Pesticides – How Research Has Succeeded and Failed in Informing Policy: DDT and the Link with Breast Cancer

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Investigation of chemical exposures as possible etiologic factors for breast cancer has not been a research priority in the United States, which is surprising given the evidence from animal studies that environmental chemicals cause cancer and reproductive dysfunction. Study of environmental chemicals has also been indicated by the failure of traditional epidemiologic methods to account for significant proportions of breast cancer incidence with other risk factors. The fact that breast cancer risk is strongly associated with reproductive hormones is a further clue that environmental chemicals should be investigated. In addition to cancer, specific outcomes that need to be explored are reproductive dysfunction, immunotoxicity and neurotoxicity. Policy guiding our research should encourage toxicologic investigations of exposures to environmental chemicals that use state-of-the-art methods to determine exposure and human health effects. Using the approach suggested by John McLachlan, functional toxicology should be used to assess the activity of chemicals with regard to these outcomes. Just as dioxin toxicity can be expressed as toxic equivalents, estrogenic activity, for example, can be characterized in terms of estrogenic equivalents. In addition to the need to undertake this kind of research, needs for methods development and creative research funding mechanisms are discussed. Prevention of breast cancer may require intervention at an early age. Better understanding of breast cancer etiology, and especially its environmental components, may lead us toward that goal. — Environ Health Perspect 103(Suppl 6):87–91 (1995)

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Pesticides such as DDT have been regulated in the United States for more than two decades. The ban of DDT followed observation of adverse reproductive effects in wildlife along with evidence of carcinogenicity in animals and biological persistence in animals and humans. DDT belongs to a class of organochlorines that includes a number of other pesticides — chlordane, hexachlorobenzene, benzene hexachloride (aka lindane), for example — and halogenated biphenyls (polychlorinated biphenyls or PCBs). Many organochlorines, including DDT and PCBs, were banned in the 1970s. Chlordane was regulated more recently, and lindane remains in limited pharmaceutical use.

In some ways, the policy to ban organochlorines has worked. From the U.S. Environmental Protection Agency’s (U.S. EPA) National Human Adipose Tissue monitoring program, data clearly show that levels of DDT in adipose tissue in the U.S. population have steadily declined since 1972 (Figure 1) (1). PCB levels are also going down, albeit more slowly (2). In addition, control of DDT established a precedent that has probably facilitated regulation of other organochlorine pesticides (e.g., chlordane) and persistent halogenated hydrocarbons. An example would be polybrominated biphenyls (PBBs) that were used as a fire retardant until a disastrous contamination of cattle feed in Michigan in 1973 and 1974. Control of pesticide usage has also stimulated a search for less toxic, more readily biodegradable pesticides. Registration of pesticides is now mandatory for new products, which must satisfy requirements of safety and toxicity.

An unfortunate consequence of regulatory policy is that policymakers may take the view that banning solves the problem. It seems obvious that the efficacy of regulatory policy should be supported by scientific evaluation and systematic followup. Thus, with DDT, potential for exposure still exists even 20 years after its ban, and organochlorines continue to pervade the environment. Regulation may have halted deliberate discharge into the ecosystem in the United States, but its continued use in developing countries allows DDT to cross international borders in food produce and in the air and water. Only recently has the United States decided to restrict exports of a number of pesticides including DDT (3).

Continuing environmental contamination by organochlorines has resulted in sustained low-level exposure among wildlife and concomitant reproductive dysfunction (4). Body burdens of DDT in humans are still significant in the United States and worldwide. International studies frequently report detectable levels of DDT residues, with special concern directed toward those ubiquitous levels in human milk that often exceed exposure guidelines recommended to protect against cancer (5). Human milk is now the major source of infant exposure to DDT in the United States. Ironically lactation is the most efficient means of reducing a woman’s body burden of organochlorines.

Status of Research on DDT and Human Health Effects

After 1972, little further attention was paid to research directed specifically to identify human health effects from DDT. This complacent attitude may be attributed to the absence of overt, prominent human health effects due to DDT exposure, in spite of overwhelming evidence of tumorigenicity and reproductive failure in

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animals. Indeed some researchers concluded that DDT was quite safe for humans.

In view of the extensive animal data on reproductive dysfunction, the scientific literature has remarkably few studies on human reproduction related to DDT exposure. Moreover, existing studies are limited with respect to numbers of subjects as well as overall design sophistication. Only four human reproductive studies are cited by IARC, two focusing on prenatal effects and two on preterm abortion (6).

Attempts to determine cancer risk associated with DDT exposure have been somewhat more extensive, but the data are nevertheless quite inconclusive. Human studies have looked for elevated rates of any kind of cancer death among industrially exposed persons. Some have focused on potential risks for lung cancer, liver cancer, lymphoma, soft-tissue sarcoma, and leukemia in case-control studies. However, few of these studies had adequate exposure assessment, which lessens the power to detect an effect. In many reports, there were no adequate controls for exposures other than DDT, and most studies did not start out specifically to investigate DDT cancer risk (6). Nevertheless, hematopoietic cancer and lung cancer risk continues to be weakly associated with DDT exposure estimates in more recent studies.

As a result, existing research efforts have led to the conclusion that DDT is a possible human carcinogen, although it is designated as carcinogenic to animals (6). Evidence for reproductive toxicity is considered scant, whereas in animals clear impairment is recognized. An exception is the reported observation in 1986 that suggested a hormonal effect of DDT; this was the finding that women with higher body burdens of DDE reported shorter duration of lactation (7). A second study recently confirmed these findings (8). This research originated at the National Institute of Environmental Health Sciences (NIEHS), an agency whose intramural program has supported an innovative approach to human exposure and to experimental studies on hormonally active substances. Indeed, since these were the first strong human data of the kind, the observation relating high DDE levels to curtailed lactation led us to examine the relationship of persistent organochlorines to breast cancer risk that will be described below.

In view of this evidence, the policy that banned DDT has failed to influence our national research agenda. Not enough effort has been made to target environmental research in the area of hormonally related cancers. To some extent, this failure is now being redressed by current NIEHS/NCI (National Cancer Institute) initiatives. In defense of current policy, it could be said that animal carcinogenicity studies on organochlorines led researchers to look at the wrong outcomes, because these relatively high-dose studies found mainly liver tumors, a relatively rare tumor in humans in the United States. However, the animal data also indicate that organochlorines are estrogenic and may be tumor promoters, and therefore specific study designs should have been investigated to assess this role for DDT and comparable organochlorines in both animals and humans. (One such report exists in the animal literature.) No particular attention has yet been paid to the potential environmental link with ovarian, colon, endometrial, testicular, prostate, and breast cancer. In view of the unexplained risk and rising rates for breast cancer and prostate cancer, environmental etiology for these tumors is an important line of research that should be vigorously pursued.

Environmental links to cancer immediately afford a means of prevention. To make this failure a research priority has been criticized in characterizing the narrow approach to cancer research since declaration of the war on cancer (9). These past 20 years have seen an increase, rather than a reduction, in overall cancer rates. Critics maintain that our national approach has “neglected research aimed at prevention in favor of the search for cures” (10). Even among those researchers who subscribe to the environmental thesis, many maintain that increased rates of cancer can be attributed to diet and smoking and not industrial carcinogens. Meanwhile, environmental areas that have been explored as means of cancer prevention include viruses, vitamins, diet, tamoxifen, smoking, occupational exposures, radiation, but not pollution or ambient chemical exposures (10).

Breast Cancer and DDT

Breast cancer research has been cited as an example of setting poor research priorities in that no attempts were made to pursue a connection between cancer and exposure to carcinogenic chemicals in the food chain, even in the context of an otherwise enormous investment in studying links between diet and cancer (10). There were five studies on breast cancer and DDT exposure before 1985, and only one of these was in the United States. Yet, other risk factors have not been able to fully explain the dramatic increase in breast cancer rates in the United States during 1970 to 1990, and only some of the increase is attributable to enhanced screening.

Environmental factors have long been invoked as an explanation for breast cancer, but environmental chemicals per se have not been widely accepted as risk factors for breast cancer. Rather, epidemiologic studies have implicated the diet, alcohol consumption, drug use, and radiation as risk factors for breast cancer that might account for the environmental evidence. Unfortunately, the identification of these risk factors has not gone very far in providing us with an explanation for a major proportion of breast cancer incidence nor have these studies given us much hope for preventing a significant amount of the disease. Investigation of chemical exposures as possible etiologic factors for breast cancer has not been a priority, which is surprising given the several animal models that use chemical carcinogens [e.g., polycyclic aromatic hydrocarbons (PAH), methylnitrosourea (MNU)].

In the past few years, evidence has emerged that supports a possible relationship between breast cancer and exposure to organochlorines in the environment, whence exposure occurs predominantly through the diet. There have been four recent case–control studies linking environmental organochlorine exposures to breast cancer risk (Table 1). The relative risks reported in these studies are in the range of 2 to 10. If the data are confirmed in future research, these will rank among the higher risks observed for breast cancer in the epidemiologic literature. However, the studies were relatively small and require extensive confirmation before this association becomes an established risk factor for breast cancer.

In the late 1980s, the first of these studies in Connecticut found approximately 50% higher levels of DDE [bis(4-
chlorophenyl)-1,1-dichloroethenec*, DDT [bis(4-chlorophenyl)-1,1,1-trichloroethane], and higher chlorinated PCBs in mammary adipose among 20 breast cancer cases compared with 20 controls (12). The risk for DDT was not statistically significant. There was approximately a 3-fold increased risk for the highest versus the lowest tertile of these chemicals in adipose tissue.

A second study took advantage of a well-designed nested case–control study in which blood had been collected before diagnosis of breast cancer (12). Again, levels of DDE and PCBs in serum were higher among breast cancer cases than among carefully matched controls, but only differences for DDE were statistically significant. Women with the highest levels of DDE (upper 10%) had about a 4-fold increased risk compared with levels in the lowest 10%. There was approximately a 9% increased risk for every one part per billion (ppb) of DDE in blood serum.

Quite recently, a Canadian study found significantly higher levels of DDE in estrogen receptor-positive (ER) breast cancer cases compared with ER-negative cases and with controls (13). For ER-positive breast cancer, the relative risk was approximately 9 for the highest versus the lowest tertile of these chemicals in adipose tissue. In support of this evidence, H. Mussalo-Rahamaa (14) has more recently reported a correlation between DDE levels and ER levels in their patients, although the findings require cautious interpretation since no age adjustment was made.

Similar relative risks for breast cancer were found among the Finnish women with elevated levels of β-hexachlorocyclohexane, a lindane-related residue, although no association was found with other organochlorines including DDE (15). The relative risks in these four studies are in the same range as those estimated from the animal data (16,17). The potential association with ER status is of some interest, given the estrogenic activity of DDT and the rising rates of ER-positive cancer among older women (18).

Since DDT levels in the U.S. population are gradually receding, this trend should accompany reduced risk of any disease associated with DDT exposures in the United States. However, DDT and other organochlorines are still widely used in developing countries where it may affect public health or it may cross international borders. Furthermore, besides DDT there are myriad other potentially estrogenic chemicals in commerce that require our vigilance (4,19). Many of these new chemicals are not detectable long after exposure, e.g., atrazine and methoxychlor.

Future Research Priorities

How can our scientific research establishment be more effective in protecting human health? Whether or not the DDT-breast cancer link is confirmed, these findings have great potential for teaching us more about breast cancer etiology and in leading us toward preventive strategies. Several lines of research can be suggested. In addition to the potential for prevention, much can be learned about etiology by understanding environmental contributions to breast cancer (Table 2).

Research Areas to Emphasize in Environmental Research

Recent work on breast cancer, as well as accumulating evidence about reproductive failure in animals, should encourage vigorous exploration of chemical factors in the environment. Cancer, reproductive dysfunction, and neurotoxicity need to be investigated. One prominent researcher in the field of environmental estrogens has recently suggested that we should design our research using functional toxicology, i.e., research that defines chemicals more by their function than by their chemistry (20). One such area of toxicology that merits research attention in both basic science and epidemiology is reproductive dysfunction by environmental chemicals (e.g., estrogenicity or endocrine disruption). In a similar context, toxic equivalent (TEQ) factors have been developed for dioxin-like activity, which may also parallel antiestrogenic activity (21). From the available literature, it is possible to construct estrogenicity or endocrine equivalents (EEQ?) that might be useful in terms of relative biological activity for regulatory purposes (22,23). This database can be easily expanded to include a wide range of environmental contaminants.

Functional toxicology also touches a further field that is of potentially great relevance to breast carcinogenesis, i.e. the relationship between P450 activity and exposures to DDT and other organochlorines. Association of elevated P450 activity with DDT and PCB exposure in humans has been known for many years (24,25). Organochlorines have been widely studied for their ability to induce P450 enzymes whose baseline activity is genetically determined. The cytochrome P450 enzymes are responsible for metabolizing endogenous, as well as xenogenous, chemicals in the body (e.g., estrogen and PAH). Certain of these metabolites may act as ultimate carcinogens that bind directly to DNA and cause mutations. The genes for P450 are polymorphic in humans, and the distributions of the polymorphisms vary between different ethnic populations. Hormones are also metabolized by these enzymes. However, while the P450 enzymes have been widely studied, only recently has this area begun to reach fruition in the study of human cancer (26). Although no information is currently available on breast cancer, a number of investigations on breast cancer are now underway.

Methods Development Needs

Research priority should be placed upon improving methods for exposure assessment and into developing innovative epidemi-
logic and statistical methodologies for study design and analysis. Better epidemiologic tools and improved quantitation will allow us to design epidemiologic studies to trace putative carcinogenic pathways. Other endpoints besides cancer are important to study as well. Reproductive and neurotoxic effects may be important risk outcomes to consider.

Existing methodologies are often inadequate to study complex diseases like cancer, reproductive dysfunction, and neurotoxicity, especially when attempting to link subtle biological effects with complex and low-level exposures. Therefore, research testing of environmental hypotheses would be greatly facilitated by the availability of better epidemiologic instruments and sophisticated statistical techniques. Improved methods would enable us to more adequately evaluate associations between indicators of preclinical disease, genetic factors, causal agents, and risk.

Techniques are needed for exposure assessment that will provide quantitative individual measurements. These techniques must be able to detect very low levels of exposure that are common in environmental circumstances. Internal biological markers of exposure and disease are usually more sensitive and specific than estimates using external methods (i.e., air pollution or water contamination levels). This may be useful for DDT, where cumulative body burdens persist for many years, reflecting integrated past exposure. However, many of the newly developed pesticides that have replaced organochlorines are not persistent, presenting a difficult problem in exposure assessment. With respect to cancer risk, exposure assessment is even more difficult because initiating events may have taken place 10 to 30 years before cancer diagnosis. Similarly, PAH and nitro compounds are potential etiologic agents for cancer and are not persistent in the body. For this reason, historical exposure information has often been used; this is another means of external exposure assessment methods.

**Funding Mechanisms**

Our scientific research and funding strategies must allow more creative ideas to be tested. En route to soliciting and establishing new methodology and to confirming and extending our research on DDT and breast cancer, it may be necessary to fine-tune our research review and funding policies. Traditional funding mechanisms possess a certain rigidity toward new, unconventional ideas. The National Institutes of Health (NIH) likes to fund a sure thing. As a result, it is a constant struggle to eke out support appropriate funding mechanisms for new, untested ideas, especially in the current climate of tight funding. Multiple reviews or special screening panels for special projects might be considered. The Request for Application (RFA) mechanism may also be suitable for circumventing the entrenched review process and for encouraging scientific flights of fancy. Recently NCI and NIEHS have issued RFAs that will allow researchers to confirm and expand these findings. Criticism has been leveled at the U.S. EPA on another front—that of whether a regulatory agency can successfully undertake and administer a research program (27). Since the U.S. EPA’s budget is a significant proportion of funding for environmental research, its record of performance in predicting as well as preventing environmental disease may be a starting point for examining the structure of this agency.

**Relevance to Environmental Health Effects among Children**

The example of breast cancer relates to children’s environmental health, especially with respect to the potential for prevention of exposures. Evidence in animals demonstrates that developing tissues are more sensitive to carcinogenic exposures. Recent evidence, though limited, suggests that exposure to cigarette exposure or alcohol at an early age may be associated with increased risk for breast cancer among young women. Women in the United States have markedly higher age-specific rates of breast cancer compared with Japanese women, and the differences are most dramatic among premenopausal women. Part of the difference may be dietary or environmental factors that alter the onset of puberty, which occurs much later in Japanese women. Therefore preventive measures such as dietary intervention may need to be undertaken at an early age. Prevention of environmental exposures related to breast cancer is also an important potential means of prevention that should be vigorously pursued.

Rates of breast cancer occurrence in the United States have steadily risen since 1940. During that same period, levels of pesticide and PCB residues in human adipose tissue in the United States have shown parallel increase, following their introduction into commerce around the time of World War II. Since then, despite much research on the question, only three factors have been generally agreed to be strongly linked to breast cancer: age, country of birth, and family history. These factors are not readily amenable to change. Medicine has done its job well in finding new avenues of treatment and detection. However, the existence of a cure without a cause continues because no pathways for prevention have been found. Innovative research should be undertaken to develop better methods and to elucidate potential mechanisms for environmental exposures and breast cancer.

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