This column is provided to help practitioners discuss potential environmental and workplace carcinogens, offering reassurance when patients' fears are unfounded and focusing legitimate concern when they are warranted.

Organochlorines and Breast Cancer Risk

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ABSTRACT Organochlorines are a diverse group of synthetic chemicals that include polychlorinated biphenyls (PCBs), dioxins, and organochlorine pesticides such as dichlorodiphenyl-trichloroethane (DDT), lindane, and hexachlorobenzene. Although use of DDT and PCBs has been banned in the United States since the 1970s, some organochlorine compounds have accumulated and persisted within the environment. As a result, measurable amounts can still be found in human tissue. Because some organochlorine compounds act as estrogen agonists or antagonists within in vitro and experimental animal systems, a possible association of breast cancer risk with organochlorine exposure has been hypothesized and investigated. Although a few studies support this hypothesis, the vast majority of epidemiological studies do not. While some of these compounds may have other adverse environmental or health effects, organochlorine exposure is not believed to be causally related to breast cancer. Women concerned about possible organochlorine exposure can be reassured that available evidence does not suggest an association between these chemicals and breast cancer. (*CA Cancer J Clin 2002;52:301-309*.)

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INTRODUCTION

Organochlorines are a diverse group of synthetic chemicals, many of which were released into the environment in past decades through their use as pesticides or industrial products. Organochlorine pesticides, including dichlorodiphenyl-trichloroethane (DDT), were used widely in the United States from the early 1940s until the 1960s for insect control in forestry, agriculture, and building protection. Use of DDT peaked in the United States in the early 1960s and was banned in 1972. Polychlorinated biphenyls (PCBs) were extensively used in the United States as dielectric fluids in electrical transformers and capacitors, as plasticizers, lubricants, and heat transfer fluids, and in the manufacture of such products as paints and paper until their use was discontinued in 1977. While often perceived as a single entity, PCBs represent a large and diverse class of organochlorine chemicals that includes 209 possible congeners with some congeners more commonly used in commercial products than others.[1] Dioxins are also organochlorines that are produced as combustion byproducts of industrial processes or as contaminants of herbicides. Other organochlorines include pesticides used in lesser amounts, such as lindane and hexachlorobenzene.

Organochlorine compounds degrade slowly, are lipid soluble, bioaccumulate in the food chain, and may be found in human adipose tissue, blood, and breast milk. The most prevalent organochlorine residues found in human tissues are dichlorodiphenyl-dichloroethylene (DDE), the major metabolite of DDT, and PCBs.[1] Levels in human tissues are positively associated with age[2] as a result of accumulation from the environment and historically higher levels of exposure. Measured levels have been consistently higher in African Americans than among Caucasians,[3-6] probably reflecting differences in exposure. Since discontinuation of the use of DDT and PCBs in the 1970s, levels of DDT, DDE, and PCBs detected in food and in human blood and tissue have declined in Western countries.[2]

In recent years, attention has been focused on the potential of some chemicals to act as "endocrine disruptors." An endocrine disruptor is a chemical that interferes with the function of the endocrine system by mimicking a hormone, blocking the effects of a hormone, or by stimulating or inhibiting the production or transport of hormones.[7] Many organochlorine compounds, including DDE and some PCBs, are considered endocrine disruptors because they are weakly estrogenic or antiestrogenic in experimental assays.[8-10] They have also been found to be carcinogenic in animal models.[11,12] These characteristics, in combination with the temporal concordance of their widespread use with increasing age-adjusted incidence rates of breast cancer, stimulated the hypothesis that exposure to these compounds may contribute to the occurrence of breast cancer.

EPIDEMIOLOGICAL STUDIES

In 1993, a case-control study conducted by Wolff and colleagues[13] in New York found two- to four-fold elevations in the occurrence of breast cancer among women with the highest serum levels of DDE and PCBs compared to those with the lowest levels. Before 1993, the possible association between adipose or blood organochlorine levels and breast cancer had been examined in only a handful of very small studies, most of which examined organochlorine levels in breast tissue; results from these studies were inconsistent, but overall did not suggest a positive association.

Since 1993, approximately 30 published studies have attempted to replicate the associations observed in the Wolff study, and to investigate further the potential association between breast cancer and individual PCB congeners as well as other organochlorine chemicals. With rare exceptions,[14-16] there is consistent evidence from many methodologically sound studies of no association between levels of persistent organochlorine compounds, notably DDE and PCBs, and breast cancer. The lack of association has been observed in an ecological correlation study,[6] in case-control studies,[17-26] in prospective follow-up studies,[5,27-32] in studies of serum/plasma,[5,17,23-32] in studies of adipose tissue,[18-22,33-35] and in studies conducted in the United States,[5,6,26,27,32,36] Canada,[21,23] Europe,[18,29,30,34,35] and elsewhere.[17,37,38]

Many studies have been conducted in the northeastern United States to address the possibility that exposure to organochlorine compounds may explain the higher rates of breast cancer observed there.[19,20,22,24,25,28,31,38a] Collectively, results from these studies indicate that women with breast cancer have the same blood levels of DDE and PCBs as women without breast cancer. In a pooled analysis of five large studies,[24,25,27,28,39] the relative risks for breast cancer comparing women in the highest to the lowest quintiles of blood levels of DDE and PCBs were 0.99 and 0.94, respectively.[40] Results from the long awaited and recently published study of breast cancer on Long Island, NY, also did not support an increased risk of breast cancer among women with the highest serum levels of DDE or PCBs.[38a] Exposure to DDT and PCBs, as experienced by

women in these studies, does not appear to explain regional differences in breast cancer rates.

Recent studies have considered the potential association of several detectable organochlorine compounds other than DDE and PCBs, as well as individual PCB congeners, with breast cancer.[20,21,23,28-30,32,41,42] Results from these studies have been null or yielded sporadic but inconsistent evidence of associations. The increased risk associated with higher body burdens of the organochlorine dieldrin observed in a study of Danish women[42] was not observed in a second study of the same population,[29] nor in three other studies, one in Norway and two in the United States.[30,32,38a] Likewise, the suggestion of an increased risk associated with PCB congener 118,[21,29,41] a potentially antiestrogenic dioxin-like compound,[43] has not been observed consistently.[20,23,30,32,44] Several other organochlorine compounds or PCB congeners have been reported to be associated with breast cancer in single studies, but these results have not been replicated.

While exposure to organochlorine compounds does not appear to increase the risk of breast cancer overall, several investigators have examined the hypothesis in subgroups of women defined by race, menopausal status, history of parity and breastfeeding, body mass, tumor characteristics, and genetic factors. No consistent subgroup findings have emerged. Results from two studies suggested that a positive association between organochlorine compounds and breast cancer may be more evident in African-American women than in Caucasian women,[5,26] but a third study did not support differences by race.[24] Individual studies have suggested that organochlorine compounds may be a risk factor for breast cancer among women who have never lactated,[25,26] but a pooled analysis of five large studies revealed no differences among subgroups of women by parity or lactation history.[40] The same pooled analysis found no differences in the associations between DDE or PCBs and breast cancer in subgroups defined by menopausal status, age, or hormone replacement therapy use.

Women with breast cancer have been grouped by tumor characteristics such as estrogen receptor (ER) and progesterone receptor (PR) status, tumor size and grade, and nodal involvement to investigate the possibility that organochlorine levels are associated with a particular tumor type or aggressivity. The tumor characteristic most often studied has been ER status. While one study found positive associations between organochlorine levels and ER-negative breast cancer,[45] most have not.[20,28,30,31,39] Finally, the investigation of subgroups of women defined by genetic susceptibility (e.g., germline polymorphisms associated with breast cancer) is likely to be an active area of future research. Results from one US study found no evidence of an association between several putative high-risk polymorphisms (GSTM1, GSTT1, GSTP1, and COMT), serum DDE, or PCBs and breast cancer.[28] A second study found an increased risk of breast cancer associated with higher than average serum PCB levels only among women with a given polymorphism in CYP1A1.[46]

Several studies have been conducted in countries where DDT has been used more recently or is still in use, and hence there is greater potential for women to be exposed to sprayed DDT versus the preformed DDE metabolite in food products. This difference may be important because sprayed DDT may differ in its estrogenic potency compared to preformed ingested DDE.[47] Results from these studies have been mixed. A small study conducted in North Vietnam[37] found no increase in risk for breast cancer with higher serum levels of DDT or DDE. Two studies conducted in Mexico City had conflicting results. In the first study, no association was found between serum DDE and breast cancer,[38] while a more recent study found significantly

higher serum levels of DDE in breast cancer cases than among controls.[15] In this study, women with the highest levels of DDE had over a three-fold increased risk of breast cancer. The reason for the differing results for these two studies of women in Mexico City is not clear. The studies were similar in size and both adjusted for important confounders in the analysis. No association between DDE levels and breast cancer was seen in a study conducted in Brazil,[17] while a two-fold higher risk of breast cancer was observed in Colombian women with the highest levels of serum DDE.[16]

Collectively, the epidemiological studies conducted to date do not support a positive association between body burdens of persistent organochlorines, most notably DDE and PCBs, and the occurrence of breast cancer. One strength of the epidemiological evidence is the consistency of findings across multiple studies and subgroups. Another strength is that the studies relied on measured levels of organochlorines rather than on reported exposures. To the extent that measured body burdens reflect actual exposures to biologically important compounds, the studies are informative and reassuring.

One limitation of the epidemiological evidence is that exposures generally occurred years before biological measurements were made. The important question is whether contemporary measurements of organochlorine body burdens can adequately reflect past exposures. If not, then differences between cases and controls might be missed, obscuring a true association between exposure and disease. The answer to this question likely depends on the persistence of the compound of interest in both the environment and in human tissues. Because of the long half-life of DDE (7 to 11 years[31]) and PCBs (5 to 25 years[31]) and their persistence in the environment, relative differences between groups of individuals should be detectable for many years following exposures. Also, in a few studies, blood or adipose tissue was collected in the 1960s and 1970s in the United States when exposures were ongoing and body burdens were higher.[5,6,28] Results from the studies of historically-collected tissue do not support an association between DDE, PCBs, and breast cancer.

However, different organochlorine compounds persist for different periods of time and not all are long-lived. The PCB congeners with the highest-potential estrogenicity are also the most quickly metabolized.[43] The extent to which exposure to these short-lived congeners is correlated with exposure to the more persistent (and thus measurable) congeners will vary according to the nature of the exposure. Thus, results of existing studies may not be able to assess the importance of short-lived organochlorine compounds.

The studies reviewed above assessed general community levels of exposure, not occupational exposures, which may be higher than experienced by general populations of women. However, the few available studies of occupational exposure to PCBs and dioxin have not supported an association with elevated breast cancer risk.[48] In addition, most studies have been conducted in populations of largely Caucasian women in the United States, Canada, and Europe. Few studies have been conducted among African-American women, Hispanic women, and women in developing countries where heavy DDT spraying is still in use. Additional studies of recent and ongoing exposures would be informative.

ANIMAL AND LABORATORY STUDIES

Animal and laboratory evidence has demonstrated carcinogenic activity for some organochlorines. PCBs have consistently induced hepatocellular carcinomas in rats, as well as thyroid adenomas and gastric and intestinal tumors in individual studies. PCBs

have also been shown to have a tumor-promoting effect in studies using rats and mice when administered together with tumor initiators. Mammary gland tumors have not been seen in animal studies of PCBs. In vitro genotoxicity studies of PCBs performed in bacterial systems, mammalian cells, and human cells have generally given negative results.[12,49]

Animal studies of DDT have shown a number of positive results. Mice are relatively susceptible; mouse studies of DDT and/or DDE have yielded tumors of the liver, lung, thyroid, and lymphomas. Results from other species, including rats, guinea pigs, hamsters, and primates have been more equivocal. Some in vitro laboratory tests of DDT and DDE have shown chromosomal aberrations and dominant lethal mutations, although many such assays have been negative.[11,50]

AGENCY ASSESSMENTS OF CARCINOGENICITY

Based on experimental and human evidence, expert and regulatory agencies have evaluated whether DDT and PCBs are carcinogenic.

The National Toxicology Program evaluates exposures to determine if they may be carcinogenic. Exposures that are thought to be carcinogenic are included in the *Reports on Carcinogens*, published every two years. Each exposure is assigned to one of two categories: "known to be human carcinogens" and "reasonably anticipated to be human carcinogens." The first category includes substances for which human studies (epidemiology studies and/or experimental studies) provide "sufficient evidence of carcinogenicity in humans." The second category includes substances for which there is "limited evidence of carcinogenicity in humans" and/or "sufficient evidence of carcinogenicity in experimental animals." Using this scheme, the National Toxicology Program classifies both DDT and PCBs as "reasonably anticipated to be human carcinogens."[51]

The International Agency for Research on Cancer (IARC) also evaluates exposures that may be carcinogenic. IARC classifies exposures into one of four categories: Group 1 exposures are those "known to be carcinogenic to humans," usually based on "sufficient human evidence," but sometimes based on "sufficient evidence in experimental animals" and "strong human evidence." Group 2 exposures are divided into two categories. Group 2A ("probably carcinogenic to humans") has stronger evidence, and Group 2B ("possibly carcinogenic to humans") has weaker evidence. Group 3 exposures are not considered classifiable because available evidence is limited or inadequate. Finally, Group 4 exposures are "probably not carcinogenic to humans" based on evidence suggesting lack of carcinogenicity in humans and in experimental animals. The IARC rated DDT as "possibly carcinogenic to humans" (Group 2B), and PCBs as "probably carcinogenic to humans" (Group 2A).[11,12]

The Environmental Protection Agency, through its Integrated Risk Information System, uses a classification scheme very similar to that of IARC. It classifies exposures into one of five categories: (Category A) human carcinogen, (Category B) probable human carcinogen, (Category C) possible human carcinogen, (Category D) not classifiable as to human carcinogenicity, and (Category E) evidence of noncarcinogenicity for humans. The EPA classified both DDT and PCBs as probable human carcinogens (Category B2).[52]

These agency determinations should be placed in context in two important ways. First, agency procedures rely preferentially on human data, but when human data are insufficient to support a conclusion, animal and laboratory data assume greater importance. In the case of the organochlorines, because human data are limited, the agency conclusions were driven entirely by animal and laboratory data. Second,

the animal data have not suggested an increased risk for breast cancer, specifically.

ASSOCIATION WITH OTHER HEALTH PROBLEMS

Other Cancers

Many epidemiological studies have examined possible associations between exposure to DDT (or pesticides), PCBs, and cancers other than breast cancer. While results of some individual studies have suggested increased risks for cancers of several sites, few if any of these associations can be considered established.[1,11,12,53] Exposures have been defined in some studies by serum or tissue levels, and in other studies by occupational records or reported exposures. Epidemiological data on cancer risks (e.g., lymphatic and hematopoietic cancers and soft tissue sarcoma) associated with exposure to DDT have been limited by the assessments of exposure and the finding of small and inconsistent excesses. For these reasons, the IARC has determined that there is "inadequate" evidence in humans for the carcinogenicity of DDT.[11]

Results from epidemiological studies of exposure to PCBs based primarily on occupationally-exposed populations have suggested possible increases in risk for cancer of the liver and biliary passages, and of the kidney. However, these findings are based on very small numbers of cancers in individual studies, and dose-response relationships could not be evaluated. The IARC has determined that the human evidence for carcinogenicity of PCBs is "limited."[12]

Noncancer Outcomes

DDT has been associated with several noncancer health effects. Acute, high-level exposures may cause nervous system excitation with tremors, seizures, and nonspecific symptoms such as sweating, headache, nausea, and vomiting. No effects of low-level chronic exposures have been described in humans, but in animals there is evidence of liver and adrenal toxicity and reproductive dysfunction.[50]

PCBs have also been associated with several noncancer health effects. With acute, high-level exposures, skin lesions such as chloracne may occur, as may liver inflammation. Lower exposures over longer periods of time, especially prenatal exposures, have been associated with neurodevelopmental deficits. Other possible health effects suggested by human and/or animal evidence include immune dysfunction and thyroid abnormalities.[49]

HOW SHOULD HEALTH PROFESSIONALS ADVISE PATIENTS?

Patients may be concerned about the risk of breast cancer in relation to organochlorine exposure. They may be reassured on several points. First, the available evidence does not suggest an association between these chemicals and breast cancer. Second, overall exposure to organochlorines is declining, so that the possibility of such an effect has diminishing importance with the passage of time. PCB production ended in the 1970s, and while there are residual levels in the environment (and in some older electrical equipment), exposures to PCBs are increasingly rare. DDT is no longer used in the United States, and while some countries continue to use it in malaria eradication, this use is declining. In fact, these and other organochlorines are part of a group of "persistent organic pollutants" (POPs) that are being phased out globally in accordance with the United Nations-sponsored Stockholm Convention, signed on May 22, 2001.[54] The driving concerns for this

phaseout are ecosystem effects, effects on nonhuman species, and human health effects other than breast cancer.

Patients may ask about assessing their body burdens of organochlorines, but given the lack of evidence for an association with breast cancer, the value of such information is unclear. Laboratory testing is available for assessing both PCBs and DDE, the principal metabolite of DDT, in blood or in adipose tissue. Normative data are available from national testing. Interpretation of these test results is complex because commercial laboratories use varying test methods, and in the case of PCBs, the laboratories report results from varying combinations of congeners. Physicians who wish to send patient samples should consult with occupational and environmental medicine specialists in selecting a laboratory and in interpreting test results.

Women may ask about the advisability of breast feeding if they have been exposed to organochlorines since organochlorines may concentrate in breast milk.[55] While this is a personal decision, the health benefits of breast feeding are generally felt to outweigh any risk of organochlorine exposure to the baby.[56-58]

SUMMARY

At present, there is substantial epidemiological evidence regarding the possible association between organochlorines (as measured in blood and adipose tissue) and risk of breast cancer. The evidence does not support an association. This conclusion applies particularly to the study of DDT and its major metabolite, DDE, and to all PCBs combined, as well as to exposure levels experienced by general populations of women in North America and Europe. CA

OTHER SOURCES OF INFORMATION

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, NE, Mail Stop E-29
Atlanta, GA 30333
Agency home page: http://www.atsdr.cdc.gov/

Public Health Statement for Polychlorinated Biphenyls (PCBs), November 2000:
http://www.atsdr.cdc.gov/toxprofiles/phs17.html

Toxicological Profile for Polychlorinated Biphenyls (PCBs), November 2000:
http://www.atsdr.cdc.gov/toxprofiles/tp17.html

Public Health Statement for DDT, DDD, DDE May, 1994:
http://www.atsdr.cdc.gov/toxprofiles/phs35.html

Toxicological Profile for DDT, DDD, DDE, September 2000:
http://www.atsdr.cdc.gov/toxprofiles/tp35.html

Environmental Protection Agency
EPA West Building
National Program Chemicals Division
1200 Pennsylvania Avenue, NW
Mail Code 7404T
Washington, DC 20460
Agency home page: http://www.epa.gov/
PCB home page:
http://www.epa.gov/opptintr/pcb/
Integrated Risk Information System on PCBs:
http://www.epa.gov/iris/subst/0294.htm
Integrated Risk Information System on DDD:
http://www.epa.gov/iris/subst/0347.htm
Integrated Risk Information System on DDE:
http://www.epa.gov/iris/subst/0328.htm
Integrated Risk Information System on DDT:
http://www.epa.gov/iris/subst/0147.htm

International Agency for Cancer Research
150 cours Albert Thomas
F-69372 Lyon cedex 08, France
Agency home page: http://www.iarc.fr/
Click on "cancer data bases" to search for PCBs or DDT.

National Toxicology Program
P.O. Box 12233
Mail Drop A3-01
Research Triangle Park, NC 27709-2233
Program home page:
http://ntp-server.niehs.nih.gov/
Click on "search" for information on PCBs and DDT.

National Cancer Institute
NCI Public Inquiries Office
Building 31, Room 10A03
Bethesda, MD 20892-2580
(301) 435-3848
Institute home page: http://www.nci.nih.gov/
Click on "search" for information on PCBs and DDT.

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