae of anhydrous ammonia exposure.[52]

## Reproductive Effects

For many pesticides the animal data necessary to evaluate potential reproductive toxicity are not available and, when animal data are available, even minimal human data are lacking.[53] Agricultural chemicals, including the organochlorine and organophosphate insecticides, have been shown to be reproductive toxicants in female laboratory animals, but there have been no reports of female reproductive toxicity in humans.[53]

In contrast, the organochlorine pesticides dibromochloropropane (DBCP) and chlordecone (Kepone) are reproductive toxicants in the human male. Azoospermia, oligospermia, and decreased sperm motility have been reported with DBCP, whereas chlordecone causes oligospermia and decreased sperm motility. A higher than expected prevalence of female births and an increase in spontaneous abortions in females whose husbands were exposed to DBCP have been reported.[53] Ethylene dibromide exposure also affects the human male reproductive system, resulting in decreased sperm counts, decreased sperm motility and viability, and abnormal morphology, as well as decreased fertility.[53] Exposure of males to carbaryl, a carbamate insecticide, has been reported to result in an increased number of abnormal sperm.[53] A recent study of male workers exposed to 2,4-D also revealed decreased sperm counts, decreased sperm motility and viability, and abnormal morphology.[54] Thus, human reproductive effects due to a variety of pesticides have been clearly demonstrated in males. However, large data gaps in our current knowledge of the reproductive effects of pesticides are evident and much additional research in this area is needed.[53]

### Developmental Effects

The extent to which pesticides contribute to the incidence of developmentally related problems in humans is unknown, although approximately 50% of the active pesticide ingredients that have been tested are teratogenic in animals.[55] The final outcome of a developmental disturbance can be death, malformations, growth retardation, functional disorders, or any of these manifestations in combination. However, functional deficit studies are currently not required for the registration of a pesticide.

Most studies of humans exposed to pesticides have failed to find an increase in fetal malformations.[56,57] However, a study of Vietnam veterans revealed an increase of spina bifida, facial clefts, coloboma of the eye, and neoplasms in the first year of life in offspring.[58] Studies by the Vietnamese also revealed increases in anencephaly, orofacial defects and clefts, and molar pregnancy in persons exposed to pesticides during the war, although these latter studies are difficult to evaluate.[59] Epidemiologic studies also have linked a variety of congenital malformations to the rural setting and pesticide use, including limb reduction defects, musculoskeletal defects, facial clefts, and cardiac and urogenital defects.[60-62] Perinatal pesticide exposure in humans has been reported to cause chronic neurotoxicity, including cerebral palsy.[11] Recently, an increase in abortions, infant prematurity, and congenital malformations was detected in female floriculture workers exposed to pesticides.[63] These findings suggest that extensive evaluation and quantitation of human exposure levels and the developmental consequences of such exposures are needed. Future epidemiologic studies should concentrate on pregnant women at high risk for exposure to pesticides, particularly those involved in agricultural work.

## CONCLUSION

Experimental and epidemiologic investigations indicate that pesticides can cause a variety of adverse acute and chronic health effects in humans and that these effects are not restricted to only a few chemical classes. Therefore, enhanced efforts are needed to control and eliminate human pesticide exposures whenever possible. Additional research is needed in all of the above-mentioned areas to better characterize and quantitate the adverse health effects of agrichemicals in humans. In particular, future studies should concentrate on those individuals at high risk for specific pesticide exposures, such as farm workers and commercial applicators.

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