Surgeon General's Conference on Agricultural Safety and Health
FarmSafe 2000 • A National Coalition for Local Action
Convened by the National Institute for Occupational Safety and Health
April 30 - May 3, 1991, Des Moines, Iowa

AN OVERVIEW OF POTENTIAL HEALTH HAZARDS AMONG FARMERS FROM USE OF PESTICIDES

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Beginning in the mid-1940's, pesticides have become an increasingly important weapon in the attempt to control troublesome agricultural pests. Consequently, agriculture has become a major consumer of pesticides and now accounts for about 65 percent of the total domestic use.[1] Pesticide use varies by the crops and livestock raised, but a majority of farmers report application of some.

In a 1982 survey, approximately 75 percent of the farmers with crops and 70 percent with livestock used pesticides.[2] With 2 million farmers, 6 million additional farm family members, and nearly 3 million hired farm workers, there is a large number of persons with potential contact with pesticides through agricultural use.[3]

Use of pesticides has been an integral component of the agricultural revolution, which over the past 50 years has greatly increased yields. Losses that would occur without the use of pesticides are difficult to estimate, but they could be sizable.[4]

Despite efforts to tailor the toxicologic properties of pesticides to specific pests, the fundamental similarity of all organisms at the subcellular level raises concerns about potential pesticide exposure of a large segment of the population.

Although we should not lose sight of the benefits pesticides provide, the purpose of this review is to evaluate the potential for, and evidence of, adverse health outcomes from pesticide exposure in humans. Acute effects have been well established, and the major focus of this presentation will be on chronic effects.

ACUTE EFFECTS

Effects from acute exposure to pesticides are well established, but statistics on injury and death from acute exposures are incomplete for the United States as a whole. Some results indicate that the number of fatalities fell between the 1950's and the 1970's.[5] Based on extrapolation from a survey of a small number of hospitals, EPA estimated that there were fewer than 3,000 annual admissions to hospitals for pesticide poisoning.[6]

In California, however, where physicians are required by law to report suspected pesticide poisonings to the Department of Food and Agriculture, approximately 2,000 poisonings have been reported annually in recent years.[7] About 50 percent of these were from occupational exposures.

More effective reporting systems are needed before the magnitude of adverse health conditions from acute exposures can be well monitored. Assessments in agriculture should include migrant workers, farm laborers, and dependents of farmers, as well as farm operators.

CHRONIC EFFECTS

Of growing concern are chronic health outcomes that do not occur immediately after exposure, including carcinogenic, developmental, immunological, reproductive, and neurological effects.[8,9] The lengthy interval between exposure and chronic effects makes risk assessment for these outcomes more difficult to evaluate than acute effects.

As testing procedures have improved, concern has increased over long-term health effects from pesticides. Today significant efforts are devoted toward experimental and epidemiologic evaluation of pesticides. The quantity and quality of the data available, however, vary by disease outcome.

Establishment of a formal testing program by the National Cancer Institute (NCI) in 1968 and continued by the National Toxicology Program (NTP) in 1978 gave carcinogenicity screening of chemicals, of which pesticides were an important concern, an early start. This experimental effort stimulated epidemiologic investigation of pesticides and cancer.

The availability of cancer registries also enhanced opportunities for cancer research by providing a readily available source of well-diagnosed cases. Registries for other chronic disease endpoints are only beginning to be established. Since we lack some of these resources, the occurrence of nonmalignant chronic disease from pesticide exposure has not been evaluated as thoroughly.

CARCINOGENIC EFFECTS

Some 47 pesticides have been evaluated in the NCI-NTP bioassay program (Table I).[10] Information from other sources is available, but is not considered here because study protocols sometimes deviate from the preferred model and because the purpose of this paper is to provide an indication of hazards presented by pesticides and not to provide a comprehensive review of all available data.

In the NCI-NTP assays, six pesticides, or 13 percent(chlordecone, dichlorvos, aminotrizole, sulfallate, dibromochloropropane (DBCP), and EDB) were positive in both sexes in mice and rats. Another 10 (21 percent) were positive in both sexes of one species (chlordane, chlorobenzilate, dieldrin, heptachlor, tetrachlorvinphos, toxaphene, nitrofen, captan, chlorthalonil, and dichloropropene). Five (11 percent) were positive in one sex of at least one species (aldrin, dicofol, piperonyl sulphoxide, chloramben, and trifluralin). For 19 (40 percent) there was no evidence of carcinogenicity in any sex/species group and seven (15 percent) provided inadequate or equivocal evidence for carcinogenicity.

Several of the pesticides positive in bioassays are no longer on the market, or their use is severely restricted, but others are widely used. The 16 chemicals positive in both sexes in at least one species include organochlorine and organophosphate insecticides, herbicides, fungicides, and fumigants, suggesting that no chemical class of pesticides can be considered problem free.

Pesticides are selected for testing for various reasons, including suspicion of carcinogenicity. With 45 percent of the pesticides tested showing some evidence of carcinogenicity, the concern about chronic human exposure would seem well founded.

Table I. Results of Carcinogenicity Testing of Pesticides from the National Toxicology Program of Bioassays in Mice and Rats (modified from reference 10).

	MICE		RATS	
	M ▼	F ▼	M ▼	F ▼
INSECTICIDES				
Aldicarb	–	–	–	–
Aldrin	+	–	E	E
Azinphosmethyl	–	–	E	E
Chlordane	+	+	–	–
Chlordecone	+	+	+	+
Chlorobenzilate	+	+	E	E
Coumaphos	–	–	–	–
Diazinon	–	–	–	–
Dichlorvos	+	+	+	+
Dicofol	+	–	–	–
Dieldren	+	+	–	–
Dimethoate	–	–	–	–
Dioxathion	–	–	–	–
Endosulphan	I	–	I	–
Endrin	–	–	–	–
Fenthion	E	–	–	–
Heptachlor	+	+	–	–
Lindane	–	–	–	–
Malathion	–	–	–	–
Maloxon	–	–	–	–
Methoxychlor	–	–	–	–
Methyl parathion	–	–	–	–
Mexacarbate	–	–	–	–
Parathion	–	–	E	E
Phosphamidon	–	–	E	E
Photodieldrin	–	–	–	–
Piperonyl butoxide	–	–	–	–
Piperonyl sulphoxide	+	–	–	–
Tetrachlorvinphos	+	+	–	+
Toxaphene	+	+	E	E

	MICE		RATS	
	M ▼	F ▼	M ▼	F ▼
HERBICIDES				
Aminotriazole	+	+	+	+
Chlorambene	+	–	–	–
Fluometuron	E	–	–	–
Monuron	–	–	+	–
Nitrofen	+	+	E	+
Sulfallate	+	+	+	+
Trifluralin	–	+	–	–
FUNGICIDES				
Anilazine	–	–	–	–
Captan	+	+	–	–
Chlorthalonil	–	–	+	+
Fenaminosulf	–	–	–	–
O-Phenylpheno-l	–	–	–	–
Pentachloro-nitrobenzene	–	–	–	–
Triphenyltin-OH	–	–	–	–
FUMIGANTS				
DBCP	+	+	+	+
Dichloropropene	I	+	+	+
EDB	+	+	+	+

E = Equivocal
I = Inadequate evidence
M = Male
F = Female

Pesticides may exert their carcinogenic effects through several mechanisms, including mutation, inhibition of gap-junctional cellular communication, peroxisome proliferation, and other promotional activities.[11] In an evaluation of genetic damage from 65 pesticides in 14 *in vivo* and *in vitro* tests, the nine chemicals were found to be active in most assays. These included organophosphate insecticides (acephate, demeton, monocrotophos, and trichlorfon), phthalimide fungicides (captan and folpet), and thio-

carbamate herbicides (diallate, sulfallate, and triallate).[12]

Another group of 26 chemicals were positive in some tests, but were generally less active than the nine chemicals above. Pesticides in this group included phenoxy herbicides (2,4-D and 2,4-DB); organophosphate insecticides (azinphos-methyl, crotoxyphos, disulfoton, and methyl parathion); ethylenebisdithiocarbamate fungicides (manzeb, maneb, mancozeb, and zineb); and pyrethroid insecticides (allethrin, chrysanthemic acid, and ethyl chrysanthemate). Thirty pesticides gave no evidence of genetic toxicity.

Some pesticides may influence the carcinogenic process in an epigenetic manner. For example, inhibition of intercellular communication can disrupt development or promote cancer.[13]

Broad occupational surveys from around the world have noted rather consistent excesses of leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the brain, skin, lip, stomach, and prostate among farmers.

A number of pesticides have been shown to inhibit gap junction intercellular communication including DDT, dieldrin, chlordane, heptachlor, Kepone, mirex, and endrin.[14] Several of these pesticides have been shown to have a promotional effect on liver carcinogenesis in the rat.[11]

Peroxisome proliferation and the resultant increased generation of hydrogen peroxide represent another possible non-genotoxic carcinogenic mechanism. Phenoxy acid herbicides appear to be peroxisome proliferators in several rodent species.[11] Much of the epidemiologic data available on the carcinogenicity of pesticides comes from studies of persons employed in agriculture.

Broad occupational surveys from around the world have noted rather consistent excesses of leukemia, non-Hodgkin's lymphoma, multiple myeloma, soft-tissue sarcoma, and cancers of the brain, skin, lip, stomach, and prostate among farmers.[15-17] These excesses occur against a background of lower overall mortality, particularly for heart disease and other cancers including lung, colon, bladder, kidney, esophagus, and liver. This pattern of low mortality from most causes of death, but excesses for a few cancers, suggests a role for work-related factors.

The low prevalence of smoking among farmers is probably related to their more favorable rates for heart disease and cancers of the lung, esophagus, and bladder.[15] High levels of physical fitness may contribute to their lower rates of colon cancer and heart disease.[17]

Case-control and other studies provide further evidence that farmers are at higher risk for selected cancers than the general population. In a recent survey of the literature,[17] excesses among farmers were seen in 12 of 13 studies of leukemia, 12 of 15 studies of Hodgkin's disease, 14 of 19 studies of multiple myeloma, 18 of 29 studies of non-Hodgkin's lymphoma, three of three studies of lip cancer, three of three studies of skin cancer, five of seven studies of brain cancer, three of five studies of soft-tissue sarcoma, six of six studies of stomach cancer, and two of three studies of prostate cancer.

The excesses for specific cancers among farmers may have broad public health implications, since several of the high-rate tumors appear to be increasing in the general population of many developed countries.[18] Of special interest are the rising rates for multiple myeloma, non-Hodgkin's lymphoma, melanoma, and cancer of the brain.

In England and Wales[19] and the United States[20], prostate cancer has also been increasing. Changes in diagnosis and reporting may account for some of the increase for these tumors.[20, 21]

The rising rates for non-Hodgkin's lymphoma, multiple myeloma, and leukemia in agricultural areas of the central United States, however, is a further indication of the possible involvement of agricultural exposures. Excesses of cancer of the brain and lymphatic and hematopoietic system have also been observed in rural farm populations in Quebec.[62]

Risks were correlated with pesticide usage and were observed among women, as well as men, raising the possibility of effects from nonoccupational exposure. The specific agricultural factors that might account for the cancers excessive among farmers have not been definitively identified, but a number of etiologic clues exist.

Exposures of interest include pesticides, fertilizers, fuels and engine exhausts, organic and inorganic dusts, solvents, ultraviolet light, and zoonotic viruses.[3] Many, perhaps even most, of the members of the general population may also have contact with some of these substances. Studies of farmers may, therefore, provide explanations for the rising incidence of certain cancers among the general population.

Although farmers come into contact with a variety of potentially hazardous substances, pesticides have received the most attention in epidemiologic studies, possibly because several pesticides are carcinogenic in bioassays.[10] Early epidemiologic investigations evaluated cancer risks associated with pesticide exposure in general.

The International Agency for Research on Cancer (IARC) in a recent deliberation concluded that exposures occurring during the application of insecticides were probably carcinogenic in man.[22] Cohort studies of applicators and manufacturers of insecticides have tended to show excesses of cancers of the lung and the lymphatic and hematopoietic system, although some investigations show deficits.[10, 11]

In these studies it was not possible to determine the specific chemicals accounting for these excesses, but most subjects were employed during a time when organochlorine insecticides were the chemicals used predominately. Although many epidemiologic studies have evaluated cancer risks among farmers and other pesticide-exposed workers,[17] only recently have there been attempts to assess risks from exposure to specific pesticides.[23]

Among those studies that have, soft-tissue sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma, leukemia, and lung cancer have been associated with DDT;[22, 24-28] non-Hodgkin's lymphoma with organophosphates;[25] soft-tissue sarcoma with a variety of animal insecticides[24]; leukemia with crotoxyphos, dichlorvos, famphur, pyrethrins, methoxychlor, and nicotine[26]; and non-Hodgkin's lymphoma[25, 29-33] and soft-tissue sarcoma[34-38] with phenoxyacid herbicides. A potential problem for other cancers is suggested by an important study of workers engaged in the production of 2,4,5-

Table II. Pesticide Effects on the Immune System (modified from reference 39).

Pesticide	Species	Summary of Effects
▸ ORGANOPHOSPHATES		
Methylparathion	Rabbit	Thymus atrophy and reduced DTH response.
	Mouse	Decreased host resistance to infection *Salmonella typimurium*.
Parathion	Mouse	Altered colony forming activities of bone marrow stem cells.
Malathion	Mouse	Suppression of CTL response *in vitro*.
▸ ORGANOCHLORINES		
DDT	Rabbit	Thymus atrophy and reduced DTH response.
Mirex	Chicken	Decreased IgG levels.
Hexachlorobenzene	Mouse	Increased sensitivity to endotoxin and malaria challenge.
	Rat	Increased humoral immune responses to tetanus toxoid and delayed-type hypersensitivity to ovalbumin.
Dieldrin	Mouse	Decreased AFC response and increased susceptibility to viral infection.
Chlordane	Mouse	Decreased contact hypersensitivity after *in utero* exposure.
	Mouse	Suppression of AFC responses and T-cell activity in a MLC reaction following *in vitro* exposure.
▸ CHLOROPHENOXY COMPOUNDS		
Pentachlorophenol	Mouse	Decreased host resistance to virus-induced tumor metastases.
2,4-D	Mouse	Enhanced T- and B-cell responses following dermal application.
▸ CARBAMATES		
Carbofuran	Rabbit	Reduced DTH response.
	Mouse	Decreased host resistance to *Salmonella typhimurium* infection.
Aldicarb	Mouse	Decreased AFC response to sheep erythrocytes.
	Human	Increased response to Candida antigen, increased number of lymphocytes expressing CD8 markers and decreased CD4+/CD8+ cell ratio.
	Mouse	No alterations in AFC response, B- or T-lymphocyte mitogenesis, host resistance to influenza virus infection, CTL response or percentages of T-cells, T-cell subpopulations or B-cells.

DTH = delayed-type hypersensitivity.
CTL = cytotoxic T lymphocytes.
AFC = antibody-forming cells.
MLC = mixed lymphocyte culture.

trichlorophenol and derivative herbicides, products contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin.[38] In this report, 20 years after first exposure, a significant 50 percent excess of total cancer occurred among workers employed for more than one year while no excess occurred among those employed for less than one year.

Risks were elevated for soft-tissue sarcomas and cancers of the esophagus, stomach, intestines, larynx, lung, and prostate. In the 20-year latency category, lung cancer increased with duration of exposure

with standardized mortality ratios (SMRs) of 96, 126, 146, and 156 for duration of exposure categories of < 1 year, 1 to < 5 years, 5 to < 15 years, and 15 or more years, respectively.

IMMUNOLOGIC EFFECTS

Pesticides have immune effects that are of interest in their own right, but they may also be an important mechanism in carcinogenesis. A critical role for suppression of immune responsiveness by pesticides has been demonstrated for infectious disease and maybe for other diseases.[39]

Pesticides have displayed a variety of effects on the immune system (Table II), including suppression of cytotoxic T lymphocyte (CTL) response by malathion, thymus atrophy and delayed-type hypersensitivity (DTH) response by methyl-parathion and DDT, decreased antibody-forming cells (AFC) responses from dieldrin and chlordane, enhanced T-and B-cell responses by 2,4-D, and reduced DTH and host resistance by carbofuran. As with carcinogenicity, immunologic effects are observed from pesticides in various chemical classes (organochlorines, organophosphates, carbamates, and phenoxy-acids). *In vitro* studies of human leukocyte functions have also shown inhibition of blastogenic stimulation[41].

Lymphocyte PHA stimulation was reduced 10 percent by carbamates, 11 to 18 percent by organophosphates, and 11 to 17 percent by organochlorines. Contact dermatitis and allergic chemical dermatitis are well-recognized health effects from pesticide exposure and can occur from exposure to various insecticides, fungicides, and fumigants.[42,42]

Immunologic evaluations of pesticide exposure in humans are in their infancy. Effects observed in animals are not always seen in human studies.[40] For example, altered numbers of T-cells and a decreased ratio of CD4/CD8 T-cells were found in women exposed to aldicarb-contaminated drinking water.[43] In investigations of aldicarb in mice, one noted an inverse dose-related suppression of antibody response,[44] while the another study did not.[45]

A critical role for suppression of immune responsiveness by pesticides has been demonstrated for infectious disease and maybe for other diseases.

There is also the possibility of a linkage between immunologic effects from pesticide exposure and cancer. It is well documented that patients with naturally occurring or medically induced immunodeficiencies experience striking excesses of non-Hodgkin's lymphoma.[46-50]

In addition, excesses of leukemia and stomach cancer have been observed among persons with primary immunodeficiency syndromes, while increases of soft-tissue sarcoma, melanoma of the skin, and squamous carcinomas of the skin and lip have been observed in renal transplant patients.[49,50] The fact that several of the tumors excessive among farmers (e.g., non-Hodgkin's lymphoma, leukemia, skin, lip, and stomach) also occur among immunodepressed patients could be a coincidence, but it may suggest that effects on the immune system play a role in farming-related cancers.

Epidemiologic investigations of alterations of the immune system are difficult because

of large interindividual variability and the confounding effects from infections, drug use and other factors that influence immune responses. Alterations in immune responses may also be short lived.

Monitoring of the immune system over an extended period may be necessary to determine the relevance of any alterations to subsequent disease risk. Consequently, it may be necessary to rely primarily upon experimental investigations in the near future. Thomas, *et al.*,[40] note two important criteria in extrapolating experimental results to humans.

- First, the pharmacologic pattern for the pesticide should be the same in humans as in the animal model. This is difficult to achieve because information on absorption, distribution, biotransformation and excretion for the chemical of interest is rarely available in both humans and the animal model.

- Second, the human end point of interest must be appropriate for the species selected.

NEUROTOXIC EFFECTS

The nervous system of the pest is the target for many pesticides, so the fact that there are acute neurotoxic effects in humans is not surprising. Anecdotal case reports and epidemiologic studies also suggest that some neurologic symptoms may persist for years.[51]

Chronic effects observed include tremors, anorexia, anemia, muscular weakness, hyperexcitability, EEG pattern changes, insomnia, irritability, convulsions, headache, dizziness, and depression. These occur from various insecticide classes including organochlorines, organophosphates, and carbamates.[51]

Many of the above symptoms developed among workers with prolonged exposure to Kepone (chlordecone) in the Hopewell incident.[52] The symptoms gradually disappeared over an 18-month period, but symptoms persisted after several years in seven of the 23 most severely affected patients.[53]

Less information is available concerning neurotoxic effects from herbicide exposure. Neuromuscular rigidity has been observed in rats after phenoxyacid exposure (2,4-D and MCPA)[54,55] and peripheral nerve conduction velocities were slowed among workers engaged in the manufacture of 2,4-D and 2,4,5-T.[56]

Other nervous system conditions may be associated with pesticide exposure. A case report of Guillain-Barré syndrome noted recent skin exposure to the cotton defoliant, merphos.[57]

An association with spraying of pesticides was reported in a case-control study of idiopathic Parkinson's disease.[58] Risk of Parkinson's disease was also associated with longer duration farming and exposure to pesticides in a study in Hong Kong.[59]

In another case-control study, however, it was associated with a rural residence and drinking well water, but not with use of pesticides.[60] The subjective end points noted in most human studies of neurologic conditions make epidemiologic investigations difficult.

Evaluation of these end points is generally not possible in animals. Closing the gap between the two approaches is critical for a thorough evaluation of neurotoxic effects of chronic pesticide exposure.

REPRODUCTIVE EFFECTS

Mattison *et al.* classify reproductive toxicants as direct-acting or indirect-acting.[61] Direct-acting toxicants may resemble a biologically important molecule and function as agonists or antagonists in the reproductive process.

They may also have direct effects because of their chemical reactivity. Most chemically-reactive substances are cytotoxic, carcinogenic, or mutagenic.

Indirect-acting reproductive toxicants include chemicals that must be metabolized to produce effects, those that interfere with critical enzyme systems, or those that enhance or suppress secretion or clearance of critical control chemicals. Some chemicals may act both directly and indirectly. For example, activities for organochlorine insecticides are suspected to act directly through estrogen receptors and indirectly through prohormone hepatic induction.

Reproductive effects of specific pesticides have recently been reviewed by Mattison *et al.*, 1990.[61] Adverse outcomes in experimental and/or epidemiologic investigations have been reported for DBCP, chlordecone, ethylene dibromide, and carbaryl in males and DDT, chlordecone, lindane, organophosphates, and carbamates among females.

Effects among males have included disruption of spermatogenesis by DBCP, reduced sperm motility and viability by chlordecone, abnormal sperm morphology and sterility by ethylene dibromide, and sperm abnormalities by carbaryl. In animals, studies have noted reduced egg shell thicknesses from DDT, reduced egg production and number of offspring from chlordecone, increased estrone metabolisms by liver microsomal enzymes by lindane, reduced egg production by organophosphates, and reduced fertility by carbamates.

CONCLUSIONS

Experimental and epidemiologic investigations indicate that pesticides can cause a variety of adverse effects including carcinogenicity, immunotoxicity, neurotoxicity, and reproductive toxicity. From this brief review several points stand out.

- First, the carcinogenicity of pesticides has been more thoroughly evaluated than other toxic effects and approximately 45 percent of the chemicals tested had an effect in at least one sex of one species in NCI-NTP bioassays. If this experience is relevant to other end points, the potential for any type of adverse outcome from pesticide exposure could be considerable.

- Second, the specific pesticides that are positive in the various toxicologic tests do not appear to be restricted to a few chemical classes. Effects are noted from insecticides (organochlorines, organophosphates, carbamates, and pyrethrins), herbicides, and fungicides.

- Third, adverse outcomes have been noted in epidemiologic, as well as experimental investigations, indicating that humans are also at risk.

RECOMMENDATIONS

1. Given the evidence for adverse health outcomes from pesticides, enhanced efforts are needed to control exposures in agriculture and elsewhere.

2. More thorough evaluations (experimental and epidemiologic) are needed to more fully characterize the potential adverse effects that may occur from pesticide exposures.

3. Epidemiologic investigations must focus on exposures to specific pesticides. This will require detailed exposure assessment procedures to characterize the type and intensity of exposures.

4. Studies of farm populations should receive a high priority given the widespread use of pesticides in agriculture and the potential for exposure among farmers and farmer laborers, and their dependents.

Retrospective designs can be used to address specific questions, but prospective studies should also be initiated. Prospective investigations provide the opportunity to obtain information on exposure as it occurs, which would eliminate the potential for response bias and would minimize exposure misclassification. Once exposures are well characterized, prospective designs can also be used to evaluate a number of adverse health outcomes, a highly efficient approach in these times of funding limitations.□

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