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DELAYED HEALTH HAZARDS OF PESTICIDE EXPOSURE

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INTRODUCTION

Pesticides have profoundly improved the human condition. Their dramatic effects in preventing crop loss and controlling vectors of disease have led to their acceptance and expanded use throughout the world (21). However, the powerful chemicals for killing pests have raised concern that they are agents of environmental pollution and human disease.

The greatest concern involves potential delayed health effects of pesticide exposure, rather than the relatively well understood acute effects. This concern is especially great in developed nations, where the delicate balance between starvation and food production and between mass epidemics and vector control has ceased to be an issue. Indeed, particularly in developed countries, pesticides help to increase life expectancy and thus to manifest the adverse effects of long-term exposure (113).

In this review we focus on the delayed health hazards of pesticide use and present the evidence for pesticides causing various cancers, deleterious reproductive outcomes, and subtle neurologic sequelae.

Epidemiologic evidence provides the focus of the review. In some cases, however, pertinent animal and clinical research is presented to support or

contrast with significant epidemiologic conclusions about specific pesticides' hazards. In the concluding section, we suggest future directions and priorities for research for each of the three types of delayed health outcomes: cancer, reproductive, and neurotoxic. In each case further advances in knowledge will be enhanced by changing epidemiologic research methods and focus. Replicating the study designs and focus of the past may merely add to the confusion, rather than generating information for prompt and effective public health action.

CANCER HAZARDS

Many methods and study populations have been used to investigate the relationship between pesticide exposure and cancer. In some studies it is not clear whether pesticides or other agents are related to increased rates of cancer. Studies of farming occupations constitute an indirect, albeit consistent, line of inquiry into the carcinogenicity of pesticides.

A second line of inquiry has been the study of pest control operators and cohorts of workers with known exposure to pesticides. Rarely have these studies been able to address effects of specific pesticides, but appear to implicate some type of pesticide exposure in association with a cancer outcome.

Specific agents of primary concern for cancer are phenoxy herbicides and related compounds, dioxin impurities, arsenicals, and organochlorines such as DDT. These agents have engendered considerable attention in the scientific literature, and have given rise to a large number of studies attempting to assess risk of cancer to specific pesticides.

We first examine implied exposures to pesticides (the farmer studies), then present the studies involving definite but nonspecific pesticide exposure, and, last, review studies of specific agents.

The Farmer Studies

The farmer studies have generally shown an increased level of certain cancers in agricultural occupations. Table 1 briefly summarizes a number of these studies (3, 7, 14, 22, 24–28, 37, 46, 107, 124, 133). Many of these attempted to assess possible modes of exposure by examining relative cancer mortality rates in smaller geographical units, such as counties with higher production of poultry and greater pesticide use. All the listed studies showed elevated relative risks of the listed cancers for farmers or listed agricultural occupation. Greater or newly significant associations were noted upon stratification by production or usage of the products listed in the last column. The relative risks for these studies are generally less than three.

The outcomes for these studies were determined on individuals. However, the measures of exposure and stratification are either indirect indexes of

Table 1 Summary of farmer studies

Ref.	Region	Outcome	Type of Activity
(46)	California	leukemia	farming
		Hodgkin's lymphoma	farming
		multiple myeloma	farming
(107)	Washington	leukemia	poultry
		multiple myeloma	farming
(133)	SE USA	multiple myeloma	poultry
		uterine cervix	farming
		ovarian cancer	farming
(14)	Nebraska	leukemia	corn, insecticide, poultry, cattle, hogs
(3)	Texas	leukemia	farming
(24)	Iowa	leukemia	farming
		lymphoma	farming
		multiple myeloma	farming
		prostatic cancer	farming
		stomach cancer	farming
(26)	Iowa	leukemia	poultry, herbicides
(27)	Wisconsin	lymphosarcoma	none noted
		reticulum cell sarcoma	cattle/dairy, small grains/insecticides, wheat
(25)	Iowa	multiple myeloma	poultry, hogs, insecticides, herbicides
		non-Hodgkin's lymphoma	poultry, hogs, herbicides, milk production
		prostatic cancer	none noted
		stomach cancer	corn, cattle, milk production
(7)	Britain	soft tissue sarcoma	farming
(22)	Illinois	non-Hodgkin's lymphoma	farming
		prostatic cancer	farming
(28)	Wisconsin	multiple myeloma	poultry, insecticides, fertilizers
(37)	N Carolina	melanoma	whites: poultry, cattle, dairying whites: poultry, cattle
		prostatic cancer	nonwhites: peanuts, chemical use
		brain cancer	nonwhites: corn, tobacco, peanuts, chemicals
		non-Hodgkin's lymphoma	nonwhites: none noted
		leukemia	
(124)	New Zealand	lymphoma	farming
		multiple myeloma	farming
		both	orchard (poultry)

exposure (e.g. occupation) or group summaries (e.g. county usage or production of product). Thus, the exposure and stratification measures have characteristics of ecologic measures, and are fraught with problems of validity and precision. Any inferences drawn about causality from these significant associations are tenuous. However, features common among studies lend credibility to inferences that may be pursued with more direct epidemiologic and experimental approaches.

Studies that stratified on age at death (14, 26–28, 46) demonstrated, with only one exception (28), significantly higher rates of leukemia, multiple myeloma, and lymphomas in younger people (usually less than 65 years) and/or in later birth cohorts (usually born after 1900).

Seven studies (14, 25, 26, 28, 107, 124, 133) found significant associations between high levels of exposure to poultry, and leukemias, multiple myeloma, and lymphomas. Five of these seven also demonstrate associations with pesticide use. This consistency across some studies suggests the possibility of interaction between agents. Indirect evidence for relationships between animal and human leukemias and lymphomas mediated by viruses have been studied in cattle, cats, and poultry (124). The evidence is not unequivocally suggestive of a relationship. However, the issue of exposure to multiple agents, such as viruses and chemicals and their interaction, has not yet been adequately studied.

Pesticide User Studies

Pesticide user studies involve cohorts of workers with known exposure to pesticides, but to multiple agents under a variety of conditions. Thus, it is not always clear which agent, or combination, may be responsible for observed associations.

Barthel (10, 11) found that a cohort of 1658 male agricultural workers using pesticides and employed between 1948–1972 in the German Democratic Republic manifested significantly higher rates of lung cancer (SMR=2.0), independently of smoking status. A positive trend was noted between cancer rate and duration of employment, thereby suggesting a dose-effect relationship. It was not possible to disentangle specific pesticides as possible causal agents due to the multitude of agents (e.g. arsenic, asbestos, chlorinated dibenzodioxins, DDT). The likelihood of the cause being arsenicals was assessed by examining lung cancer rates of those workers employed before 1960 and those employed after 1960, when arsenicals were banned. No differences were found.

Riihimaki et al (137, 138) examined a cohort of 1926 Finnish male workers involved with brush control who were exposed to 2,4-D, 2,4,5-T, and other agents between 1951–1971. The follow-up period was from 1972–1980; 16,694 person-years were represented. Only 26 cancer deaths were noted with 36.5 expected. No lymphomas or soft tissue sarcomas were observed.

The authors point out, however, that the small size of the cohort and brief follow-up period limited the utility of this study.

Blair et al (13) demonstrated significantly increased lung cancer mortality rates (SMR=1.35) in a cohort of 3827 licensed pesticide applicators in Florida. A positive trend was noted between duration of licensure and cancer rate. It was not possible to assess smoking habits among the cohort, and the possibility of confounding accounting for the association cannot be excluded.

Wang & MacMahon (167) demonstrated elevated Standardized Mortality Ratios (SMR) for skin (1.73) and bladder cancer (2.77) in an historical cohort study of 16,126 males employed at least three months between 1967–1976 in one of three nationwide pest control companies. Only the bladder cancer SMR was statistically significant. The lung cancer SMR was 1.15.

One of the few studies focusing on women examined the association between ovarian mesothelial tumors and nonspecific herbicides use (39). Sixty incident cases of this tumor diagnosed between 1974 and 1980 by the National Cancer Institute in Milano, Italy, were matched with 135 other cancer controls on year of diagnosis, age, and residence district. Herbicide exposure potential was assessed by interview. A significant odds ratio of 4.4 suggested an association. Stratification by age demonstrated a marked increase in the odds ratio to 9.1 for women under 55 years.

Phenoxy Herbicides, Chlorophenols, Dioxins, and Amitrole

Phenoxy herbicides were introduced commercially in the 1940s. They later catapulted into public view when linked to various adverse reproductive and cancer sequelae, although whether phenoxy herbicides or their dioxin contaminants are responsible for the apparent association with various human cancers is still controversial.

Hardell (61) in 1977 noted that five patients in a series of seven cases of mesenchymal tumors had extensive exposure to phenoxy herbicides. This paper heralded publication in *The Lancet* of a large number of letters-to-the-editor, an editorial, and a review article over the next five years (12, 29, 31, 34, 41, 57, 62, 64, 66, 72, 77, 84, 108, 112, 119, 141). These reflected the ongoing epidemiologic research and contentions of that period. After 1982 one further letter suggested disproportionate rates of Hodgkin's disease among sawmill and pulp workers exposed to chlorophenols in British Columbia, Canada (52).

These letters and articles delineated three lines of epidemiologic evidence in studying the association among various mesenchymally derived tumors and phenoxy herbicides, chlorophenols, and dioxins. These were the Swedish studies, the industrial cohort studies, and the New Zealand studies.

THE SWEDISH STUDIES In 1974, Axelson & Sundell (5) examined a cohort of railway workers engaged in brush control. Between 1957–1972 six cases of cancer were detected in 207 workers exposed at least 45 days to herbicides and

representing 1747 person-years of observation. While statistically significant increases in rates were noted for those workers exposed to the possible human carcinogenic herbicide, amitrole (81), none was noted for those exposed to any of the phenoxy herbicides. In 1980 Axelson et al (6) updated their study of this cohort. With 348 workers followed up to 1978 for 5541 person-years, a total of 17 tumors were observed, with only 11.8 expected. The excess was noted particularly in workers exposed to both amitrole and phenoxy herbicides. Examination of workers exposed just to phenoxy herbicides, and accounting for a ten-year latency period, revealed a statistically significant increased rate of stomach cancer (2 observed, 0.33 expected).

In 1979 Hardell & Sandstrom (69) published results of a case-control study of 52 cases of soft tissue sarcoma registered from the three northern-most counties in Sweden. A detailed assessment of exposure to specific phenoxy herbicides such as 2,4,5-T, 2,4-D, and MCPA was undertaken by mailed questionnaire and telephone follow-up. Population-based controls were chosen for living cases. Controls from the National Registry for Causes of Death were chosen for dead cases. The odds for exposure in cases was 5.7 times that of controls. In most circumstances exposure was to multiple agents. Exposure to phenoxy herbicides and chlorophenols was 5.3 and 6.6 times more likely to be reported in cases than in controls, respectively. An odds ratio of 9.9 was noted when the analysis was limited to the 21 living cases and their controls. The odds ratio was 3.8 for the 31 dead cases. This study was followed by a series of four additional ones (45, 63, 67, 68).

Exposure to phenoxy herbicides and chlorophenols in 110 cases of soft tissue sarcoma and in 220 controls from five southern Swedish counties (45) was assessed in order to confirm the findings in northern Sweden. The overall odds ratio for exposure to phenoxy herbicides was 6.8. When stratified on exposure just to 2,4-D and MCPA, the odds ratio remained significant at 4.2. It was claimed that these agents were not contaminated by 2,3,7,8-TCDD, a potent carcinogen in animals, as was 2,4,5-T, thus suggesting evidence for the carcinogenicity of phenoxy herbicides in their own right. However, Hay (72) claimed that such an inference could not be unequivocally justified, since 2,4-D was often contaminated with dichloro and trichloro dioxins. When occupation was used as an index of exposure the relative odds of exposure dropped to an insignificant 1.4. This observation seemed to underscore the importance of better methods of assessing personal exposure to agents of concern; although it also raised the issue of recall bias in falsely elevating odds ratios when exposure is assessed from interview data.

Hardell et al (67) extended their studies to include malignant lymphomas, demonstrating in 169 cases with 338 controls an overall relative odds of exposure of 5.3. When exposure just to phenoxy herbicides was examined, the odds ratio remained significant at 4.8, and a dose-effect relationship was

suggested for exposure to chlorophenols by using duration of exposure as the surrogate measure for dose. The issue of 2,3,7,8-TCDD contamination could not be assessed. Hardell & Bengtsson (65) reanalyzed these data in order to assess possible confounding effects by SES and concurrent disease/health conditions but were unable to demonstrate any such confounding.

Hardell (63) next examined the relationship between colon cancer and herbicide exposure. The study was motivated by criticisms that use of general population controls would result in recall bias. Cancer cases would be expected to recall differentially past chemical agent exposure in such a way as to falsely elevate the odds ratio. Hardell (63) expected to find no significant measure of association using colon cancer cases and population controls. Odds ratios of 1.3 and 1.8 for exposure to phenoxy herbicides and chlorophenols, respectively, were not statistically significant, confirming his expectation. Hoar et al (76) have demonstrated similar findings in failing to find a significant association between herbicide use and colon cancer in Kansas farmers between 1976–1982. Using colon cancer as a control, Hardell (63) reanalyzed the previous studies of soft tissue sarcoma in northern Sweden (69) and malignant lymphoma (67), and reported significant overall relative odds of exposure of 5.5 and 4.5, respectively.

Finally, Hardell et al (68) examined the role of herbicide exposure in nasal-pharyngeal cancer. Seventy-one cases, and 541 controls derived from previous studies (67, 69), demonstrated a statistically insignificant odds ratio of 2.1 for phenoxy herbicide exposure, but a significant 6.5 for chlorophenol exposure. There was some suggestion of an interaction between chlorophenol exposure and woodworking occupations, but poor statistical power limited such inferences.

THE INDUSTRIAL COHORT STUDIES Three US studies (32, 122, 178) of workers exposed to a variety of dioxins and phenoxy herbicides in manufacturing facilities were published in 1980. Two of the studies (32, 178) examined cohorts of workers involved in acute accidental exposures.

Cook et al (32) examined 61 males between 1964–1978 who were accidentally exposed to 2,3,7,8-TCDD in 1964. Forty-nine of these men developed chloracne as a result of this accident, thus indicating significant exposure. Three cancers developed during this period (one a fibrosarcoma), with 1.6 expected ($p=0.13$). Orris (120) raised several criticisms of this study, the most cogent being that an insufficient latency period had transpired to detect any real carcinogenic effect from this accidental exposure.

Zack & Suskind (178) reported cancer outcomes of a cohort of 121 males accidentally exposed to 2,3,7,8-TCDD in 1949. Development of chloracne was a criterion for inclusion into the study. Between 1949–1978 100% follow-up revealed 9 cancer deaths, with 9.04 expected. However, three of these were

lymphatic or hematopoietic in origin (0.88 expected, $p=0.047$), and one was a primary dermal fibrous histiocytoma (0.15 expected). Although the cohort size was small, the degree of exposure was significant, as indicated by development of chloracne.

Ott et al (122) examined a cohort of 204 workers involved in manufacture of 2,4,5-T for at least one month between 1950–1971. Only one lung cancer death was noted, in a worker who happened to be a smoker.

In 1983 Zack & Gaffey (177) reported the mortality status of 884 white male employees of the Nitro, West Virginia, Monsanto plant who had been employed at least one year between 1955–1977. The nine cases of bladder cancer were significantly in excess of expected (0.91). However, the plant had used a bladder carcinogen, *para*-aminobiphenyl, between 1941–1952 in rubber processing. One case of generalized liposarcoma was reported.

Honchar & Halperin (77) suggested that although each of these US manufacturer studies failed to report an excess risk for soft tissue sarcoma, in combination the three reported soft tissue sarcoma cases might be significant. Four additional cases were subsequently identified (31, 84, 112).

In 1984 Fingerhut et al (49) reviewed the seven cases, examining the pathologic evidence directly for the correct diagnosis of soft tissue sarcoma by using two reviewers. Two of the seven cases were independently reported by both reviewers as carcinomas.

Although Fingerhut's reassessment (49) moderates the degree of association suggested by the four cohort studies (32, 122, 177, 178) and their addendums (31, 84, 112), the five confirmed cases still represent an excess number. However, three of these five cases did not directly work in manufacturing, and the extent of their exposure to 2,3,7,8-TCDD is in doubt.

Thiess et al (157) examined mortality outcomes in a cohort of 74 workers in the Federal Republic of Germany who were accidentally exposed to dioxins in 1953, 66 of whom developed chloracne. Mortality status was determined for 100% of the cohort up to 1979, representing 1698 person-years of observation. Several internal and external control populations were used. The most significant finding was an excess of stomach cancer in the exposed cohort (3 observed, 0.7 expected). No lymphatic, hematopoietic, or soft tissue sarcomas were noted.

The recent Danish study by Lynge (98), however, demonstrated 5 soft tissue sarcoma cases (1.84 expected) in a cohort of 3390 males (49,879 person-years of observation) involved in the manufacture of phenoxy herbicides prior to 1982. The primary herbicides manufactured were 2,4-D and MCPA, and the likelihood of dioxin contamination was thought to be minimal. No excess of malignant lymphoma was noted. The study differs significantly from the other industrial cohort studies reported so far by virtue of the large cohort size.

A number of studies attempted to assess various clinical and laboratory

indices of workers exposed primarily to dioxins (16, 100, 123, 154). These studies were often plagued by poor participation rates (16, 154). The nonspecific nature of various measures of liver function, lipid metabolism, and peripheral nerve function limit the inferences one can draw about risk of disease, especially of cancer.

THE NEW ZEALAND STUDIES To test the association between herbicide exposure and soft tissue sarcoma Smith et al (148) initiated a case-control study comprising 102 male soft tissue sarcoma cases registered nationally between 1976–1980. They randomly selected 306 controls from cases of other cancers, matched on age and registration year. Using occupation as the indicator of exposure, an odds ratio of 1.03 was noted for those designated as general agricultural and forestry workers. Examination of only farmers raised the odds ratio to 1.45, but this was not statistically significant. A more thorough assessment of exposure by telephone interview of 80 of these cases and 92 controls failed to reveal any odds ratio greater than 1.6 for various categories of exposure to phenoxy herbicides (146, 150). None of these were statistically significant.

A second case-control study of non–Hodgkin's lymphoma also failed to reveal an association with phenoxy herbicides (odds ratio = 1.4) or with chlorophenols (odds ratio = 1.3) (125). Cases were more likely to have done fencing work or been employed in meat processing, but no conclusions could be reached about possible causative agents.

The design of the New Zealand studies is comparable to that of Swedish case-control studies. Tumor registry data identified incident cases. Both occupational and personal exposure data were determined by questionnaire and/or telephone interview. The New Zealand soft tissue sarcoma study's use of other cancer patients as controls contrasts with the Swedish use of general population controls. However, the New Zealand non–Hodgkins lymphoma study utilized both cancer and general population controls, and the two control groups gave comparable results. The lack of concordance between the Swedish and New Zealand studies therefore requires some explanation.

One possible explanation is that the 2,4,5-T herbicides used in New Zealand might have been less contaminated with dioxins. Unfortunately, the exact levels of contamination in New Zealand phenoxy herbicides during early use are not available. However, evidence from the southern counties Swedish study (45) detracts from this explanation, since significant relative risks of exposure were noted from use of phenoxy herbicides free from 2,3,7,8-TCDD contamination.

VIETNAM VETERAN STUDIES Studies of Vietnam veterans exposed to Agent Orange have been limited in their assessment of cancer outcomes. A study of

mortality patterns involving 4558 Vietnam era veterans in New York State suggested no excess of deaths from death certificate diagnoses of soft tissue sarcoma and lymphomas (92). However, a study of veterans in The Commonwealth of Massachusetts did demonstrate significantly greater numbers of veterans with death certificate diagnoses of soft tissue sarcoma and kidney cancer (2). A longer period of follow-up for this cohort and other Vietnam Veteran studies are needed to encompass a reasonable latency period.

CONCLUSIONS Neither phenoxy herbicides nor dioxins can be unequivocally stated to cause cancer in humans. However, animal data refute claims that they are harmless. For example, an extensive investigation of over 20,000 ewes at slaughter demonstrated significant increases in the prevalence of small intestinal adenocarcinoma in sheep exposed to phenoxy and picolinic herbicides (116). Tumor rates appeared to be independent of exposure to 2,3,7,8-TCDD-contaminated phenoxy herbicides. More importantly, the experimental animal data are consistent enough that the International Agency for Research on Cancer has concluded that 2,3,7,8-TCDD is a potent rodent carcinogen (81).

The Swedish case-control studies provide the strongest evidence for causality in humans. However, the industrial cohort studies are inconsistent in suggesting such associations, and the New Zealand study demonstrates no association. Inconsistent findings such as these are unlikely in the presence of true causal associations. The possibility of different levels of dioxin contamination of phenoxy herbicides in these populations has already been raised. Similarly, the possibility of interaction of more than one exposure or characteristic should not be overlooked. Swedish populations might be exposed to two necessary agents (one being phenoxy herbicides or dioxin contaminants) that cause cancer; industrial cohorts and New Zealand populations might not be exposed to the second factor.

Arsenical Pesticides

The carcinogenic potential of arsenic, having been suspected for almost a century (127), is well established (80). Arsenical pesticides are rarely used for this reason. A number of the nonspecific exposure studies (10, 11, 13) have suggested a role for arsenicals in demonstrating increased rates of lung cancer in occupations using pesticides. A possible role of arsenic in association with human lymphatic and hematopoietic cancers has also been suggested (4, 121, 125).

Ott et al (121) demonstrated a significant increase in respiratory cancers in 173 decedents with occupational exposure to arsenical insecticides. Using proportional mortality analysis, they demonstrated that 16.2% of deaths in the arsenical-exposed group were due to respiratory system cancer, as compared to 5.7% in controls. The study also demonstrated a dose-effect relationship where dose was assessed by a determination of time-weighted average concentration-months.

Mabuchi et al (99) attempted to assess the role of arsenical pesticide exposure in a manufacturing plant cohort of 1393 workers employed between 1946–1977. They were able to determine the status of 82% of the cohort. When limited to just the 1050 males (87% follow-up, 19,248 person-years of observation), 23 deaths from lung cancer were noted (13.7 expected regionally, 8.7 nationally). A dose-effect relationship was noted in workers exposed to high levels of arsenicals, using duration of exposure as the measure of dose. Accounting for 15+ years latency increased the SMR to 16.7. Unfortunately, the investigators were unable to account for possible confounding effects from smoking. Nevertheless, they felt the evidence was strong enough to infer causality.

In contrast to the strong epidemiologic evidence for arsenic's role as a respiratory carcinogen, animal data demonstrate no causal role for arsenic in the genesis of cancer, and in some cases even an antagonistic effect (51, 117). Nordberg & Andersen (117) have suggested that environmental exposure to arsenic is always coupled with exposure to other metals, sulfur dioxide, or organic carcinogens. Some epidemiologic studies have also suggested that arsenic acts more as a promoter of lung cancer than as an initiator (19, 43). An interactive effect with smoking was noted in a study by Pershagen et al (129), thus supporting arsenic's role as a promoter (128).

Organochlorine Pesticides

The organochlorine pesticides include products such as DDT, chlordane, heptachlor, aldrin, and dieldrin. The IARC (81) has listed some of these agents (e.g. DDT) as "probably carcinogenic to humans," although it also categorizes them as being inadequately assessed for human carcinogenic potential. Their carcinogenicity has been demonstrated in animal studies, but insufficient data has accrued from human studies. In particular, DDT has demonstrated significant liver, lymphatic, and lung neoplastic activity in rodents, while dieldrin is more equivocal in suggesting such activity (81).

A number of studies assessed the level of agents such as DDT and dieldrin in adipose tissue and blood in cancer patients. These studies extend back into the 1960s, and are reviewed in the *IARC Monograph* literature (79, 81, 82). The results of such studies have not been conclusive in assessing causality.

A report by Infante et al (78) is representative of a number of case reports implicating organochlorines as possible causal agents for a variety of blood dyscrasias. They presented six cases with various disorders and history of chlordane exposure, as well as summarized 25 similar cases reported in the literature since 1955. One cannot assess the reliability of these associations in case reports without comparative population data.

In response to these reports, Wang & Grufferman (166) conducted a case-control study of aplastic anemia mortality in North Carolina males for the period 1968–1977. Using stated occupation on the death certificate, they were unable to show an association between the disease and any occupation involved with pesticide use. Failure to detect an association does not necessarily eliminate the likelihood of one because of inaccuracies introduced in using occupation recorded at time of death as an exposure index.

The Swedish case-control studies of soft tissue sarcoma, lymphomas, and colon cancer assessed DDT exposure and failed to demonstrate any association (45, 63, 67, 69). Some studies have shown associations between organochlorine pesticide exposure and development of hypertension, cerebrovascular disease, and arteriosclerotic cardiovascular disease, but not for any cancer (109, 168, 174). Ditraglia et al (38) reexamined two cohorts previously studied by Wang & MacMahon (168), adding two more industrial plants involved in organochlorine pesticide production. With 2141 workers (171 lost to follow-up, 46,566 person-years of observation) there was no suggestion of increased death rates from 12 categories of cancer.

Human evidence for organochlorine carcinogenic potential is not strong. However, limitations in these studies as well as consistent animal data suggest that these agents could be human carcinogens. Their persistence in the environment, and continued use in third world countries in the case of DDT, mandate further study.

REPRODUCTIVE HAZARDS

Dibromochloropropane (DBCP), 2,4,5-T, and DDT were all used for many years before they were suspected of having reproductive toxicity. However, only in the case of DBCP, which had profound effects on male fertility, were these suspicions confirmed. Why then, was it so difficult to confirm or refute our suspicions about DDT and the phenoxy herbicides?

1. Their effects might not be as profound as those for DBCP.
2. Many of the studies lacked adequate statistical power to examine outcomes such as individual congenital malformations. For some populations, such as in Seveso, Italy, and Vietnam, baseline information on reproductive outcomes was unknown.
3. Accurate exposure data were lacking, particularly for the studies on Agent Orange and the ecologic studies in which not only the levels of exposure, but also who was exposed, were unknown.

We are left with unconfirmed suspicions based on inconsistent data that exposure to phenoxy herbicides, particularly Agent Orange, may be associated with congenital malformations such as neural tube defects and facial clefts, with molar pregnancies, and with spontaneous abortions. Similarly, an association between exposure to organochlorine pesticides (particularly DDT) and spontaneous abortion and premature delivery are only suspect at this time.

Dibromochloropropane (DBCP)

The human reproductive toxicity of DBCP is more apparent than for DDT or the phenoxy herbicides. Interest in the reproductive effects of DBCP was sparked when wives of DBCP production workers in a northern California chemical plant complained about an inability to become pregnant. Studies by Whorton and co-workers (106, 170, 171) showed that almost half of the workers had lower than normal sperm counts compared to less than 10% in nonexposed workers. Testicular biopsy studies revealed hyalized seminiferous tubules with no spermatogenic activity in the workers with azoospermia (90, 132, 171).

Although changes in sperm count were noted, changes in sperm morphology were not related to DBCP exposure (54, 86). The degree and length of exposure was directly related to sperm count. Pesticide applicators or farm workers exposed to DBCP had some reduction in semen quality but to a lesser extent than production workers and formulators (54, 140). Production workers with abnormal counts had worked longer than three years. One year after exposure ended, six of nine oligospermic men became normospermic, two of nine showed improvement but remained oligospermic, and none of the 12 azoospermic men showed any improvement (106). In other studies approximately a third of azoospermic men improved after four years without exposure (56, 130).

Some studies have not found dose-related reductions in sperm counts following DBCP exposure. However, workers were examined one year after exposure (97), or were exposed for less than three years (90).

Serum levels of follicle-stimulating hormone tended to be increased in exposed workers (42, 97, 131, 132). Elevated levels of luteinizing hormones have been found in some studies (42, 170), but not in others (131, 132). In most studies (131, 132, 140) testosterone levels are unaltered by DBCP exposure, although one study found depressed levels in exposed workers (90).

Two studies have observed a preponderance of female offspring in DBCP-exposed workers (56)—a finding suggestive of increased rates of Y-chromosome non-dysjunction. Kharrazi et al (87) found an increase in the rate of spontaneous abortions in the wives of pesticide applicators after their husbands' exposure (20%) compared to before (7%). However, their baseline rate was rather low, suggesting under reporting.

No studies have examined the offspring of women who have been exposed.

Phenoxy Herbicides and Their Contaminants

Studies investigating human reproductive effects focus on five major populations:

1. Vietnam veterans exposed to Agent Orange (a mixture of 2,4-D and 2,4,5-T contaminated with TCDD);
2. Vietnamese civilians exposed to Agent Orange;
3. men exposed to phenoxy herbicides in production or in application;
4. residents in Seveso, Italy, accidentally exposed to TCDD;
5. residents living near areas sprayed with phenoxy herbicides.

VIETNAM VETERANS There has been enormous public concern about the exposure of Vietnam Veterans to Agent Orange and its possible effects on their offspring. Nevertheless, studies of veterans done in the United States, Australia, and Vietnam have been largely inconclusive. In a case-control study of infants born between 1968–1980, the Centers for Disease Control found no difference in the proportion of fathers who served in Vietnam and those who did not (9% in both groups) (44). However, rates of spina bifida, facial cleft, and neuroblastoma increased with the father's estimated dose of Agent Orange. The Australian study (165) of infants born between 1966–1979 found that only 1.5% of the fathers in each group served in Vietnam, and that Australian soldiers were exposed to much smaller quantities of Agent Orange than American soldiers (30).

The United States Air Force is following a cohort of over 1000 men (Ranch Hands) who flew aircraft that sprayed Agent Orange. The initial studies showed no differences between the Ranch Hands and other unexposed veterans in semen quality and number of children fathered (91). Based on the veteran's report the study found a significant increase in miscarriage rate in one exposed group (officers), a higher overall rate of birth defects compared to unexposed controls (in part due to a cluster of skin anomalies), and a larger number of neonatal deaths in postexposure years compared to pre-exposure years.

Hatch (71) reviewed a few of the unpublished studies examining the offspring of Vietnamese veterans. Two studies found a slightly increased risk for birth defects, particularly of the neural tube and facial clefts, in offspring of fathers who served in South Vietnam, where most of the exposure to Agent Orange had occurred. Another study found that wives of veterans who served in South Vietnam had twice the number of miscarriages (16% versus 8.5%).

VIETNAMESE CIVILIANS Investigations of civilian populations in Vietnam suffer from both poor exposure estimates and inaccurate birth records (71). Two studies of Vietnamese civilians found congenital malformations of the neural tube and the palate with potential herbicide exposure. Meselson and co-workers (103) examined the records of children who received surgery at Saigon Children's Hospital, the major hospital for surgical correction of congenital malformations in South Vietnam, and noted a major change in the relative frequency of spina bifida and pure cleft palate in the two years of heavy spraying (1967 and 1968). Kunstadter, at the National Academy of Sciences (89), observed similar peaks in rates of cleft lip in 1963, 1966, 1969 (the highest), with a subsequent decline. However, Kunstadter (89), with access to dates, times, and location of spraying, found no link between maternal residence (within five miles of spraying) and overall risk for birth defects or risk for a specific birth defect.

A number of studies investigated the association between molar pregnancy and herbicide exposure. The initial studies (35) found no increase in molar pregnancy and stillbirths in the years of heavy spraying (1966–1969) compared to the years of light spraying. However, most of the pregnancies occurred in Saigon and were relatively unexposed. When these pregnancies were eliminated from the analysis (103), almost twice the rate of molar pregnancies was noted in the heavy spraying years, and the highest rate of stillbirths was in the province of Tay Ninh (68 per 1000)—an area heavily exposed.

Hatch (71) cites an investigation in Vietnam—matched for maternal age, parity, and social conditions—that observed a ten-fold excess in herbicide exposure in women hospitalized for molar pregnancy compared to women with normal deliveries. Because the incidence of molar pregnancies increased about 10 years after heavy spraying in South, but not in North Vietnam, Hatch (71) suggested that the effect might be maternally mediated.

OCCUPATIONAL EXPOSURE In general, women whose husbands have worked with chlorophenols have not had a higher rate of infants with congenital malformations, spontaneous abortions, stillbirths, or infant deaths (161). Even men with relatively high levels of TCDD exposure, as evidenced by chloracne, demonstrated no increase in fathering infants with congenital malformations or in their wives' having pregnancies that ended in spontaneous abortion (100, 111, 154). However, these studies are limited by small numbers and by recall of pregnancies up to 30 years previously.

Smith et al (149) compared reported reproductive histories of pesticide applicators (mostly 2,4,5-T) in New Zealand to those of agricultural contractors. Since wives often help their husbands in the field, they may have also been exposed. Smith et al found no significant differences in congenital malformations, stillbirths, miscarriages, and overall fertility rates. In addition, analysis specifically for 2,4,5-T use did not identify any reproductive hazard (147).

Only one study yielded a positive association between men exposed to pesticides, but not specifically to phenoxy herbicides (8). The study compared the rates of spina bifida, anencephaly, and facial clefts for offspring of fathers whose job title suggested exposure to agricultural chemicals (e.g. farmers, gardeners) with rates in offspring of fathers with all other occupations. Defect rates were consistently higher (no significance levels given) for a variety of

agricultural occupations, including gardeners and agricultural workers. However, a case-control study by Golding & Sladden (55) of infants born with anencephaly, spina bifida, and facial clefts was unable to confirm these findings.

THE SEVESO ACCIDENT The release of TCDD from a plant producing trichlorophenol occurred in July 1976 in Seveso, Italy. More than two weeks elapsed before the health authorities responded by relocating children and pregnant women. A number of Italian investigators claimed that the rates of spontaneous abortion increased following the accident (20, 160), and that these rates did not completely drop until after 1978. However, no differences were observed when rates were compared across high, moderate, and low contamination areas (136). There were also claims that rates of congenital malformation had increased in the contaminated areas. Bruzzi et al (20) reported an excess between 1977–1980 in the overall rates of multiple malformations in the contaminated areas compared to the less contaminated areas, and an excess in hypospadias, hemangiomas, and neural tube defects (mostly spina bifida) compared to other Italian registries.

The true effects of the Seveso accident could not be determined for a number of reasons:

1. No baseline rates existed.
2. Numbers were too small.
3. Exact numbers of induced abortions were unknown.
4. Cases of chloracne (n=53) existed outside the "exposure zones," and thus the exposed population could not be readily defined.
5. Political turmoil surrounding the management of health services prevented the immediate collection of data.

ECOLOGIC STUDIES Ecologic studies pose many problems for the epidemiologist. Although this type of study is relatively inexpensive and simple to implement, interpretation may be difficult, since little is known about individual exposure. Field & Kerr (48) compared the annual combined rate of anencephaly and meningomyelocele in New South Wales with the previous year's use of 2,4,5-T in all of Australia. A linear correlation was found. Highest rates were for conceptions in the summer, supposedly the season of maximal spraying. A study of a different area of Australia (18) demonstrated an increase in facial clefts for infants conceived in spring and summer months; the authors suggested that these were related to pesticide use. No levels of statistical significance were provided in the above studies.

In contrast, an investigation by Hanify et al (59) in New Zealand evaluated the relationship between malformations (confirmed by hospital records) and aerial spraying (monthly density). Rates of heart malformations, hypospadias, and talipes were elevated in the years of spraying (1972–1976) compared to years prior to use of 2,4,5-T. When more precise estimates of exposure (reflecting year, area of exposure, and fractional removal rate) were used, only talipes remained significantly correlated with exposure.

Other studies have reported equivocal or negative relationships between estimates of 2,4,5-T exposure and birth defects. No relationship was observed between previous year's usage of 2,4,5-T in Hungary and cystic kidney, facial clefts, anencephaly, spina bifida, and still births (158). Nelson et al (115) subdivided 75 Arkansas counties into high (n=15), medium (n=9), and low (n=51) exposure groups based on their rice acreage. Higher rates of facial clefts were found in the low- and high-exposure counties than in the medium.

Perhaps the ecologic study that stirred the most controversy was the "Alsea" study (162). Women from Oregon coastal areas had complained about miscarriages, which they thought might be due to the spraying of 2,4,5-T in nearby forests. The EPA responded with an ecologic study examining the spontaneous abortion rate of women of that area who were hospitalized between 1972–1977. An increased rate in the study population compared to two control areas, one rural the other urban, was noted. The study area rates peaked during June. The EPA noted that poundage of 2,4,5-T used correlated with rates of spontaneous abortion when a lag time of two to three months was imposed. This study has been criticized for a number of reasons:

1. Only a small part of the study area was sprayed.
2. The rates of spontaneous abortion were within the expected rates.
3. No potential confounders were assessed.
4. Differences in medical care between rural and urban areas confused comparisons.
5. The area of study was a vacation area with an influx of people during the summer, thus affecting estimates of both the case population and the target population.

Organochlorine Pesticides

Organochlorine pesticides such as DDT pass through the placenta, with an average level in the newborn blood reaching around a third of that in maternal blood (1, 135). These pesticides are stored in human fat, and levels are higher in breast milk than in maternal blood (144, 173). Although DDT is no longer in use in most parts of the world, its residues are persistent (1). However, information is scarce on human reproductive effects of DDT and organochlorine pesticides in general.

Limited evidence suggests that DDT body burden is related to premature delivery or spontaneous abortion. Procianoy & Schvartsman (134) reported

DDT levels significantly higher in the cord blood of preterm infants ($M=33$ wk) than of term infants in Brazil. In an Indian study (142) comparing cases of premature abortion or delivery (10–32 wk) and term deliveries, DDT levels were five times higher in placental tissue of cases. The highest DDT levels were seen in the most premature deliveries.

Although DDT levels have been shown to be elevated in the cord blood of infants delivered prematurely or in fetuses spontaneously aborted, the DDT levels in their mothers are not consistently elevated. DDT levels were not found to be higher in blood of women who had spontaneous abortions than in those who had normal pregnancies (118). Procianoy & Schvartsman (134) found that mothers of preterm ($M=33$ wk) and term infants had comparable DDT levels. However, Saxena et al (142) found that women having spontaneous abortions and mothers of premature infants had 10 times the DDT levels of mothers with term infants.

A number of theories attempt to explain the elevated DDT levels seen in the preterm infants or aborted fetuses. Saxena et al (143) proposed that organochlorine pesticides are known to have weak estrogenic effects, and may precipitate labor. Procianoy & Schvartsman (134) suggested that preterm infants may have an increased placental permeability to DDT; or, more DDT is found in the blood because preterm infants have less adipose tissue. They suggested that the latter hypothesis is supported by the significant negative correlation of birth weight and DDT levels. However, in a larger study (36) of women and their newborns ($n=350$), where only 3% of the infants were preterm [compared to 44% in Procianoy & Schvartsman's study (134)], birth weight did not correlate significantly with DDT levels.

Conclusions

Apart from male infertility due to DBCP, the most impressive result of the findings for human reproductive effects from exposure to pesticides is their inconsistency. This inconsistency is particularly apparent in the wide range and large numbers of studies of phenoxy herbicides. The inconsistency stems from one of two causes: either the effects are weak at exposure levels experienced by humans, and therefore difficult to detect epidemiologically; or there are no effects, and the apparent findings result from multiple comparisons—each study looking at a variety of outcomes, some of which are by chance statistically significant.

NEUROTOXIC HAZARDS

The nervous system has been recognized as a target organ for pesticide toxicity for several decades. Indeed, the desired pesticidal action of the organophosphates (OPs) is caused by the inhibition of acetylcholine esterase and the subsequent accumulation of the neurotransmitter, acetylcholine. The initial use

of organophosphates in chemical warfare led to a large literature describing the biochemical mechanisms of action and the clinical observations of excess cholinergic activity in humans (114). The suggestion that chronic neurobehavioral sequelae may result from acute organophosphate intoxication or chronic lower level exposure is important in light of the continued risk of OP poisoning to the estimated 2.5 million seasonal and migrant farm workers and 340,000 pesticide production workers in the United States.

The emphasis in this review is on organophosphates. However, organophosphates are not the only pesticides with neurotoxic effects. Organochlorines were widely used until organophosphates were substituted for them in the 1960s and 1970s.

The chlorinated hydrocarbon insecticide, chlordecone, was responsible for over 75 cases of neurologic disease among workers at the Life Sciences Products Company in Hopewell, Virginia in 1975 (156). Tremor and opsoclonus were the most frequent abnormalities, with signs and symptoms gradually diminishing over 18 months. However, several workers continued to manifest a mildly incapacitating tremor after four years. Chlordecone appears to be unique in that chronic sequelae have not been reported following acute intoxication with other chlorinated hydrocarbon insecticides.

Peripheral neuropathy has been reported following occupational exposure to the phenoxy herbicides, 2,4,5-T and 2,4-D (111, 123, 145). Neurologic toxicity has also been noted from acute exposure to pesticides containing arsenic, the fumigant methyl bromide, and rodenticides containing thallium (9, 74, 75, 93). Scattered reports of prolonged sensory or motor neuropathy have been recorded (156). However, the main concern about neurotoxic effects of pesticides involves organophosphates.

Organophosphates

Acute OP poisoning can generally be measured with in vitro measurement of red blood cell or plasma cholinesterase, although central nervous system symptoms may be absent with mild depression of cholinesterase values (73). Continued case reports of acute poisoning among farm workers exposed to residual crop levels have emphasized the need for baseline cholinesterase measurement, continuing surveillance, and further coordination of emergency treatment by local health care professionals (105). In California alone, over 1200 cases of suspected pesticide poisoning are reported yearly, the majority due to organophosphates.

In addition to the neurologic signs and symptoms of acute intoxication, organophosphate pesticides may cause two delayed or chronic effects from acute high dose or chronic low dose exposure: (*a*) delayed polyneuropathy, consisting of a symmetrical distal axonal degeneration, and (*b*) neurobehavioral effects.

ORGANOPHOSPHATE POLYNEUROPATHY Most reported cases of organophosphate neuropathy have been caused by tri-ortho-cresyl-phosphate (TOCP), which has been responsible for thousands of paralytic cases due to contaminated alcohol [Ginger Jake paralysis (110)] and cooking oil. The pesticides mipafox, trichlorphon, tamaron, trichlornate, and leptophos have also been reported to cause such a neuropathy. Acute exposure is followed within 8 to 18 days by progressive lower extremity weakness and subsequent hand weakness associated with varying degrees of sensory loss. Recovery is generally poor.

The mechanism of this toxic effect is due to the inhibition of neurotoxic esterase (NTE), although recently Seifert & Casida (143a,b) have clearly demonstrated a second target of action. These agents act to enhance brain cytoplasmic microtubule protease activity and thus alter levels of high molecular weight proteins associated with cytoplasmic microtubule stability and assembly. It is unclear, however, whether these actions are an effect rather than a cause of neurotoxicity (143a).

Elegant assays have been developed for neurotoxic esterase activity utilizing the hen, where inhibition of approximately 75% or greater of whole hen brain NTE one day after dosing is used as an indicator of neurotoxic potential. Good correlation has been found between inhibition of brain NTE and functional ataxia 10 to 14 days later. Johnson has reviewed this subject extensively (85).

ORGANOPHOSPHATE NEUROBEHAVIORAL EFFECTS The acute effects of organophosphate intoxication result from the nicotinic, muscarinic, and central nervous system manifestations of cholinergic excess. Individuals may have difficulty concentrating, and may be confused and drowsy. Symptoms begin within 24 hours after exposure, and, if severe anoxia has not occurred, complete symptomatic recovery usually occurs within ten days. However, follow-up of survivors of acute pesticide poisoning suggests that a few individuals may continue to experience persistent neurobehavioral symptoms.

The effect of a single dose of an organophosphate anticholinesterase was assessed by Bowers et al (17) in normal volunteers by using serial administrations of a behavioral checklist. Impaired concentration and increased distraction were noted at whole blood cholinesterase levels of less than 40%. Tabershaw & Cooper (155) examined 117 individuals three years after systemic poisoning by organophosphates. Continued visual disturbances, gastrointestinal symptoms, headaches, and nervousness were the most common complaints. No control group was examined, however. Harmon et al (70) assessed six patients 9 to 48 months after organophosphate poisoning but did not administer a standard questionnaire to elicit symptoms. The neurologic examination was normal.

Chronic exposure to organophosphates has been anecdotally reported to cause impairment in concentration in agricultural and scientific workers as well as agricultural pilots (53, 102, 126, 151). Metcalf & Holmes (104) interviewed 56 men with organophosphate exposure and reported disturbed memory and difficulty in maintaining alertness and appropriate focusing of attention. Work history, cholinesterase levels, and severity and duration of exposure were unknown. Whorton & Obrinsky (172) noted persistent complaints of blurred vision in 12 of 19 farm field workers examined four months after organophosphate poisoning.

Rodnitzky & Levin (139) were the first to assess a variety of neurobehavioral functions in subjects occupationally exposed to organophosphates. Twenty-three farmers and pesticide applicators exposed to organophosphates, matched for age and education with a control group of farmers, were given a battery of neuropsychiatric tests. Plasma cholinesterase was slightly depressed among the pesticide applicators. All workers were asymptomatic. No visuomotor or memory abnormalities were found, although pesticide control applicators scored significantly higher on the Taylor Manifest Anxiety Scale (94).

As it was known that organophosphates in large doses induce prominent electroencephalographic (EEG) changes and convulsions in humans and other higher mammals, Burchfiel et al (23) investigated the persistent effects of a single dose of sarin on the primate EEG. Seizures were induced by a single injection of sarin while the animals were paralyzed and artificially respired. Spectral analysis of serial EEGs over a one-year period revealed a persistent increase in the relative amount of beta voltage in two out of three treated monkeys, compared with none of the controls. Duffy et al (40) followed up this finding with EEG studies of 77 industrial workers with histories of accidental exposure to sarin at least one year previously: 41 of the 77 had at least three exposures within the six years preceding the study; 38 industrial workers from the same plant served as controls. Spectral analysis revealed increased beta activity in both the total of exposed and the highly exposed subgroup compared with controls. Visual inspection of the tracing was inconsistent and showed decreased alpha activity with nonspecific abnormalities. Despite real statistical differences, expert visual inspection did not permit diagnosis of individual subjects.

Methodologic Issues

Research on the neurobehavioral effects of pesticides is fraught with inconsistencies and methodologic problems not unique to the study of pesticides (15, 47, 50, 60, 101, 159, 163, 164). Study results are limited by the neuropsychologic and neurophysiologic tests used to evaluate workers, the sensitivity of these tests, their validity, and their reliability. It is often unclear what significant findings mean to the workers' performance and functioning. Test administrators often are not blind to exposure status. Appropriate worker control groups matched on age, education, and habits are usually not employed. The lack of a comparative population leads to problems in interpretation, since

exposed groups may function within normal limits but show deficits relative to controls. Another possible comparison is with baseline or pre-exposure performance. However, baseline performance, although assumed from the subsequent pattern of performance, is rarely known.

The recent use of computers to administer versions of the standard paper and pencil tests to large groups of worker populations has minimized tester variability, cost and time of administration, and problems in data storage. However, use of computers has also raised other problems in the field of neurobehavioral toxicology. For example, the computer versions of these tests have not been well validated on large control populations. Even when validated, normative data should not preclude the use of control populations on a study-by-study basis.

In summary, the discipline of neurobehavioral toxicology is in its infancy. Our knowledge of delayed neurobehavioral effects of pesticide exposure is limited by our techniques to assess these effects and our understanding of what performance on these tests mean to human function.

FUTURE DIRECTIONS

Improvement of future research in delayed health hazards of exposure to pesticides will necessitate changes in the direction and emphasis of epidemiologic research. These changes are specific to the three types of outcomes discussed in this review.

Cancer Hazards

The present epidemiologic approach to detecting human cancer hazards faces two major concerns:

1. The effect of cancer latency is that cancer hazards cannot be detected by traditional means for 20 years or more after sufficient numbers of the population have been exposed. This problem has fueled the move to increasing reliance on animal studies. However, use of genetically pure strains of animals in constant environmental conditions and on controlled diets may not detect human risks, particularly if interaction of several agents and conditions is involved.

2. The magnitude of exposure to particular chemicals, at least in the industrialized world, is declining with improved industrial practices and increasing environmental awareness. While this trend is highly desirable, it reduces the likelihood of epidemiologic studies detecting an effect. Therefore, it is imperative that cancer epidemiology turn to investigating biologic markers of risk that can be tested cross-sectionally in exposed populations.

Tests of sister chromatid exchange and chromosomal aberrations have been criticized because they do not necessarily indicate increased cancer risk. However, public health decisions do not require scientific certainty—exposures linked to these effects should be reduced. A particularly attractive feature of this approach is that markers of risk should decrease after reduced exposure, thereby confirming that intervention has been appropriate. Early studies of pesticide applicators through use of sister chromatid exchange techniques have produced valuable results (33, 96, 176), and better tests will become available, such as quantification of DNA adduct levels (169). Along this same line of inquiry is the detection of genetic susceptibility to chemical exposure in developing cancer (88). The strongest potential for such testing may lie in the development of linkage analysis techniques to map "susceptibility" genes. However, it will be many years before such techniques are practicable.

Reproductive Hazards

Many studies in the past were ecological, and concentrated on general population exposure. Such studies will continue to give controversial results due to the multiple comparisons involved and the unknown exposures. That the effects of low exposures in the general population cannot be detected by epidemiologic methods must be confronted. Emphasis should be placed on high exposure groups.

Surveillance of potentially high risk groups such as manufacturers and applicators is needed, and is easy to implement for congenital defects and for birth rates (58, 95, 152, 153, 175). More sensitive indices, such as early spontaneous abortion and semen analyses, may be necessary in specific circumstances, but the cost and personal resistance in participating render use of such techniques on a large scale unpractical (175).

DBCP is the only pesticide discovered so far to have a clear reproductive effect in humans. This may be simply because occupational studies have concentrated on males. Greater participation of women in the work force should result in more epidemiologic studies of women exposed to pesticides. Future epidemiologic studies of reproductive hazards due to pesticides should concentrate on identifying exposed women, particularly in agricultural work.

Neurotoxic Hazards

Johnson & Anger (83) have emphasized the need for pragmatic standards-based research to clarify the relationship of work place chemicals to neurobehavioral deficits, particularly at levels below which routine neurologic testing or biologic monitoring may detect abnormalities. For organophosphate field exposure in particular, demonstration of neurobehavioral abnormalities during chronic low level exposure sufficient to cause mild decreases in acetylcholinesterase, but insufficient to cause symptoms, would have important implications for medical surveillance and worker protection.

Additional neurophysiologic measures, such as the EMG and sensory-evoked potential, are tools to explore the possible physiologic correlates of decrements in behavioral performance. These tools may help to disentangle the secondary psychologic effects following exposure from the organic effects. Computer-generated neurobehavioral batteries may provide cheaper and more easily administered research tools allowing for screening of larger populations.

The greatest issue surrounding the field of long-term neurobehavioral effects of chemical exposures is simply whether the problems are real, and if so how extensive they are. The former can only be assessed by careful studies including pre-exposure assessment, since it is not clear whether the behavioral measures are measures of outcome, or measures of pre-existing psychologic characteristics whereby people choose certain jobs and adopt work practices that lead them to become heavily exposed.

CONCLUSIONS

With few exceptions, the delayed effects of pesticides on human health have been difficult to detect. Perhaps the health risks are sufficiently small that they are below the power of epidemiologic studies to detect. Yet, it is possible that there are very few effects at all. Concerns may have arisen from the inevitable false positive associations of studies testing a large number of exposures and outcomes. Undoubtedly, however, the need continues for surveillance and assessment of delayed human health effects from pesticide exposure, albeit with some changes in emphasis and methods.

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