In the last 5 years, there has been a resurgence of international interest in research on exposure to DDT (dichlorodiphenyl trichloroethane) as a possible avoidable cause of breast cancer. Due to the estrogenic activity of DDT (1), it has recently been proposed that this compound acts as a xenoestrogen that increases the risk of breast cancer in women who are not necessarily exposed in an occupational environment. Given the tremendous public interest in breast cancer, developing effective research strategies in this area is a real challenge for environmental health researchers. Current evidence suggests that exposure to DDT may elevate the risk of developing breast cancer. So far, that evidence remains tantalizingly incomplete (2–5).

Based on research carried out in populations occupationally exposed to DDT, it has also been suggested that DDT could play an important role in the etiology of pancreatic cancer (6) and leukemias (7–9), as well as producing alterations in reproductive function, such as decreases in sperm count (10), increases in the frequencies of preterm births (11,12) and congenital malformations (13), and decreases in the duration of lactation (14).

Since the 1940s, DDT has been widely used throughout the world to combat agricultural pests, indoor insects, and in sanitation campaigns against malaria. At present its use has been totally banned in developed countries due to its persistence (low biodegradability), accumulation, and bioconcentration in lipid systems, including subcutaneous fat, breast tissue, brain, and adrenal glands (15,16). In Mexico, DDT application in sanitation campaigns against malaria began intermittently in 1956 and has continued sporadically since 1960 (17). Currently, the World Health Organization recommends the use of DDT for malarial outbreaks, although public health experts do not uniformly endorse this use. DDT targets adult insects and cannot kill larvae. Resistance of insects to DDT has occurred worldwide (18).

Devastating and obvious effects of DDT on wildlife, such as endangerment of the American bald eagle and the peregrine falcon, were the grounds for the banning of DDT in the United States in the 1970s. As ecological levels of DDT have dropped in the United States, these previously endangered species have recovered (19). More recently, a spill of the pesticide dicofol (which contained 10% DDT as an active ingredient) into Lake Apopka, Florida, has been tied to alterations in the sex ratio of alligators and increased defects in male alligators (20).

Breast cancer is the second cause of death among Mexican women, with a rate of 2.8 per 100,000 women in 1994 (21). Diagnosis of this malignant neoplasm generally occurs when the disease is at stage II or greater, as is shown in the information of the Mexico Cancer Registry (MCR) for 1989. During 1989, 1521 new cases were reported to the MCR. Only in 2% of these patients was the tumor discovered when it was still in situ (30 cases) (22).

Exposure to endogenous estrogens is the risk factor that links most known causes of breast cancer. Early age at menarche, late age at menopause, nulliparity, and absence of breastfeeding increase lifetime estrogen exposures and are all associated with an elevated risk of breast cancer (23). Estrogen replacement therapy in postmenopausal women and alcohol and saturated fat consumption are factors that have been inconsistently linked to an increase in the risk of breast cancer. In spite of the progress made in knowledge of the etiology of breast cancer, it is estimated that only 30% of breast tumors can be explained by these factors (24,25).

A number of epidemiological studies have been carried out to evaluate the association between exposure to DDT and breast cancer. These studies have been conducted in populations in which DDT use has been banned for over 27 years and are subject to a number of methodological limitations (2–5,26–28).

In this article, we first present comparative information about the production and consumption of DDT in Mexico. Second, we document the levels of accumulated DDT in blood, adipose tissue, and breast milk samples from women who reside in Mexico City, including data about the levels of DDT in foods. Finally, we discuss the methodological limitations of epidemiological studies on breast cancer and DDT, exploring how these studies may have been biased toward a certain conclusion about this possible association. We propose that given the unusual agricultural exposures among populations living in urban areas of Mexico, a number of research studies should be conducted to clarify whether DDT is an avoidable cause of breast cancer.
Production and Consumption of DDT in Mexico and the United States

After the Second World War (1945), industrial production of DDT began, largely for the treatment of lice in soldiers. The production and consumption patterns of DDT have varied substantially between developed and developing countries. Malaria control campaigns have been undertaken in both developed and developing regions. Agricultural uses have occurred solely in developing countries. The production and uses of DDT in Mexico and the United States are a good example of these differences (29).

In Mexico, production of DDT by two firms began in 1959 (Table 1). In the 1960s in the United States, Rachel Carson’s book Silent Spring (30) generated widespread concern about the indiscriminate use of pesticides. Eventually this led to the regulation of DDT in 1969 and the ban on domestic use in the United States in 1972. However, in Mexico during the same decade, DDT and other organochlorine pesticides were widely used, and during the 1971–1984 period, 60,609 tons of these products were sprayed; DDT accounted for approximately 10% of these products (31). During this same period, (1971–1984), the capacity for DDT production in Mexico was 8000 tons annually, representing between 43% and 45% of the total national capacity for organochlorine pesticide production (29).

The evolution of DDT production and consumption in Mexico between 1971 and 1991 is shown in Figure 1. During the second part of the 1970s and the beginning of the 1980s, both production and consumption varied between 3400 and 4100 tons annually. Between 1982 and 1986, production and consumption decreased notably, almost to zero, although beginning in 1986 production began to grow again and consumption followed in 1987 (31).

The pronounced decrease in production and consumption of DDT observed during the first half of the 1980s in Mexico was principally due to two causes. First, a severe economic crisis affected Mexico in 1982, which resulted in a drastic drop in production and commercial activities in the country. Second, an international trend reduced the use of organochlorine pesticides, which were widely recognized to persist in the environment (32). This trend resulted in restriction of DDT use in official Mexican sanitary campaigns, and therefore a notable decrease in demand and production of DDT.

As shown in Figure 2, approximately 226,000 tons of DDT were used in the antimalaria campaign during 1971–1993, averaging 500 g per household sprayed. Since 1988, malaria incidence has reportedly decreased by 90%, and the proportion of rural towns with blood samples positive for malaria has decreased by 75%. However, current use of DDT in Mexico is still greater than in other Latin American countries, as can be seen in Figure 3 (17–33).

To illustrate the widespread production and marketing of DDT in Mexico, it should be noted that in 1987 there were two large firms that produced DDT as an active ingredient. This product was used in turn by 23 firms to develop 6 different formulations, resulting in 35 different registered brands of pesticides sold in the national market. Currently DDT is produced in only a few countries; in Mexico DDT is produced in a single industrial plant, located in the city of Salamanca. Less than 5000 tons of DDT have been exported from Mexico since 1971 (28,34).

Recently the Mexico Secretary of Health made a commitment to eliminate

Table 1. Evolution of DDT use in the United States and Mexico

| Year   | United States | Year   | Mexico |
|--------|---------------|--------|--------|
| 1945   | Use begins    | 1945   | Use begins |
| 1962   | Publication of Silent Spring (30) | 1959   | Production begins |
| 1969   | Regulation begins | 1960–70 | Use spreads |
| 1972   | Domestic use banned | 1971–84 | 60,609 tons of organochlorine pesticides, including 6,061 tons of DDT per year |

Figure 1. Apparent DDT production and consumption in Mexico, 1975–1991 (37,34).

Figure 2. The Mexican malaria campaign, 1959–1993. The number of cases of malaria and households sprayed are shown (17).
the use of DDT and to look for alternatives for malaria control with technical support from United States and Canada (35).

**DDT Levels in Serum, Adipose Tissue, and Breast Milk**

Due to the lipophilic nature of DDT and its principal metabolite, dichlorodiphenyl dichloroethene (DDE), these compounds have been found in diverse human samples of serum, adipose tissue, and breast milk. The half-life of DDT in human adipose tissue is approximately 7.5 years. The amount of serum DDT varies according to the levels of lipids circulating in the blood. It has been estimated that the ratio between levels of DDT in adipose tissue and blood is 300 to 1. The presence of DDE levels in organisms is a good biological indicator of chronic exposure to DDT (36).

Information about levels of DDT and its metabolites in human samples in Mexico is scarce (Table 2). The results of a study carried out in 1975 (37) showed that levels of DDE in abdominal adipose tissue samples, expressed in parts per million in a lipid base (μg/g of extractable lipids), ranged from 2.65 ± 2.35 in 9 adipose tissue samples from necropsies in the city of Puebla located in the central region of Mexico to 18.36 ± 33.27 in 19 similar samples obtained in the city of Torreon (located in the northern part of Mexico). Corresponding levels detected in 9 samples from biopsies from Mexico City had a mean value of 6.05 ± 3.49 (37). The results of another study carried out in a city on the northern border of Mexico (Ciudad Juarez) showed that accumulated levels of DDT and its derivatives in 62 human adipose tissue samples obtained in 1977 were 20.59 ± 13.18 ppm, and in 1992, Waliszewski et al. (38,39) found average levels of DDE to be 18.91 ± 23.29 ppm in necropsy tissue from individuals who had lived in the state of Veracruz (Gulf of Mexico). The initial results obtained by our research team in 1995 showed that the geometric mean of DDE in adipose breast tissue samples from 160 women living in Mexico City is 6.66 ± 1.66 ppb.

Although the representativeness of the biological samples analyzed in some of these studies can be questioned, these studies suggest that there is a DDT accumulation gradient that is greater in tropical areas and/or regions with greater agricultural activity (Veracruz, Torreon, Ciudad Juarez). These data also show that inhabitants of urban areas are exposed to DDT (Torreon, Ciudad Juarez, Puebla, Veracruz, and Mexico City).

Since the end of the 1970s, Mexican studies have episodically documented the presence of DDE and total DDT in breast milk, with levels varying between 0.20 and 0.26 mg/kg (ppm) of total milk. Thus, levels of DDE in breast milk in Mexico are two to three times greater than corresponding levels in samples analyzed in the United States during that same period (40).

Our 1995 study showed that women living in Mexico City had DDE levels in of breast milk of 0.594 mg/kg in a lipid base. In contrast, in women living in tropical Mexico these levels reached an average level of 5.02 mg/kg, which is extremely high (Waliszewski et al., submitted). Thus, there is a 10-fold difference in DDE levels within Mexico.

As mentioned previously, use of DDT in Mexico has been restricted to sanitary campaigns against malaria. These campaigns have been carried out in all states, except those which are not considered endemic (Tlaxcala, Mexico City, Baja California Norte). Despite this, high accumulation levels of DDE have been found in the biological samples from Mexico City residents. It is quite likely that exposures to DDT have occurred in these urban areas not only from malarial campaigns but also from other sources, such as lipophilic foods.

**DDT Levels in Foods**

According to the information provided by the Public Health Laboratory of the Ministry of Health, out of a total of 439 food samples analyzed between February 1993 and March 1995, diverse organochlorine and organophosphate pesticide residues were found in 146 (unpublished data).

The foods that contained DDT and its derivatives were principally meats and dairy products. For example, in 43.5% of the milk samples analyzed (86/202), p,p'-DDT, DDE, and p,p'-TDE were found. DDT levels varied widely, from 0.01 ppm to 0.082 ppm. Likewise, in 13 of the 30 meat samples (30%), DDE and p,p'-DDT were found at levels from 0.001 ppm to 0.06 ppm. Sixty-eight percent of the milk sam-
amples and all the meat products came from states located in the central-southern part of the country.

Butter samples (345) from the state of Veracruz (Gulf of Mexico) were analyzed in 1994. The results showed that DDE levels did not exceed those recommended by the World Health Organization (1.25 ppm) (Waliszewski et al., submitted). The same authors found that in 192 cows' milk samples, DDE levels did not exceed the corresponding Food and Agriculture Organization recommended level (Waliszewski et al., submitted); levels were also acceptable in 53 samples of bovine liver fat samples from the same area (41).

Information about residues of DDT and its derivatives in Mexican foods should be interpreted with caution. It is possible that the results described above are not representative of the actual DDT contamination values, since none of the samples analyzed was obtained through probabilistic sampling methods.

Methodological Limitations of Epidemiological Studies of DDT Exposure and Breast Cancer

A number of articles have discussed the methodological limitations of the eight epidemiological studies that have provided controversial results on DDT exposure and breast cancer (42). Given the small sample size of most of these studies, they lacked the minimum power necessary to detect a difference, if one exists, between DDT levels in breast cancer patients and the corresponding levels in women without the disease. Another criticism has been the lack of control of confounding variables, principally parity, breastfeeding, and obesity, which are factors associated both with breast cancer incidence and accumulation or elimination of DDT from the body.

In addition to these limitations, other factors could account for some of the discrepancies in the results. For example, different tumor types may have distinct susceptibilities to xenoestrogens, so that estrogen-positive and -negative tumors may have different etiologies. In addition, levels of DDT or metabolites can be reported in either a lipid base or a wet base, thus affecting comparability across the studies.

In the only study that considered the presence of estrogenic receptors in patients with breast cancer (5), a highly significant difference was found between the levels of DDE in adipose tissue and serum in women with breast cancer (cases) and controls with benign breast disease (× DDE adipose tissue: 2732 ± 2749.9 µg/kg versus 765 ± 52.9 µg/kg, serum: 8.5 µg/l versus 3.5 µg/l). The groups of women compared were similar in terms of age, parity, and weight loss during the year before diagnosis. However, there was a greater prevalence of non-breastfeeding among cases (88.9% versus 76.5%). In spite of a small sample size (9 cases and 17 controls), the authors estimated an 8.9 times greater breast cancer risk in those women in whom DDE levels were above 1292 µg/kg in adipose tissue (5).

In contrast, the epidemiological study with the largest sample size, carried out by Krieger et al. (24), compared women with breast cancer and women without the disease among a cohort established between 1964 and 1971. The 150 cases and controls consisted of 50 whites, 50 blacks, and 50 Asian-Americans. Although approximately 50% of the patients with breast cancer showed higher DDE levels, the difference between these levels and those of the control group was not statistically significant. However, when Asian-Americans were removed from the analysis, a two-to-threefold excess of breast cancer was evident for blacks and whites with the highest levels of DDE in the sera. In addition, there was no information about breastfeeding or the proportion of estrogen-dependent breast tumors. Levels were not adjusted by total lipids, and no information of DDE levels in adipose tissue was provided, which is the best way to measure chronic DDT accumulation. This could have influenced the observed results (43).

A similarly designed study, controlled for breastfeeding, found that breast cancer risk was 3.68 times greater in women with DDE serum levels of 19.1 ng/ml as compared to women with DDE serum levels of 2.0 ng/ml (4). Another study reported that p,p'-DDE levels in adipose tissue of women with breast cancer are greater than corresponding levels in those with benign breast disease (3).

In a study that compared only nine samples of adipose breast tissue from breast cancer patients and five adipose tissue samples from women who died in accidents, greater concentrations of o,p'-DDT were found in the women with breast cancer (2). Finally, two more studies with the same type of limitations mentioned earlier did not report higher levels of DDT or its metabolites in women with breast cancer in comparison to women without the disease (26,27).

It is difficult to conclude whether exposure to DDT contributes to an increase in breast cancer. All of the recent studies have yielded evidence of a dose-response relationship, although these are subject to interpretation. There is an evident need for additional investigations that surmount the methodological limitations described here.

Conclusions

Many questions about DDT exposure and its potential impact on health are being researched at a number of levels. In terms of biomedical research, knowledge should be generated about the possible carcinogenic mechanisms of DDE in humans. Also, data are lacking about the levels of DDT accumulation in adipose tissue and serum, as well as rates of elimination of this compound in breast milk, in representative populations in developed and developing countries. High-risk populations have been identified, principally in urban and agricultural areas. In Mexico there is a need to develop systematic and representative data on DDT contamination of foods, which will probably explain the high levels found in human samples.

Identification and assessment of less toxic and less persistent alternatives for controlling malaria and educational, population-based interventions to reduce DDT exposure both in the work environment and among the general population are also needed. These interventions could be directed toward promoting use of protective gear by workers and health education for populations not occupationally exposed.

The continuing epidemiological study being carried out by the National Institute of Public Health of Mexico, which seeks to evaluate the association between DDE accumulation levels in serum and adipose tissue and breast cancer in Mexican women, is promising in terms of its methodological characteristics. These characteristics include sufficient statistical power (150 cases and 300 controls), a wide range of DDT exposure, control of confounding reproductive and dietary variables, assessment of DDT and DDE levels in lipid base, and information about estrogenic receptors in a subgroup of the cancer patients.

Efforts should continue to find alternatives to DDT while additional study results about its role in breast cancer are generated. Evidence on the long-term ecological consequences of DDT for wildlife is indisputable. The absence of clear-cut proof that DDT causes breast cancer should not be used as an excuse for further delays in phasing out this persistent, toxic organic pollutant. As many of the known causes of breast cancer cannot readily be altered, those causes that can be controlled become all the more important for public health.

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