RESEARCH COMMUNICATION

# Pesticides and Breast Cancer Risk: a Comparison between Developed and Developing Countries

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## Abstract

**Background: A large number of studies in Europe and US find little or no association between pesticides and breast cancer, adding to the increasingly dominant view that pesticides are not causally related to breast cancer. We investigated whether there are any differences in the levels of pesticides like dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCB), hexachlorobenzene (HCB) and hexachlorocyclohexane (HCH) and their effect for the development of breast cancer between developed and developing countries. Methods: A pubmed search for literature on pesticides, organochlorines, organophosphates and breast cancer risk from 1990 through 2009 was carried out. Results: The level of pesticide exposure is higher in developing world than the developed world. DDT is found to be positively associated with breast cancer risk. Results for other pesticides are equivocal. There is a dearth of studies in developing countries, which cannot be made up for generalizing the results from developed countries to the developing and third world. Conclusions: More studies are needed in the developing and third world countries, investigating the relation between pesticides and breast cancer risk as the sheer amount of pesticides being relentlessly used in these countries due to lack of proper government regulations.**

**Key Words:** Breast cancer - pesticide exposure - developing world - government regulations

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## Introduction

Breast cancer is the most common cancer among women in almost all developed countries. Incidence rates of breast cancer are approximately 90-130 per $10^5$ women in developed countries and those in developing countries are approximately ten to sixty per $10^5$ women (Curado et al., 2007). Only about half of breast cancer risk can be attributed to established risk factors such as nulliparity and late age at first child birth (McPheron et al., 2000). Certain dietary factors are also important for breast cancer and have been reviewed by WCRF (1997). Since the past decade there has been continued interest in the role of environmental contaminants that may play in unexplained breast cancer risk (Davis et al., 2001).

Organochlorine compounds degrade slowly, are lipid soluble, bioaccumulate in the food chain, and may be found in human adipose tissue, blood, and breast milk. In recent years, attention has been focused on the potential of some chemicals to act as "endocrine disruptors". According to the US Environment Protection Agency, an endocrine disruptor is a chemical that interferes with the function of the endocrine system by mimicking a hormone, blocking the effect of a hormone, or by stimulating or inhibiting the production or transport of hormones (US Environmental Protection Agency 2002). The World Health Organization reported that organochlorines have been found to be carcinogenic in animal models (WHO 1997; 1998). These characteristics, in combination with the temporal concordance of their widespread use with increasing incidence rates of breast cancer, stimulated the hypothesis that exposure to these compounds may contribute to the occurrence of breast cancer.

## Materials and Methods

A Pubmed search of literature was carried out covering studies conducted over a period of twenty years from (1990 to 2009) using keywords pesticides, organochlorines, organophosphates and "breast cancer". The full texts were obtained and information on study design, country, study period, sample size, study subjects, odds ratio (OR)/ relative risk (RR) and trend p–value were acquired if available. Only case-control and cohort studies conducted among women were considered for the present review. Reports from symposia, genetic studies, survival/ mortality studies of breast cancer patients and all studies not specifically associated with breast cancer and

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pesticides in women were excluded from the present review.

We investigated the levels of dichloro-diphenyltrichloroethane (DDT), and its metabolite dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCB), hexachlorobenzene (HCB) and hexachlorocyclohexane (HCH); also known as benzene hexachloride (BHC) and their risk for breast cancer between developed and developing countries. For this we used the World Bank classification of countries and separated the studies accordingly (www.worldbank.org/data/countryclass/classgroups.htm). The conversions used to express all values in the tables as parts per billion (ppb) are as follows.

1 ppb = ng/g = ng/kg x $10^{-3}$ = ng/mL= μg/g x $10^{3}$ = μg/L= μg/kg = mg/kg x $10^{3}$ = ppm x $10^{3}$

## Results

*Risk of DDT and DDE between developed and developing countries*

Six case-control studies from the developed countries reported positive associations with breast cancer risk (Falk et al., 1992; Djorjevic et al., 1994; Wolcott et al., 2001; Duell et al., 2000; Charlier et al., 2003; Charlier et al., 2004). Duell et al., (2000) examined the role of farming and pesticide exposure among 862 breast cancer cases and 790 controls in North Carolina. Among women who farmed, ORs were elevated for those who reported being present in fields during or shortly after pesticide application (OR=1.8; 95% CI: 1.1-2.8). Several studies found no association between pesticides and breast cancer risk (Table 1). Breast cancer mortality was inversely correlated with adipose DDE levels among both white and African American women in a study on 1968 adipose DDE levels of population samples from 22 U.S. states (Cocco et al., 2000).

Three cohort studies reported a positive association with breast cancer risk (Wolff et al., 1993; Hoyer et al., 2000; Bagga et al., 2000). Hoyer et al., (2000) found that high serum concentration of p,p'-DDT was associated with more than three fold significantly increased risk of breast cancer, and a dose-response relationship was apparent (Table 1).

Two case-control studies conducted in the developing world studies found a positive association between DDT and breast cancer risk (Olaya-Contreras et al., 1998; Pavuk et al., 2003) and two studies provided positive associations between DDE and breast cancer risk (Romieu et al., 2000; Pavuk et al., 2003). The mean levels for cases ranged from 3.30 ng/mL to 3.84 mg/g and for controls, 2.50 ng/mL to 2.52 mg/g. The ORs of these studies ranged from 1.95 to 5.26 (Table 2).

A study in 1992 reported that the average dietary intake of DDT in India was 48ng/person, which was higher than those observed in most developed countries (Kannan et al., 1992). Bhatnagar et al., (2004) found that the level of DDT in serum samples in Ahmedabad, India, were 32.61 ± 2.32 mg/L (mean ± SE) and level of pp'-DDE was 20.85 ± 1.84 mg/L. Higher levels of DDT and its metabolites in human blood samples from India were reported as compared to other parts of the world (Sharma and Bhatnagar 1996; Bhatnagar 2001). In Jordan DDT levels in human adipose tissue were 3.8 ppm (30-44 years) and 4.6 ppm (45-59 years) (Alawi et al., 1999).

There have been several studies, which investigated the relation between pesticides and breast cancer when menopausal status is taken into consideration (Lopez-Carrillo et al.,1997; Moysich et al., 1998; Helzlsouer et al., 1999; Aronson et al., 2000; Romieu et al., 2000). Aronson et al. (2000) found a non-significantly higher risk of breast cancer in pre-menopausal women with the highest levels of breast adipose tissue DDE (OR= 1.52; 95% CI: 0.7-3.33) than for post-menopausal women (OR=1.05; 95% CI: 0.5-3.33). Helzlsouer et al. (1999) found similar results (pre-menopausal women OR= 1.42, post-menopausal women OR= 0.50). Lopez-Carrillo et al. (1997) did not observe elevated breast cancer risk associated with serum DDE levels in pre-menopausal women (OR= 0.64; 95% CI: 0.22-1.90) or post-menopausal women (OR= 0.79; 95% CI: 0.27-2.28). In contrast, Romieu et al. (2000) reported elevated serum DDE levels and risk of breast cancer in post-menopausal women, but non-significant (OR= 5.26; 95% CI: 0.80-34.30).

*Risk of HCB between developed and developing countries*

Three studies from the developed countries found positive association (Liljegren et al., 1998; Charlier et al., 2003; Charlier et al., 2004) between HCB and breast cancer risk with ORs ranging from 5.0 to 7.1. A Swedish study by Liljegren et al., (1998) reported adjusted odds ratio of 7.1 (95% CI: 1.1-45.0) for HCB > 40 ng/g lipid for postmenopausal women with estrogen receptor positive (Table 1).

A cohort study by Dorgan et al. (1999) in a developed country reported that women in the upper three quartiles of HCB were at twice the risk of breast cancer compared to those in the lowest quartile. However, there was no evidence for a dose-response relationship, and the association was limited to women whose blood was collected close to the time of diagnosis.

Pavuk et al. (2003) reported higher serum levels of HCB among breast cancer cases than controls in Eastern Slovakia (developing country), but the association was insignificant (Pavuk et al., 2003). Bhatnagar et al. (2004) reported that mean (± SE) levels of HCB in India were 0.20 (± 0.02) mg/L in serum samples.

*Risk of PCB between developed and developing countries*

Two studies (Aschengrau et al., 1998; Aronson et al., 2000) found positive associations between PCB and breast cancer risk. Four studies analyzed more specific relations (Moysich et al., 1998; Liljegren et al., 1998; Aronson et al., 2000; Stellman et al., 2000). Liljegren et al., (1998) reported that the adjusted OR was 33 (95% CI: 1.8-58.8) for co-planar PCB #77 > 4.5 pg/g lipid among postmenopausal women with estrogen receptor positive tumors. A study conducted in Canada reported positive associations for PCB #105 and PCB #118 with ORs 3.17 and 2.31 respectively (Aronson et al., 2000) (Table 1). Moysich et al. (1998) reported an increased risk for women

**Table 1. Studies on Pesticides and Risk of Breast Cancer in Developed Countries**

| Reference | Country | Period | Cases/ Controls | Type of Control | Pesticides | Pesticide concentration (ppb), Cases | Controls | OR* (95% CI) | p-trend | Association |
|---|---|---|---|---|---|---|---|---|---|---|
| Gatto, 2007 | USA | | 355/ 327 | CC | PCB | 2.28 (2.48) | 2.09 (2.16) | | 0.27 | None |
| | | | | | DDE | 9.90 (12.8) | 8.13 (7.78) | | 0.29 | None |
| Ibarlueza, 2004 | Spain | 1996-98 | 198/ 260 | HC | DDE | 326.9 (2.78) | 307.3 (3.62) | 1.22 (0.68-2.21) | 0.40 | None |
| | | | | | TEXB-α | 44.6 (14.7)[1] | 31.79 (14.3) | 1.31 (0.74-2.31) | 0.30 | None |
| | | | | | TEXB-β | 76.48 (13.7) | 72.70 (14.4) | 0.99 (0.55-1.79) | 0.99 | None |
| Charlier, 2004 | Belgium | | 231/ 290 | CC | DDE | 3.46 (3.48) | 1.85 (2.09) | | < 0.0001 | |
| | | | | | HCB | 0.66 (0.25) | 0.2 (1.02) | | < 0.0001 | |
| | | | | | DDE | | | 2.21, 1.41-3.48 | | |
| | | | | | HCB | | | 4.99, 2.95-8.43 | | Positive |
| Charlier, 2003 | Belgium | 1999-2000 | 159/ 250 | CC | TotDDT | 3.94 (3.88) | 1.83 (1.98) | 5.36 (1.9-15.2) | < 0.0001 | Positive |
| | | | | | HCB | 0.79 (1.65) | 0.09 (0.41) | 8.68 (2.8 to 26.6) | 0.0005 | Positive |
| Gammon, 2002 | USA | 1996-97 | 646/ 429 | CC | DDE | 672.0 (2.76) | 645.7 (2.59) | 1.20 (0.76-1.90) | 0.52 | None |
| | | | | | DDT | 68.98 (1.83) | 69.32 (1.79) | 1.15 (0.74-1.79) | 0.89 | None |
| | | PCBs, SUM OF 118,153,138,180 | | | | 386.7 (1.69) | 391.7 (1.74) | 0.83 (0.54-1.29) | 0.7 | None |
| Wolcott, 2001 | Canada | 1995-1997 | 217/ 213 | HC | All PCBs | 102 (86-121) | 87 (81-92) | 1.7 (0.8-3.9) | | None |
| | | | | | DDE | 906 (682-1203) | 596 (530-670) | 2.4 (1,0-5.4) | 0.03 | Positive |
| | | | | | β-HCH | 56.2 (38-82) | 41.5 (36-47.6) | 1.4 (0.6-3.2) | | None |
| | | | | | DDT | 23.5 (17.3-32.0) | | 19.3 (17.3-21.6) | | |
| WOLFF, 2000a | USA | | 175/ 355 | BBD,CC | pp-DDE | 610 (302) | 660 (2730) | 0.93 (0.56-1.5) | 0.49 | None |
| | | | | | pp-DDT | 30 (2140) | 28 (2090) | 1.34 (0.82-2.2) | 0.24 | None |
| | | | | | HPCB | 600 (1880) | 620 (1860) | 0.78 (0.45-1.3) | 0.22 | None |
| | | | | | LPCB | 110 (2000) | 110 (1890) | 0.96 (0.53-1.7) | 0.75 | None |
| Zheng 2000a | USA | 1995-1997 | 475/ 502 | BBD | DDE | 460.1[b] | 456.2ppb[b] | 0.96, 0.67-1.36) | 0.60 | None |
| | | | | | PCB | 733.1[a] | 747.6ppb[a] | 0.95, 0.68-1.32) | | None |
| Demers, 2000 | Canada | 1994-1997 | 314/ 218 | HC | β-HCH | 21.1 (40.5) | 19.4 (37.1) | 0.80 (0.47-1.35 ) | 0.54 | None |
| | | | | | pp-DDE | 508.9 (491.1)[b] | 462.7 (447.7)[b] | 1.00 (0.60-1.67) | 0.39 | None |
| | | | | | pp-DDT | 12.7 (17.1) | 12.5 (11.8) | 0.81 (0.48-1.37) | 0.70 | None |
| | | | | | PCB 153 | 58.7 (27.5) | 53.3 (20.9) | 1.28 (0.74-2.19) | 0.85 | None |
| Aronson, 2000 | Canada | 1990's | 217/ 213 | BBD | PCB 99 | 19.5 (18-21.2) | 17.7 (16-19.3) | 1.92 (0.95-3.86) | | None |
| | | | | | PCB 105 | 7.1 (6.4-7.8) | 6.3 (5.7-7.0) | 3.17(1.51-6.68) | | Positive |
| | | | | | PCB 118 | 30.3 (27.7-32) | 24.7 (22.4-27.3) | 2.31(1.11-4.78) | | Positive |
| | | | | | PCB 138 | 73.8 (68.9-79) | 66.8 (62.1-72) | 1.56 (0.80-3.06) | None | |
| | | | | | PCB 153 | 105 (98-112) | 98.3 (91.8-105) | 1.04 (0.51-2.11) | | None |
| | | | | | PCB 156 | 18.6 (17-19.9) | 17.2 (16.0-18.5) | 1.35(0.68-2.69) | | None |
| | | | | | PCB 170 | 34.3 (32-36.6) | 32.0 (29.7-34.4) | 1.15 (0.60-2.22) | | None |
| | | | | | PCB 180 | 71.9 (67-76.5) | 65.7 (61.5-70.2) | 1.27 (0.66-2.46) | None | |
| | | | | | PCB 183 | 10.3 (9.6-11.1) | 9.5 (8.8-10.2) | 1.27 (0.66-2.45) | | None |
| | | | | | PCB 187 | 25.7 (24-27.7) | 24.2 (22.6-26.0) | 1.26 (0.66-2.40) | None | |
| | | | | | pp-DDE | 693 (615-780) | 596 (530-670) | 1.62 (0.84-3.11p | | None |
| | | | | | pp-DDT | 22.0 (19.6-25) | 19.3 (17.3-22) | 1.18 (0.61-2.29) | None | |
| | | | | | HCB | 32.0 (29-35) | 30.1 (28-33) | 1.15 (0.57-2.34) | None | |
| | | | | | β-HCH | 43.1 (38-49) | 41.5 (36-48) | 0.69 (0.34-1.40) | | None |
| Millikan, 2000 | USA, AM | | 292/ 270 | CC | DDE | 9.96 (11.1) | 8.82 (8.9) | | 0.45 | None |
| | | | | | All PCBs | 2.79 (2.2) | 2.56 (2.3) | | 0.21 | None |
| | USA,WH | | 456/ 389 | CC | DDE | 3.52 (4.4) | 3.94 (5.8) | | 0.09 | None |
| Zheng, 1999 | USA | 1994-1997 | 304/ 186 | BBD | DDE | 736.5 ppb | 784.1 ppb | 0.9, 0.5-1.5 p | 0.46 | None |
| | | | | | DDT | 51.8ppb | 55.6ppb | 0.8, 0.5-1.5 p | | None |
| Zheng, 1999a) | USA | 1994-1997 | 304/ 186 | BBD | HCB | 21.0ppb (17.7) | 19.1ppb (15.0) | 0.9, 0.5-1.6 | 0.37 | None |
| Liljegren, 1998 | Sweden | 1993-1995 | 43/ 35 | BBD | DDE | 767 | 1026ng/g | 0.4 (0.1-1.2) | | None |
| Moysich, 1998 | USA | 1986-1991 | 154/ 192 | CC | DDE | 11.5 (10.49)[b] | 10.77 (10.64) ng/g | b1.34( 0.71-2.55) | p0.25 | None |
| Guttes, 1998 | Germany | 1993-1994 | 45/ 20 | BBD | β-HCH | 79 | 93 | | 0.36 | |
| | | | | | HCB | 309 | 261 | | 0.40 | |
| | | | | | pp-DDE | 805 | 496 | | 0.02 | Positive |
| | | | | | pp-DDT | 30 | 28 | | 0.71 | |
| | | | | | PCB 118 | 81 | 65 | | 0.04 | |
| Hunter, 1997 | USA | 1989-1990 | 236/ 236 | CC | DDE | 6.01 (4.56) | 6.97 (5.99) | 0.72, 0.37-1.40 | 0.47 | None |
| | | | 230/230 | | PCBs | 5.08 (2.51) | 5.16 (2.26) | 0.66, 0.32-1.37 | 0.72 | None |
| Van't Veer, 1997 | Europe | 1991-92 | 265/ 341 | HC, CC | DDE | 1350 (1150-1580) | 1510 (1310-1730) | 0.73 (0.44-1.21) | 0.16 | None |
| Djordjevic, 1994 | USA | 1990's | 05/05/09 | HC | HCB | 16.1 (6.8) | 10.0 (6.9) | | | |
| | | | | | β-HCH | 12.5 (8.5) | 10.1 (9.5) | | | |
| | | | | | pp-DDE | 379 (286) | 160 (149)ppb | | | Positive |
| | | | | | pp-DDT | 10.7 (10.4) | 4.1 (4.5) | | | |
| | | | | | PCB | 223 (145) | 124 (65.7)ppb | | | |
| Dewailly, 1994 | Canada | 1991-1992 | 9/17 | BBD | DDE | 765.3 (526.9) | 608.9 (338.9) | | | |
| | | | | | HCB | 33.4 (13.2) | 31.1 (11.5) | | | |
| | | | | | α-HCH | 39.7 (23.4) | 34.7 (15.7) | | | |
| | | | | | All PCBs | 397 (161.5) | 331.5 (74.7) | | | |
| Falk, 1992 | USA | 1987 | 20/20 | BBD | HCB | 23 (8) | 20 (10) | | | |
| | | | | | DDE | 1877 (1283) | 1174 (630) | | | |
| | | | | | DDT | 179 (135) | 14 (49) | | | |
| | | | 41/33 | | PCBs | 1669 (894) | 1105 (424) | | | |
| Mussalo-Rauhamaa, 1990 | Finland | 1985-1986 | 44/ 33 | PMW | pp-DDT | 70 (90) | 60 (70) | | | |
| | | | | | pp-DDD | 30 (50) | 80 (130) | | | |
| | | | | | pp-DDE | 96 (63) | 980.0 (890.0) | | | None |
| | | | | | PCB | 1050 (630) | 1300 (750) | | | |
| | | | | | HCB | 140 (80) | 110 (50) | | | |
| | | | | | β-HCH | 130 (60) | 80 (30) | 10.5 (2.00-55.3) | | Positive |

**Table 1 (continued). Studies on Pesticides and Risk of Breast Cancer in Developed Countries**

| Reference | Country | Period | Cases/ Controls | Type of Control | Pesticides | Pesticide concentration (ppb), Cases | Controls | OR* (95% CI) | p-trend | Association |
|---|---|---|---|---|---|---|---|---|---|---|
| Iwasaki, 2008 | Japan | 1990- 2002 | 139/ 278 | CC | p,p' DDT | Median (IQR)1.10 (0.64- 2.04) | | 1.12 (0.72, 1.83) | 0.19 | None |
| | | | | | p,p' DDE | 7.04 (4.36, 10.42) | | 6.08 (3.72- 9.70) | 0.42 | None |
| | | | | | HCB | 0.29 (0.15, 0.51) | | 0.29 (0.18- 0.51) | 0.73 | None |
| | | | | | β-HCH | 0.51 (0.22- 1.10) | 0.50 (Not Detailed, 0.94) | | 0.77 | None |
| Laden, 2001 | USA | 1997-Follow | 381/ 381 | DDE | 768 | 817 | | 0.82, 0.49-1.37e | 0.15 | None |
| | | | | | All PCBs | 544 | 543 | 0.84, 0.47-1.52e | 0.56 | None |
| | | | | | PCB | 327.7 (306.3) | 332.9 (279.6) | 0.76 (0.38-1.51) | 0.60 | None |
| Wolff, 2000 | USA | 1987-1992 | 110/213 | | DDE | 977(2.46)[b] | 1097 (2.29)[b] | 1.30, 0.51-3.35 p | 0.99 | None |
| | | | | | PCBs | 683 (1.64) | 663 (1.62) | 2.02, 0.76-5.37 | 0.23 | None |
| Bagga, 2000 | USA | 1995-1996 | 73/73 | BBD | DDT | 231.4 (130.1- 332.8) | 197.6 (96.3- 298.9) | | 0.22 | None |
| | | | | | DDE | 693.6 (570-817) | 642.1 (382.7- 901.4) | | < 0.01 | Positive |
| | | | | | DDD | 9.2 (2.4- 16.0) | 21.7 (1.5- 41.9) | | 0.8 | None |
| | | | | DDT+ DDE+ DDD | | 934.3 (742-1126) | 861.4 (569-1153) | | 0.02 | Positive |
| Ward, 2000 | USA | 1973-1991 | | | p,p' DDE | 1230 | 1260 | | 0.84 | None |
| | | | | | p,p' DDT | 119.5 | 137.7 | | 0.27 | None |
| | | | | | All PCBs | 776.1 | 806.6 | 0.47 | None | |
| Zheng, 2000 | USA | 1994- 1997 | 304/ 186 | | PCB | 478.6 (454-504) | 494 (462-528) | 0.7 (0.4, 1.1) | 0.46 | None |
| Dorgan, 1999 | USA | 1977-1987 | 105/ 208 | | DDE | NA | 16.3 | 0.8, 0.4-1.5p | 0.77 | None |
| Helzlsouer, 1999 | USA | 1989 | 105/105 | | DDE | 1311.9 (1036)[b] | 1586.3 (1557)[b] | 0.58 (0.29-1.17) | 0.15 | None |
| Krieger 1994 | USA | 1964-1971 | 150/ 150 | | DDE | 43.3 (25.9) | 43.1 (23.7) | 1.33, 0.68-2.2 p | 0.43 | None |
| | | | | | PCB | 4.4 (1.8) | 4.8 (2.5) | 0.59 | 0.90 | |
| Wolff, 1993 | USA | 1985-1991 | 58/ 171 | | DDE | 11.0 (9.1) | 7.7 (6.8) | 3.68, 1.01-13.50p | 0.04 | Positive |
| | | | | | PCB | 8.0 (4.1) | 6.7 (2.9) | 4.35 | 0.16 | |

Std.dev- Standard deviation, *-All OR's, except where otherwise noted; PMW- post-menopausal women; BBD-Benign Breast Disease Controls; HC- Hospital Controls (Hospitalized for non-breast disease and non-cancer related conditions); CC- Community or population controls; TEXB-alpha- Total Effective Xenoestrogen Burden mg/g- microg/g; HPCB, LPCB- higher and lower chlorinated biphenyls; a- geometric mean serum levels; b- serum DDE adjusted for lipid concentration; c- age and lipid-adjusted geometric mean adipose-tissue levels; d- HR estimates for the highest compared to lowest exposure categories; e- Multivariate relative risk of breast cancer for women in the highest quintile of exposure as compared with women in the lowest quintile; f- Plasma DDE adjusted for cholesterol; g- Lipid adjusted geometric mean ; p OR adjusted for potential confounding factors, comparison between highest and lowest levels (i.e. tertile, quartile, or quintile); Ref. No.- Reference number ; Std.dev- Standard deviation; *-All OR's, except where otherwise noted; PMW- post-menopausal women; OP-Organophosphates; DDT-Total amount of DDT isomers; SIR- Standardized Incidence Ratio; Eeq/g- Picomolar of Estradiol equivalent of lipid; Total DDT -- DDT+DDE isomers; AM: African American, WH: whites

with detectable levels of less chlorinated PCBs (OR=1.66; 95% CI: 1.07-2.88). Among parous women who had never lactated, increased risk was observed for total PCBs (OR=2.87; 95% CI: 1.01-7.29), moderately chlorinated PCBs (OR=3.57; 95% CI: 1.10-8.60), and greater numbers of detected PCB congeners (OR=3.31; 95% CI: 1.04-11.3) in serum concentrations. Stellman et al., (2000) found that PCB congener 183 (2, 2', 3, 4, 4', 5', 6-heptachloro-biphenyl) was significantly associated with breast cancer risk (OR=2.0; 95% CI: 1.2-3.4).

None of the cohort studies from developed countries found any association between PCB and breast cancer risk (Hunter et al., 1997; Helzlsouer et al., 1999; Hoyer et al., 2000; Wolff et al., 2000; Laden et al., 2001) (Table 1). A study conducted by Pavuk et al. (2003), reported no association between PCBs and risk of breast cancer in eastern Slovakia (developing country). The median levels of total PCBs were similar in cases (2586 ng/g of lipid) and controls (2682 ng/g of lipid) (Table 2).

*Risk for HCH between developing and developed countries*

Mussalo-Rauhamaa et al. (1990) conducted a study in Finland and reported that residues of β- HCH were found more frequently in breast cancer patients. After adjusted for age and parity, β-HCH was found as a significant risk factor for breast cancer. Using a cutoff point for the residue level of β-HCH in breast adipose tissue of more than 0.1 mg/kg fat the OR was 10.51 (95% CI: 2.00-55.26).

Studies which assessed the storage of HCH-derived material in adipose tissue of the general population, reported that in Jordan (Alawi et al., 1999) it was reported to be 1.9 ppm respectively. An Egyptian study (Soliman et al., 2003) found no association between β-HCH and breast cancer risk. In India the average dietary intake of HCH was reported to be 115 ng/person, which was higher than those observed in most developed countries (Kannan et al., 1992). Joshi et al., (1996) conducted a study in India on the effect of HCH exposure in spray men (n= 260) and general population. The mean residue level of α, β, and γ isomers and the total β, β, and β isomers in spray men were twice those of the general population. A significant association ($p< 0.05$) was observed between their length of exposure and the levels of HCH isomers in the blood of spray men. In another study by Bhatnagar et al., (2004), the mean levels (± SE) of α, β, and γ-HCH in serum samples in India were found to be 4.49 (±0.73), 35.06 (±3.50), and 1.69 (±0.15), respectively. The study also reported HCH level as 41.23 (±3.77). In a pilot study in Kerala, India, Rusieki et al. (2005) reported that the mean concentrations of β-HCH among the breast cancer cases were 14.45 ppb and 2876.15 ppb for lipid unadjusted and adjusted respectively. Also the Indian Council of Medical Research (ICMR, 2001) reported levels of β-HCH in human fat samples to range from 1,060 ppb to 16,850 ppb (μ=3,490 ppb) (ICMR 2001; 2003). It is reported that the average Indian dietary intake of HCH exceeds that of the US and UK by a hundred fold (PAN, 1993) (Table 1).

## Discussion

In the present review, it is observed that the data are

**Table 2. Studies on Pesticides and Risk of Breast Cancer in Developed Countries**

| Reference | Country | Period | Cases/ Controls | Type of Control | Pesticides | Pesticide concentration (ppb), Cases | Controls | OR* (95% CI) | p-trend | Association |
|---|---|---|---|---|---|---|---|---|---|---|
| Waliszewski, 2005 | Mexico | | 127/ 127 | | HCB | 0.099 (0.091) | 0.045 (0.032) | 2.01 (1.94- 2.07) | 0.05 | Positive |
| | | | | | β-HCH | 0.265 (0.210) | 0.163 (0.119) | 1.58 (1.54- 1.62) | 0.05 | Positive |
| | | | | | p,p'-DDE | 0.980 (0.627) | 0.782 (0.282) | 1.17 (1.11- 1.23) | 0.05 | Positive |
| | | | | | op DDT | 0.094 (0.098) | 0.035 (0.027) | 2.27 (2.18-2.37) | 0.05 | Positive |
| | | | | | p,p'-DDT | 0.351 (0.291) | 0.296 (0.230) | 1.33 (1.25- 1.41) | | |
| Pavuk, 2003 | Slovakia | 1998-1999 | 24/88 | CC | All PCBs | 2586ng/g | 2682ng/g | 0.42, 0.10-1.82 | 0.31 | None |
| Soliman, 2003 | Egypt | | 69/53 | HC | DDE | 12.7 (20.3)ppb | 16.6 (30.1) | | 0.60 | |
| | | | | | β-HCH | 2.1(3.8) | 2.1( 3.9) | | 0.71 | |
| | | | | | Total DDT | 13.4 (21.8) | 17.3 (31.0) | | | |
| Mathur, 2002 | India | | 135/ 50 | CC | β-HCH | 466 (45) | 80 (30) | | <0.05 | Positive |
| | | | | | DDE | 862 (154) | 47 (18) | | <0.05 | Positive |
| | | | | | DDD | 569 (73) | 249 (59) | | <0.05 | Positive |
| | | | | | DDT | 2254 (405) | 1034 (221) | | <0.05 | Positive |
| | | | | | All | 7468 (771) | 1857 (311) | | <0.05 | Positive |
| Romieu, 2000 | Mexico | 1990-1995 | 120/126 | CC | DDE | 3840 (5980)[b] | 2520 (1970)[b] | 3.81, 1.14-12.80p | 0.02 | Positive |
| Mendonca, 1999 | Brazil | 1995-1996 | 151/306 | CC | DDE | 5.1 | 4.8 | 0.83, 0.40-1.6 p | | None |
| Olaya-Contreras, 1998 | Mexico | 1995-1996 | 153/ 153 | HC | DDE | 3.30 (4.12) | 2.50 (3.60) | 1.95, 1.10-3.52 | 0.03 | Positive |
| Schechter, 1997 | North Vietnam | 1994 | 20/20 | | BBDDDE | 12.2 (2.41) | 16.7 (4.14) | 1.14, 0.23-5.68 p | | None |
| | | | | | DDT | 2.33 (0.46) | 2.37 (0.58) | 1.21 (0.15-9.65) | | None |
| | | | | | All DDT | 15.9 (3.05) | 20.95 (5.14) | 1.06 (0.18-5.67) | | None |
| Lopez-Carrillo 1997 | Mexico | 1994-1996 | 141/ 141 | | HCDDE | 562.5 (676.2)[b] | 505.5 (567.2)[b] | 0.76, 0.41-1.42 p | 0.44 | None |
| | | | | | p,p'-DDT | 61.45 (139.77) | 84.53 (180.95) | | 0.23 | |

Std.dev- Standard deviation; *-All OR's, except where otherwise noted; BBD-Benign Breast Disease Controls; HC- Hospital Controls (Hospitalized for non-breast disease and non-cancer related conditions); CC- Community or population controls; [b]Serum DDE adjusted for lipid concentration ; p - OR adjusted for potential confounding factors, comparison between highest and lowest levels (i.e. tertile, quartile, or quintile)
# All case control studies

strongest for DDT and its metabolite DDE. A total of six case-control (Falk et al., 1992; Djorjevic et al., 1994; Wolcott et al., 2001; Duell et al., 2000; Charlier et al., 2003; Charlier et al., 2004) and one cohort study (Wolff et al., 1993) in developed countries and two case-control studies (Olaya-Contreras et al., 1998; Romieu et al., 2000) in developing countries found a positive association between DDT and breast cancer. Among the studies, which investigated the relation between pesticides and breast cancer according to menopausal status, two studies found a higher risk of breast cancer in pre-menopausal women with the highest levels of breast adipose tissue DDE (Aronson et al.; 2000 and Helzlsouer et al. 1999) and one study reported a significant association between elevated serum DDE levels and risk of breast cancer in post-menopausal women (Romieu et al., 2000). Only two studies reported positive association for HCB (Charlier et al., 2003; Charlier et al., 2004) and two for α-HCH (Mussalo-Rauhamaa et al., 1990; Djordjevic et al., 1994) and no association between PCBs and cancer in either in the developing or developed world was reported.

There are huge differences in amount of exposures, type of pesticides used and mode of exposure between the developing and developed countries. There is a dearth of studies to assess the risk of breast cancer in developing countries, which cannot be made up for by generalizing the results from developed countries to the developing and third world.

As case-control and cohort studies are observational epidemiological studies, the extraneous factors could not be manipulated. Although information of such extraneous factors is collected and quantitatively adjusted for when they are known to be present, findings from observational epidemiological studies are generally less conclusive than those from experimental studies because of the less strict control of extraneous factors. The main contrast between case-control and cohort studies lies in their differing potential for bias and in the resources required. The pesticide concentration after the treatment may change though its concentration from various sources may not be the same prior to breast cancer diagnosis and after diagnosis. However cohort studies are normally considered free of the most common biases that potentially affect case-control studies such as selection and information bias. So the results from the cohort studies can be considered more authentic.

There have been discussions among researchers about the relative merits and demerits of using serum vs adipose tissue levels to determine body burden of organochlorines. There have been some case-control studies in the developed world, which analyzed adipose tissue levels (Mussalo-Rauhamaa et al., 1990; Falk et al., 1992; Djordjevic et al., 1994; Dewailly et al., 1994; van't Veer et al., 1997; Guttes et al., 1998; Aschengrau et al., 1998; Zheng et al., 1999; Aronson et al., 2000; Woolcott et al., 2001; Ibarluzea et al., 2004) and some which analyzed serum levels (Wolff et al., 2000; Zheng et al., 2000; Demers et al., 2000; Gammon et al., 2002; Charlier et al., 2003). There is evidence that blood levels of pesticides are a good approximation of the levels stored in adipose tissue (ICMR, 2001; Rusiecki et al., 2005).

There are biologically plausible reasons to suspect that the use of these pesticides may be linked to human health. Many organochlorines, including DDE and some PCBs, are considered endocrine disruptors because they are weakly estrogenic or antiestrogenic in experimental assays (Kelce et al., 1995; Soto et al., 1995). Animal and laboratory evidence have demonstrated carcinogenic activity of 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. Animal studies of DDT have shown a number of positive results. Mice are relatively susceptible; mouse studies of DDT and DDE have yielded tumors of the liver, lung, thyroid and lymphomas. Results from other species have been more equivocal (Calle et al., 2002). Still, chemicals known to cause cancer in humans were in many cases first discovered to be carcinogenic in animals (Wolff et al., 1996).

The absolute levels of pesticides found in different parts of the world vary widely, as can be inferred from the values given under each pesticide. There are also differences in types, usage and time of exposure. Due to economic conditions and disparity in developed countries, industrialized countries use more of chemicals like PCBs while developing countries use more of HCH, DDT and its derivatives. One important reason why most North American and European studies have failed to find an association between blood or adipose tissue levels of DDE and breast cancer risk may be that since the 1970s the major route of exposure to DDT has not been through the more estrogenic o,p'-DDT found in technical DDT that was sprayed as an insecticide but through the far less estrogenic p, p'-DDE via the diet. Another factor is that although pesticide use varies widely, we do not always see a proportionate rise in the tissue levels of pesticides. India uses a hundred fold more of pesticides like HCH (PAN, 1993), but we do not, fortunately, find a proportionate increase of HCH in tissue samples, or cancers. There seems to be some resilience at work here. This is consistent with the finding that Asian women in their countries of origin, and even when living in countries like the US, have lower rates of breast cancer, perhaps due to nutritional or genetic factors (Allen et al., 1997). Joshi and colleagues noticed this sort of resilience when studying spraymen in Allahabad, India (Joshi et al., 1996). Another major drawback of the studies reviewed here is that very few studies have taken into consideration the fact that there can be a synergistic effect of pesticides. Payne et al (2001) assessed the combined effects of 1-(o-chlorophenyl)-1-(p-chlorophenyl)-2,2,2-trichloroethane (o,p'-DDT), 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene (p,p'-DDE), _-HCH, and 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane (p,p'-DDT) on the induction of cell proliferation in MCF-7 cells and demonstrated that there were combination effects even when each mixture component was present at levels at or below its individual no-observed-effect-concentration. Studies provided evidence that the synergistic activity of many common pesticides may be significant (Soto et al., 1994; Arnold et al., 1996). For example, one study reported that a mixture of endosulfan and dieldrin was 160 to 1600 times more potent than each chemical acting alone (Arnold et al., 1996). Since these compounds occur as mixtures in the environment, their partnership potencies require special consideration.

In conclusion, there is a need for more studies, especially in the developing and poor countries, investigating the relation between pesticides and breast cancer before conclusions can be drawn. The most important reason for is the sheer amount of pesticides being relentlessly used in these countries due to lack of proper government regulations. The economic impact of pesticides in non-target species including humans has been estimated at approximately US $8 billion annually in developing countries (Environews Forum,1998). ICMR stresses on this, stating: "Our approach on use of pesticides should be pragmatic… all activities on pesticides should be based on scientific judgments and not commercial considerations" (ICMR, 2001).

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