PESTICIDES AND CANCER

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Pesticides, which are agents that kill weeds, insects, fungus, spiders, and other pests, are biologically active chemicals that also can affect humans. The effects on humans include acute problems, such as neurotoxicity, for which the pesticide may have been designed, and unexpected chronic outcomes, such as cancer. This chapter reviews the evidence for carcinogenicity of pesticides and describes the research needed to clarify and quantify the role of pesticides in human cancer.

EVIDENCE OF CARCINOGENICITY FROM ANIMAL STUDIES

Animal studies present ample evidence for the carcinogenicity of many pesticides.[11,44] Of 51 pesticides evaluated by the National Cancer Institute and the National Toxicology Program as of 1990, 24 demonstrated carcinogenicity in chronic bioassays.[11] Because the pesticides were selected for testing due to a high degree of a priori suspicion, one cannot assume that approximately 50% of all pesticides are animal carcinogens. However, the NCI/NTP data show that many pesticides are animal carcinogens. Table 1 presents pesticides classified by the International Agency for Research on Cancer as having limited or sufficient evidence for carcinogenicity in animals.

The carcinogenic agents belong to each type of pesticide (e.g., herbicides, insecticides, fungicides) and to several chemical classes (e.g., triazines, organophosphates, organochlorines). Similarly, among each type of pesticide and each chemical class, there are agents that do not appear to cause cancer in animals. Based on current

TABLE 1. Pesticides with Limited or Sufficient Evidence of Carcinogenicity in Animals

Pesticide	Animal Evidence of Carcinogenicity	Currently Registered in United States
Herbicides		
Amitrole	Sufficient	Y
Atrazine	Limited	Y
Diallate	Limited	Y
Monuron	Limited	Y
Nitrofen	Sufficient	N
Picloram	Limited	Y
Sulfallate	Sufficient	N
Trifluralin	Limited	Y
Insecticides		
Aldrin	Limited	N
Aramite	Sufficient	N
Arsenic and arsenical compounds	Limited	N/severely restricted
Chlordane/heptachlor	Sufficient	N
Chlordecone	Sufficient	N
Chlorobenzilate	Limited	N
DDT	Sufficient	N
Dichlorvos	Sufficient	Y
Dicofol	Limited	Y
Dieldrin	Limited	N
HCH, α-HCH	Sufficient	N
β-HCH, γ-HCH (Lindane)	Limited	Y
Methyl parathion	Limited	Y
Mirex	Sufficient	N
Tetrachlorvinphos	Limited	Y
Toxaphene	Sufficient	N
Nonarsenical insecticides	Limited	Y
Fungicides		
Captafol	Sufficient	N
Captan	Limited	Y
Chlorothalonil	Limited	Y
Ethylene thiourea (ETU)	Sufficient	Y (contaminant/metabolite of a registered product)
Formaldehyde	Sufficient	Y
Hexachlorobenzene	Sufficient	N
Pentachloronitrobenzene	Limited	Y
Pentachlorophenol	Sufficient	Y
Ortho-phenyl phenol	Sufficient	N
Sodium ortho-phenyl phenate	Sufficient	N
2,4,6-trichlorophenol	Sufficient	Y
Ziram	Limited	Y
Other		
Creosote	Sufficient	Y
1,2-Dibromo-3-chloropropane	Sufficient	N
1,3-Dichloropropene	Sufficient	Y/severely restricted
Dimethylcarbamoyl chloride	Sufficient	
1,1-Dimethyl hydrazine	Sufficient	
Ethylene dibromide	Sufficient	N
Methyl bromide	Limited	Y
Methyl mercury chloride	Sufficient	N

Information from International Agency for Research on Cancer: Monographs on the evaluation of carcinogenic risk of chemicals to humans. Volumes 1–69. Lyon, France, IARC, 1969–1997; and from Farm Chemicals Handbook. Volume 83. Willoughby, Ohio, Meister Publishing, 1997. See also references 51 and 54.

knowledge, chemical characteristics cannot be used to identify or accurately predict which pesticides are carcinogenic in animals.

Many pesticides identified as actual or possible animal carcinogens are still in use in the United States.[51,54] Furthermore, many compounds banned or severely restricted in the U.S., notably many organochlorine insecticides, are still in use in other countries. In addition to worker exposure in other countries, U.S. citizens also may be exposed through contamination of foodstuffs imported into the U.S., a process referred to by some as the "circle of poison."

Animal studies have shown that pesticides exert their carcinogenic effect through a variety of mechanisms (Table 2). Some are classic genotoxic agents: they react with cellular DNA to cause mutations or gross DNA rearrangements.[66] Examples include the organophosphate insecticides dichlorvos and methyl parathion, the fungicide captan, and the fumigants DBCP and ethylene dibromide.[11,66] Some other pesticides, however, are largely negative in genotoxicity tests but are carcinogenic in animal bioassays, such as DDT, chlordane, hexachlorobenzene, heptachlor, and lindane,[11] suggesting that other mechanisms may play a role. Several pesticides, particularly some of the organochlorine insecticides, are tumor promoters, perhaps operating through their ability to inhibit gap junctional intercellular communication.[160,182] An example is DDT-accelerated formation of mammary tumors that were induced by 2-acetamidophenanthrene in rats.[145]

Hormonal action is another mechanism by which some pesticides act. For example, the herbicide atrazine is generally nongenotoxic[28,49,90] but is associated with increased incidence of mammary tumors, uterine adenocarcinomas, and lymphatic and hematopoietic malignancies in animal bioassays.[90] It is likely that at least the mammary and uterine tumors are related to atrazine's lengthening of the estrous cycle, prolonging exposure to endogenous estrogen.[48,49,173] Several organochlorines, including DDT, methoxychlor, and chlordecone, have demonstrated estrogenic activity.[40]

Alteration of immune function is a known cause of human cancer and may be responsible for the carcinogenicity associated with some pesticides.[158,167] Malathion suppresses cytotoxic T lymphocyte cytolysis, an aspect of cell-mediated immunity.[138] DDT causes thymus atrophy and reduced DTH response.[156] The fungicide captan is a strong sensitizer.[107] 2,4-D is associated with enhanced T and B cell immune response in the mouse[23] and reductions in lymphocyte subsets, including circulating helper and suppressor T cells, cytotoxic T lymphocytes, natural killer cells, and lymphocyte mitogenic responses among farmers.[59] Organophosphates may play a role in oncogenesis through inhibition of serine esterases, which are critical components in the cytolytic activities of T lymphocytes and natural killer cells.[117]

TABLE 2. Possible Mechanisms for Pesticide Carcinogenicity

Mechanism	Examples
Genotoxicity	Captan, 1,2-dibromo-3-chloropropane, dichlorvos, ethylene dibromide, parathion, sulfallate, toxaphene
Tumor promotion	Chlordane, DDT, heptachlor, hexachlorobenzene, lindane, mirex
Hormonal action	Aminotriazoles, atrazine, chlordecone, DDT, methoxychlor, ziram
Immunotoxicity	Aldicarb, chlordane, 2,4-D, DDT, dieldrin, hexachlorobenzene, malathion, mirex, parathion, pentachlorophenol
Peroxisome proliferation	Chlorophenols, 2,4-D, lactofen, MCPA, 2,4,5-T, tridiphane

Peroxisome proliferation, a characteristic of chlorophenols and phenoxyacetic acid herbicides,[165,166] is another nongenotoxic carcinogenic mechanism in rodents, although its role in human carcinogenesis is unclear.[11]

Carcinogens that operate through nongenotoxic mechanisms are problematic in terms of identification and regulation. The lack of standardized, accepted protocols for testing nongenotoxic mechanisms means that identification is difficult and often controversial. If the testing is not required by the Environmental Protection Agency (EPA) for registration, the testing might not be done. If it is done, few established procedures exist for using the results of nongenotoxic tests in risk assessment. To date, in the absence of genotoxicity, a substance shown to be carcinogenic in animals or in epidemiologic studies is much less likely to be regulated than a genotoxic substance.

PESTICIDE EXPOSURE

Agricultural Occupations

Occupational groups potentially exposed to pesticides are presented in Table 3.[111,119] Agriculture accounts for approximately 80% of pesticides used in the U.S.,[111] including use by farmers, farmworkers, pesticide mixers and loaders, custom pesticide applicators, crop duster pilots and flaggers, agricultural extension agents, and other occupational groups. Spouses of farmers may have direct work exposure to pesticides through their involvement in farm activities and through laundering of pesticide-contaminated clothing.[20] The estimates of the frequency of women who apply pesticides vary. Sachs reported that 5% of "farm women" applied fertilizers and pesticides.[141] About 15% of Nebraska farm women reported a history of ever having applied insecticides and 3% reported past herbicide application.[194] Preliminary data from the Agricultural Health Study being conducted by the National Cancer Institute, the National Institute of Environmental Health Sciences,

TABLE 3. Occupational Groups Potentially Exposed to Pesticides

Farmers	Herbarium curators
Farmworkers	Custodians
Pesticide manufacturers and formulators	Nursery and greenhouse workers
Pesticide mixers and loaders	Wood preservation workers
Agricultural pesticide applicators	Chemical lawn care workers
Crop duster pilots	Golf course workers
Flaggers for crop duster pilots	Park maintenance workers
Agricultural extension agents	Landscape maintenance workers
Food processors	Highway, railway bed, right-of-way maintenance workers
Packing house workers	Mosquito abatement workers
Fumigation workers	Textile workers
Grain millers	Paper and pulp workers
Forestry workers	Paint manufacturers
Veterinarians	Morticians
Pet groomers	Warehouse workers
Structural pest control operators	Military personnel

Adapted from Moses M, Johnson ES, Anger WK, et al: Environmental equity and pesticide exposure. Toxicol Ind Health 9:913–959, 1993.

and the EPA show that about one-third of farm spouses apply pesticides, for an average of 13 years and 12 days per year.[4] Children can comprise as much as 25% of the agricultural workforce during the summer harvest[111] and are potentially exposed to pesticides from nearby applications and through residues on crops.[148] Some children may accompany their parents to the fields because of a lack of alternative day care.[20,189] The exposures to children are troublesome because children may be particularly susceptible to the carcinogenic effects of pesticides.[100,191]

Nonagricultural Occupations

A wide variety of nonagricultural occupational groups have potential exposure to pesticides (Table 4), including structural pest control operators, lawn care workers, grounds maintenance workers, warehouse workers, pet groomers, paint manufacturers, and custodians.[111,119] The exposures for some of these groups are substantial and the number exposed can far exceed the number of farmers.[119]

Pesticides may enter the body by dermal absorption, inhalation, or oral absorption, with the primary route being dermal absorption.[119] The extent of absorption depends on the type of formulation of the pesticide (e.g., liquid, granular), the area of the skin exposed, and the condition of the skin.[119] The latter two factors are generally a function of the type of application equipment, the use of protective equipment, the frequency of washing, weather conditions, the immediacy of removal of pesticide-contaminated clothing after pesticide application, and other personal work habits.[82,119,192] The greatest exposures appear to be associated with mixing and loading pesticides in comparison to spraying, flagging, or other tasks.[111,119] Percutaneous absorption varies by site of the body. In humans, more parathion is absorbed from the forehead than from the forearm.[171] In rats, the permeability of the skin also varies by location (the abdomen was more permeable than the back) and sex (the permeability of female skin was about twice that of male skin).[25]

TABLE 4. Nonoccupational Sources of Pesticide Exposure for the General Population

Agricultural application drift, overspray
Agricultural application off-gassing, volatilization
Ground water contamination
Surface water contamination
Soil contamination
Food contamination
Indoor air contamination at homes, schools, office, aircraft, other buildings
Homeowner indoor pest control application
Homeowner lawn and garden pest control application
Drift from lawn and garden pesticide application
Drift from public land maintenance and insect control
Recreational areas such as golf courses and parks
Pet products
Leaks, spills, accidents
Pollution from manufacturing sources
Disposal sites

Adapted from Moses M, Johnson ES, Anger WK, et al: Environmental equity and pesticide exposure. Toxicol Ind Health 9:913–959, 1993.

General Population

There is ample evidence that the general population is exposed to pesticides.[119] Residues of pesticides and their metabolites have been found in blood, urine, breast milk, adipose tissues, and other tissues in numerous studies, most notably the National Health and Nutrition Examination Survey and the National Human Adipose Tissue Survey.[98,113,119] High levels of exposure are associated with lower socioeconomic status and African-American race, even after control for socioeconomic status.[99,111,119]

Some of the general population exposure is related to agricultural use of pesticides. Exposure can occur as a result of agricultural application drift, overspray, or off-gassing.[111,119] Farm family members may be exposed through the contamination of soil, vehicles, furniture, carpets, and house dust,[20] particularly young farm children, who are likely to spend a large proportion of their time on the floor or ground and who frequently put objects in their mouths.[148] Persistence in house dust may be a special problem because pesticides have been measured in house dust in situations where they could not be detected in indoor air.[137] Pollution from sites where pesticides are manufactured also occurs. Twenty percent of Arkansas children who lived near an herbicide manufacturing plant had residues of 2,4-D in their urine.[81]

Members of the general population also may be exposed to agricultural pesticides via contamination of ground and surface water from agricultural runoff. The U.S. Department of Agriculture estimates that 50 million people in the U.S. obtain their drinking water from ground water that is potentially contaminated by pesticides and other agricultural chemicals.[118] The EPA's National Pesticide Survey of drinking water wells found one or more pesticide or pesticide degradate in 10.4% of community water systems and 4.2% of rural domestic wells.[52] Conventional drinking water treatment techniques do not remove the pesticide contaminants. A 1994 study of tests for five herbicides in 20,000 samples of tap water and drinking water sources found that 14.1 million people routinely drink water contaminated with atrazine, cyanazine, simazine, alachlor, and metolachlor.[179] Many samples contained two or more herbicides. A 1995 survey by another environmental organization found widespread contamination of tap water by herbicides, frequently at levels exceeding the EPA Lifetime Health Advisory Level.[37] Again, multiple pesticides were found simultaneously in approximately two-thirds of the cities.

Pesticides can persist in the ground water even after use has been curtailed. For example, DBCP (dibromochloropropane), a soil fumigant banned in California in 1977, is still found in sufficient quantities in California ground water[93,164] to "pose a significant health risk in agricultural areas."[164]

Food can become contaminated by pesticides, particularly insecticides, as a result of treatment in the field and from pesticides used in the home.[119] Although diet does not appear to be a major route of exposure for most pesticides,[85] concerns exist over the occasional single food item that may have extremely high residues (e.g., one potato had lethal levels of aldicarb)[129] and the effects on children, who typically eat more fruits per unit of body weight than adults and who may be particularly sensitive to toxic effects due to immature metabolism and other factors.[116] A 1995 survey of 76 jars of baby food from groçery stores found 16 pesticides in eight brand-name products. The pesticides detected included three probable human carcinogens and five possible human carcinogens, as classified by EPA.[180] Infants can also be exposed to pesticides and pesticide metabolites in breast milk and via placental transfer.[68,139]

The majority of the general population's exposure to pesticides is from non-agricultural sources (Table 4), primarily from indoor air use of pesticides in the home, particularly for children.[71] The National Home and Garden Pesticide Use Survey, conducted by the EPA, found that 82% of U.S. households used pesticides with an average of three to four different pesticide products per home.[174] Sixty-six percent of households treated the home's primary living areas one or more times per year.[174] Thirty-seven percent of households reported insecticide treatments when there was no major insect problem.[174] These data were consistent with the earlier National Household Pesticide Usage Study[144] which reported 84% of households used pesticides inside the home. In data from a childhood cancer case-control study, Leiss and Savitz[101] reported that 26% of control households had a history of home extermination and 27% reported use of pest strips. Use of termiticides outside and beneath a home can also result in indoor pesticide exposure.[119] There are also case reports of extreme pesticide use, such as the report of a child whose mattress was sprayed two times per week for most of his life with DDVP-Baygon, a combination of an organophosphate and a carbamate insecticide.[134]

Pesticide use on gardens and lawns may also result in exposure either during application, particularly if no protective equipment is used,[77] or if engaging in activities on the lawn within one day of application.[76] The National Home and Garden Pesticide Survey[174] found that 22% of households used herbicides on the yard or garden annually. Similar frequencies of use, ranging from 21–33%, have been reported in other surveys.[67,119,144] The use of lawn care pesticides is increasing 5–8% annually.[155] Cumulative lifetime use of lawn chemicals was reported to be 63%[101] and 68%[78] in the control populations of two cancer case-control studies. The amount of pesticides per treated acre of household lands is almost five times the application rate for treated agricultural lands.[130] A biomonitoring study of dogs found that animals having contact with lawns treated with 2,4-D had measurable levels in their urine for several days after application.[136] Thus, incidental contact with lawn care pesticides may lead to exposures.

Both indoor and outdoor pesticide use results in household contamination, particularly in carpets,[31,119,120] that can persist for years because of the lack of sun, rain, and other factors that speed pesticide degradation outdoors.[39,102,154,175] The number and concentration of pesticides found in household dust are greater than those found in air, soil, or food.[102,175] These residues are of great concern for children. In one study of a broadcast flea treatment, the household residues had a vertical (floor to ceiling) concentration gradient; the resulting respiratory dose estimated for a child was four to six times greater than that for an adult and the dermal dose estimates were 30 times greater.[60]

PESTICIDES AND CANCER

Occupational Studies

Most of the information known on pesticides and human cancer has come from studies of farmers.[11,17,20,92,124,188] Numerous studies have been conducted worldwide, with reasonably consistent results. Some reports, however, have observed few excesses.[176,178] Typically, farmers tend to have higher than expected rates of cancers of the lymphatic and hematopoietic system, lip, stomach, melanoma, other skin cancers, prostate, brain, testes, and soft tissue sarcoma (Table 5). On the other hand, farmers tend to have low mortality overall and for most other causes of death.

The magnitude of the excesses of the cancers reported more frequently in studies of farmers is not usually large. Farmers, however, are a heterogeneous group in

TABLE 5. Cancers Generally Found to Be Excessive among Farmers and Other Occupational Groups Potentially Exposed to Pesticides

Lip	Lung*
Stomach	Soft tissue sarcoma
Melanoma	Non-Hodgkin's lymphoma
Other skin cancers	Hodgkin's disease
Prostate	Multiple myeloma
Brain	Leukemia
Testis	

* Lung cancer generally occurs less frequently than expected among farmers but has been reported to be excessive among other pesticide-exposed occupational groups, including structural pest control operators, golf course superintendents, and some pesticide manufacturers.

terms of numerous factors, such as crops grown, animals raised, soil and climactic conditions, pests, protective equipment, work practices, and, consequently, type and amount of pesticide exposure. Grouping all farmers together without consideration for individual pesticide exposure would result in a dilution of high risk among subgroups of farmers and a small excess risk overall.

Cancer patterns among other pesticide-exposed occupational groups are similar to patterns in farmers, with the exception of lung cancer. Farmers, who have a low prevalence of smoking, tend to have a lower than expected lung cancer mortality.[16,20,124] Structural pest control operators[10,14,106,128,157] golf course superintendents,[97] and some pesticide manufacturing workers,[45,105] who share many exposures with farmers, have greater than expected lung cancer mortality. This excess may be related to a higher rate of cigarette smoking in these groups or, perhaps, particularly for the structural pest control operators, exposure to pesticides in more enclosed settings with greater respiratory exposure than farmers. Lung cancer was one of the major cancer sites contributing to the IARC classification of "the occupation of insecticide spraying" as having limited evidence of carcinogenicity in humans.[90] Lung cancer has been elevated among male farmers[157] and females exposed to pesticides[27] in case-control studies where effects of tobacco use could be controlled.

Female farmers and female members of farm families have not been evaluated as extensively as male farmers[5,108] but appear to experience excesses of many of the same malignancies as male farmers—cancers of the lymphatic and hematopoietic system, lip, and stomach[13,61,63,64,132,140,170,177,194,195]—as well as ovarian cancer.[46,47]

The number of studies that have evaluated individual or classes of pesticides is extremely small; most have considered pesticides as a group without further characterization of exposure. Studies that attempt to evaluate individual exposures are difficult to design and interpret because people are rarely exposed to one pesticide. Large numbers of subjects with varying patterns of pesticide exposures are needed to disentangle the effects of multiple exposures. A few studies have attempted to do so,[12,82,192,193] and a few have had a limited number of simultaneous exposures,[168,176] but many of the reports of associations between specific pesticides and cancer have not accounted for multiple pesticide exposures. Despite these limitations, there is strong evidence that selected phenoxyacetic acid herbicides, triazine herbicides, arsenical insecticides, organochlorine insecticides, and organophosphate insecticides play a role in certain human cancers (Table 6).

TABLE 6. Pesticides and Cancer Associations Reported in Epidemiologic Studies

Pesticide	Cancer
Phenoxyacetic acid herbicides	Non-Hodgkin's lymphoma, soft tissue sarcoma, prostate, Hodgkin's disease, multiple myeloma, stomach, lung, nasal, and nasopharyngeal
2,4-D	Non-Hodgkin's lymphoma, prostate
2,4,5-T	Soft tissue sarcoma
MCPA	Soft tissue sarcoma
Triazine herbicides	Ovary
Atrazine	Ovary
Arsenical insecticides	Lung, skin, non-Hodgkin's lymphoma
Organochlorine insecticides	Leukemia, non-Hodgkin's lymphoma, soft tissue sarcoma, pancreas, skin, lung, liver, breast, neuroblastoma, multiple myeloma
Chlordane	Lymphoma, lung, neuroblastoma
DDT	Leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, pancreas, lung, liver, multiple myeloma, skin, soft tissue sarcoma, breast
Lindane	Lymphoma, breast
Methoxychlor	Leukemia
Toxaphene	Lymphoma
Organophosphate insecticides	Non-Hodgkin's lymphoma, leukemia, lung
Crotoxyphos	Leukemia
Diazinon	Non-Hodgkin's lymphoma
Dichlorvos	Leukemia, non-Hodgkin's lymphoma
Famphur	Leukemia
Malathion	Non-Hodgkin's lymphoma

PHENOXY HERBICIDES

Phenoxy herbicides include 2,4-D (the second most commonly used herbicide in the U.S.), 2,4,5-T (banned in the U.S. in 1978), MCPA, and other related compounds. In 1981, the first of a series of studies from Sweden was published indicating a sixfold excess of malignant lymphoma among persons exposed to phenoxy herbicides or chlorophenols.[74] In 1986, Hoar et al. reported a twofold excess of non-Hodgkin's lymphoma among farmers who reported use of phenoxy herbicides.[82] Risk rose significantly with days per year of use of herbicides, surpassing sevenfold among those reporting use for 21 or more days per year and reporting use of 2,4-D. Use of other pesticides did not appear to explain the excess. Similar associations between 2,4-D and non-Hodgkin's lymphoma were observed in Nebraska,[192] Canada,[176] and Australia.[150] In New Zealand, however, duration and frequency of use of phenoxy herbicides were not associated with non-Hodgkin's lymphoma[123]; neither was non-Hodgkin's lymphoma elevated in a study of Finnish phenoxy herbicide applicators.[8] Similarly, non-Hodgkin's lymphoma was not significantly associated with 2,4-D use in a study conducted in Iowa and Minnesota,[33] but no information was collected on days per year of use in the original interviews. A later effort to collect intensity-of-use information suffered from the greater mortality among the cases than the controls and the data were judged to be biased by peer reviewers.[32] In addition, a study in Washington State[187] revealed an elevated risk of non-Hodgkin's lymphoma among farmers, but the excess did not appear to be related to phenoxy herbicides.[186] Cohorts of workers who manufacture 2,4-D and other phenoxy herbicides have not shown statistically significant excesses of non-Hodgkin's lymphoma,[24,36,104] but most were small cohorts that lacked sufficient statistical power to evaluate this relatively rare cause of death.[21] Soft tissue sarcoma[35,36,57,62,72,73,75,104,122,142,168] and prostate cancer[109] also have been linked to

exposure to phenoxy herbicides or its contaminants, such as dioxin. Use of 2,4-D on lawns has been associated with lymphoma in dogs in one study.[78]

Some military personnel who served in Vietnam were exposed to Agent Orange, a combination of the two phenoxy herbicides, 2,4-D and 2,4,5-T. Studies of Vietnam veterans have revealed excesses of non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue sarcoma, nonmelanotic skin cancer, and cancers of the kidney, testes, and, among female veterans, pancreas.[88,89]

The association between non-Hodgkin's lymphoma and 2,4-D reported in the Kansas study in 1986 was somewhat surprising because there was little toxicologic evidence of carcinogenicity for this compound.[112] 2,4-D has been negative in the Ames assay, mouse micronuclei assay, and unscheduled DNA synthesis assay,[53] although some cytogenetic studies have reported positive results.[2,50,94,115,161] The carcinogenicity bioassays of 2,4-D published before 1986 were negative but are considered inadequate by current experimental standards.[84] New studies on rats and mice that were completed in 1986 and 1987 showed a high rate of brain cancer in male rats in the highest exposure group.[79,80] The EPA requested additional studies at higher doses to clarify the finding. Reports on these studies, submitted to the EPA in 1995 and 1996,[91,152,153] showed no evidence of carcinogenicity in rats or mice in either gender at any dose level.

Triazine Herbicides

Triazine herbicides include atrazine, the most commonly used herbicide in the U.S. Atrazine has been classified by IARC as having limited evidence for carcinogenicity in animals, based on increases of mammary tumors in male rats, uterine adenocarcinomas and tumors of the hematopoietic system in female rats, and increased lymphomas in mice.[90] Triazine exposure was associated with a two- to four-fold increased risk of ovarian cancer in two studies in Italy.[46,47] The women were exposed primarily through agricultural work in corn cultivation. Almost ten times more atrazine than simazine was sold in the area, suggesting that atrazine is the triazine most likely to be responsible for the association.

Atrazine was suggested to be associated with non-Hodgkin's lymphoma in studies conducted in Kansas[82] and Nebraska.[192] However, when these studies were combined with a third study and exposures for other pesticides taken into account,[193] the association did not persist. When multiple exposures were considered, there was little or no increase in the risk of non-Hodgkin's lymphoma attributable to atrazine. A cohort study of workers at two triazine herbicide manufacturing plants reported a nonsignificant increase in deaths from non-Hodgkin's lymphoma; however, two of the three decedents with non-Hodgkin's lymphoma had worked for less than a year in triazine-related jobs.[143]

Arsenical Insecticides

Arsenic and arsenical compounds are the only pesticides classified by IARC as having sufficient evidence of being carcinogenic to humans, based on excesses of lung and skin cancer.[90] They also have been linked to a small excess risk of non-Hodgkin's lymphoma among fencing workers.[125,126] Arsenical compounds, used primarily in sheep dips and vineyards, are still used as insecticides in developing countries and as wood preservatives in many countries.

Organochlorine Insecticides

Organochlorine insecticides once represented the most commonly used insecticide class in this country. Although use has decreased because many organochlorines

have been banned or severely restricted in the U.S., some are still used and use persists in many other countries. In occupational populations, organochlorines as a group have been associated with increased risks of leukemia,[26] lymphoma,[33,127,187] and soft tissue sarcoma.[190] Chlordane has been associated with excess lymphoma[33] and lung cancer.[106] DDT has been linked to excess risks of leukemia,[26] lymphoma,[33,127,187] pancreatic cancer,[65] and lung cancer.[9,185] Lindane was associated with excess lymphoma, a relationship that persisted after adjustment for other pesticides.[12] Methoxychlor was associated with leukemia[26] and toxaphene with lymphoma.[33]

ORGANOPHOSPHATE INSECTICIDES

Organophosphate insecticides, whose use has grown as use of organochlorine has decreased, have been linked to leukemia,[26] non-Hodgkin's lymphoma,[33,192] and lung cancer.[128] Analyses for individual organophosphates have shown excess leukemia risks among farmers exposed to crotoxyphos, dichlorvos, and famphur[26] and excess non-Hodgkin's lymphoma risk among those exposed to diazinon, dichlorvos, and malathion.[33] These associations, however, have not taken into account each subject's potential for multiple exposures. A tenfold excess of hairy cell leukemia, a rare lymphoid chronic leukemia, was associated with organophosphate insecticides in one study, a relationship that remained significant after accounting for all other pesticide exposures.[34]

General Population Studies

There are far fewer studies of pesticide-related cancer among the general population than among occupational populations and most lack detailed exposure assessment, with the exception of studies based on measurements of pesticides and pesticide metabolites in biologic tissues. Typically, the general population is less able to report histories of use of individual pesticides than farmers and other occupational groups. Most general population studies use exposure categories such as pesticide use in general, broad pesticide classes, and general product types, such as pest strips. It is important to conduct and improve exposure assessment in these studies because of the widespread potential for exposure.

CHILDHOOD CANCER

Many of the studies of pesticides among the general population are of children.[191] Beginning in the late 1970s, there were case reports linking pre- and postnatal exposure to chlordane with neuroblastoma and childhood leukemia,[55,86,87] organophosphate insecticides to aplastic anemia and acute leukemia,[134,135] insecticides used in production of cotton and soybeans to colorectal cancer,[133] and pesticides in general to leukemia, lymphoma, neuroblastoma, and Wilms' tumor.[110] Case-control studies have linked pesticide exposure to childhood cancer, in some instances with greater magnitude risks than in studies of occupationally exposed adults. Maternal employment in agricultural occupations or reported exposure to pesticides during pregnancy was associated with acute lymphocytic leukemia in a case-control study in China.[147] Occupational exposure to pesticides by either parent and use of pesticides in the home or garden during childhood was linked to acute myeloid leukemia in children in the U.S.[30] Use of pesticides in the home or garden during pregnancy—by the father or mother—was associated with three- to ninefold increases in childhood leukemia in a Los Angeles study.[103] Pest strips, typically made with the organophosphate insecticide dichlorvos, were associated with childhood leukemia[101] and brain cancer[41] in one case-control study each. Childhood non-Hodgkin's

lymphoma was associated with household or garden insecticide use,[29] home extermination,[101] and parental occupational exposure to pesticides.[96] Childhood Hodgkin's disease and osteosarcoma has been associated with parental employment in chicken farming.[96] Two studies have reported excess Ewing's sarcoma among children whose parents had occupational exposure to pesticides.[83,183] Soft tissue sarcoma among children was associated with yard treatments thought to have involved 2,4-D, carbaryl, and diazinon.[101] Brain cancer has been linked to pesticide exposure of children themselves[38,41,70] or their parents during pregnancy.[41,96,149,181] Wilms' tumor has been linked to household or garden insecticide use[121] and parental occupational exposure to pesticides.[96,146]

Many of the case-control studies of pesticides and childhood cancer are limited by the small number of exposed subjects. The possibility of recall bias is also a concern. However, several studies have attempted to evaluate recall bias and have generally not found strong evidence for its occurrence in studies of pesticides.[15,18,41] These limitations could be overcome by the recently launched Agricultural Health Study, a prospective cohort study of licensed pesticide applicators and their spouses, which will also register the children for possible future follow-up.[4]

Adult Cancer

Studies of adult cancers associated with general environmental exposure to pesticides are few. Residential proximity to cranberry bogs, whose cultivation involves numerous herbicides, insecticides, and fungicides, has been linked to brain cancer, particularly astrocytoma.[7] It is noteworthy that many of the same cancers increasing in incidence in the general population are those that generally are excessive among agricultural populations.[22]

Much recent research on pesticides has evaluated the relationship between female breast cancer and measures of DDT, other organochlorines, and their metabolites in biologic tissues.[1,3,40] The studies linking organochlorines to increased breast cancer risk include ecologic studies,[42,172] prospective cohort studies,[95,184] and several case-control studies,[43,58,114,162,163,169] particularly estrogen-receptor positive breast cancer,[43] the subtype of breast cancer that has been increasing in recent decades.[69] In addition, there are differences in the pattern of p53 mutations in breast cancers in women from the Midwest, an area with intensive agriculture, and in breast cancers in other populations.[151] However, the relationship between breast cancer and pesticides remains controversial[1,3] because of unanswered questions concerning possible confounding by a high-fat diet; racial variation[95]; inconsistent ecologic evaluation of socioeconomic status, organochlorine body burdens, and breast cancer; role of lactation; possible disease effects; and other factors.

DDT and many other organochlorines have been banned in the U.S. but persist in the environment and accumulate in adipose tissue. Also, use continues in many other countries. The compounds have estrogenic properties that may increase cancer risk by altering estrogen metabolism.[40] Multiple exposures interacted synergistically in a yeast estrogen assay.[6] The pesticides with estrogenic activity include DDT, methoxychlor, hexachlorobenzene, HCH, α-HCH, β-HCH, γ-HCH (lindane), chlordane, heptachlor, mirex, chlordecone (Kepone), aldrin, and dieldrin. Atrazine, although not persistent in biologic tissues, may influence cancer in women through its endocrine disruption.[40]

RESEARCH NEEDS

A major need in research on pesticides and cancer is that studies be conducted so the effects of individual pesticides or known combinations of pesticides can be

evaluated (Table 7). It is important to clarify the general population's cancer risk from pesticides with high-volume use, such as atrazine, phenoxy herbicides, and organophosphate insecticides. More studies with crude exposure assessments will not make major contributions to our understanding. To facilitate research on specific pesticides, improvements in exposure assessment in epidemiologic studies are needed.[16,19] Validity and reliability studies of recall of pesticide use for both occupationally and nonoccupationally exposed populations are needed. The effects of exposure misclassification on risk estimates should be evaluated. The opportunities provided by recently developed techniques, such as computerized geographic information systems, should be exploited.[159]

Continued efforts should be made to obtain information on the identity of the so-called "inert" ingredients in pesticide formulations. These ingredients, while not responsible for the pesticidal action of the formulations, are not biologically inert and can be extremely important when trying to correctly assess the carcinogenic potential of a pesticide. In October 1996, a United States federal court ruled that pesticide companies must declare information about inert ingredients in six pesticides, rejecting claims that their identities were trade secrets. Although the ruling only applied to the six products named, it might become precedent-setting.

The role of epigenetic mechanisms of carcinogenicity, particularly endocrine disruption and immunotoxicity, needs more research. The implications of the synergistic activation of the estrogen receptor by combinations of estrogenic pesticides observed in yeast[6] need to be evaluated in humans, if possible. Better science-based procedures are needed for incorporating epigenetic mechanistic data and epidemiologic data into risk assessment.

As research on pesticides and cancer continues, it is important to broaden the focus to include populations that may have been understudied in the past or that may be at higher risk. For example, most epidemiologic research on pesticides and cancer has focused on white male farm owners and operators. Almost no research has evaluated cancer among migrant and seasonal farmworkers, despite their widespread opportunity for exposure to potential carcinogens, often starting at an early age.[189] The effects of low-level pesticide exposure on the general population need to be evaluated, which will require development of better exposure assessment methods. It is particularly important to evaluate the effects among children.[191] Children may have greater exposure than adults in the same household, and the effects may be different or greater because of physiologic differences. For example, newborns

TABLE 7. Research Needs on Pesticides and Cancer

Research Need	Comment
Epidemiology	Evaluate effects of individual pesticides and combinations of pesticides
Exposure assessment	Study validity and reliability of recall of pesticide use for occupationally and nonoccupationally exposed populations
	Improve epidemiologic assessment of general population exposures
	Evaluate effects of misclassification of exposure
	Continue efforts to reveal identity of inert ingredients
Mechanism of action	Clarify role of epigenetic mechanisms, particularly endocrine disruption and immunotoxicity
Special populations	Study migrant farmworkers, including women and children; the general population with indirect exposure, particularly children; genetically susceptible subgroups

have very low concentrations of the serum enzyme needed to detoxify the organophosphate chlorpyrifos.[71] Among adults, genetics also plays a role in the ability to metabolize pesticides. At least a 15-fold difference in the ability to detoxify organophosphate insecticides has been observed.[71] Metabolic polymorphisms important to pesticide carcinogenicity may exist and should be investigated. A family history of cancer, a crude measure of genetic susceptibility, appeared to enhance the carcinogenic effects of pesticides in some case-control studies,[131,194] suggesting that a search for genetic-environment interactions might be fruitful.

Continued interdisciplinary research, combining the most advanced traditional epidemiology and molecular epidemiology techniques, will help identify individual pesticides that might be contributing to human cancer and, ultimately, result in cancer prevention.

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