

Endocrine-disrupting pesticides and selected hormonally dependent cancers

by Kenneth R Muir, PhD¹

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Pesticides and other endocrine disrupters represent a credible “new” risk factor for hormonally dependent cancers. To date, most work has centered on breast cancer, and most studies have not shown increased risks. Additional epidemiologic investigations are warranted, but they would benefit from a better understanding of the mechanisms, dose, and co-factors involved.

Key terms breast cancer; dichlorodiphenyl-trichloroethane; hormone mimics; prostate cancer; xenoestrogens; 1,1-dichloro-2,2-tris(p-chlorophenyl).

Pesticides are among the most regulated of all manufactured chemicals. Such regulation and associated testing and licensing reflect their widespread use and role. The principle purpose of this group of chemicals is to damage chosen biological systems in terms of pests and parasites of crops and other produce. Importantly, equivalent toxicity to human systems must occur at higher doses than those used for pest control if such human exposures occur.

Concerns have been often raised as to the possible mutagenicity and carcinogenicity of pesticides. As a result, several specific carcinogenicity assessments have been performed and are required as part of licensing procedures. Most of this testing is based on a proposed mechanism of direct DNA (deoxyribonucleic acid) damage. More recently, however, concerns have grown that there may be other effects of pesticides on human systems, including processes that affect cancer risk, in particular, that these chemicals act through an indirect “hormonal” mechanism—so-called endocrine disruption (1, 2).

Pesticides are not the only group of compounds being investigated for such a role (3–5). Observed increases in breast and prostate cancer rates among humans have fueled the debate for such a proposed role and that on whether such increases might be in part accounted for by the increasingly widespread use of pesticides and other chemicals (6).

Breast cancer, pesticides and endocrine disrupters

Epidemiology. To date the only firmly established risk factors for breast cancer are age, body mass index (BMI), and markers of estrogen and its analogues. Both endogenous and exogenous estrogen can influence risk, particularly that for postmenopausal women.

Several theories have been developed that propose mechanisms for interactions between endogenous and exogenous hormones (7, 8).

Of particular interest over the past 25 years has been the emergence of the idea of endocrine disrupters. These comprise the weak estrogen mimics in certain dietary components that may block the effect of “stronger” natural estrogens and thus offer protection from the chemicals, including selected pesticides, that have powerful estrogenic activity in their own right, either alone or in combination (9).

A large number of studies has specifically investigated the relationship between breast cancer and the organochlorine pesticides, particularly DDT (dichlorodiphenyl-trichloroethane) and its metabolites, because of the biological credibility of the hypothesis and the suggestion that exposure to these chemicals (xenoestrogens) is sufficient to exert an estrogenic-mimicking property in breast tissue, which is sensitive to estrogens (10–12). To date the picture is unclear, and several

¹ Division of Epidemiology and Public Health, School of Community Health Sciences, University Hospital, Queens Medical Centre, Nottingham, United Kingdom.

Correspondence to: Professor KR Muir, Division of Epidemiology and Public Health, School of Community Health Sciences, University Hospital, Queens Medical Centre, Nottingham, NG7 2UH, United Kingdom.
[E-mail: kenneth.muir@nottingham.ac.uk]

questions remain, particularly concerning mechanisms, dose, and other modifying factors (13–15).

While most studies provide little evidence of association, several specific points remain, in particular, the possibility of an effect on populations likely to have either higher exposure or co-factors present, based on the following observations: (i) the strongest positive associations have been observed in studies that collected biological samples close to the time of the ban of DDT in the United States and Europe when environmental exposure was high (16–18); (ii) in a subgroup analysis stratified by menopausal status, a positive relationship with breast cancer was found to be limited to postmenopausal women and serum levels of DDE [1,1-dichloro-2,2-tris(p-chlorophenyl)] were correlated with age (13, 19) and it is therefore possible that the association found for postmenopausal women was due to high and long-duration exposure to the compounds; (iii) in stratified analyses by ethnicity, the risk effect of DDE on breast cancer was found for black women and these women had high DDE concentrations (20, 21); (iv) lactation was found to be the means of excreting the compound, through the mobilization of DDT in fat to breast milk (22, 23) and women who have not breast fed are suggested to be at increased risk (19, 21); and (v) while most of the studies examining the relationship were conducted in the United States and Europe, where DDT has been banned for over 20 years, did not observe an increased risk, some studies from developing countries, where DDT is still used, together with a lower level of protection against exposure to the chemical, have demonstrated a more positive relationship (24, 25). These observations may account for the lack of association in many studies in which levels of exposure were low.

Mechanisms. Hormones and pesticides that have hormonal properties are known to stimulate the growth of cells, including mutated cells. Speeding up the rate of cell division increases the risk of permanent mutations being transferred to daughter cells. OpDDT and beta-hexachlorehexane (B-HCH) stimulate breast-cancer cells to proliferate by acting on estrogen receptors. Indeed, B-HCH is nearly as effective as 17 β -estradiol in stimulating the growth of MCF-7 cell tumors *in vivo*. It is also antagonized by anti-estrogens. Although most xenoestrogens appear to be at least 1000 times less potent than estradiol, it is thought that the bioaccumulation of lipophilic xenoestrogens could lead to levels sufficient to induce estrogenic effects. An alternative hypothesis suggests that these compounds behave like “genotoxic estrogens” through direct DNA damage and the proliferation of aberrant DNA via an estrogen receptor. (2)

Dose. Assessing dose in epidemiologic studies is difficult. A distinction must be made between the external

dose (amount of chemical agent in environmental contact with the organism as determined by personal or area monitoring) and the internal dose (total amount of a chemical agent absorbed by the organism over a period of time). Many factors influence the conversion of external contact to internal dose. Such assessments of dose have particularly limited epidemiologic investigations of endocrine disrupters, as information is needed on *source* (occupational, dietary, environmental), *route* (dermal, ingestion, inhalation), and *modifying host factors* (protective clothing, lipid levels, genetic profile).

Many epidemiologic studies employ interviewer-administered questionnaires based on exposure assessment. This practice is generally suitable for exposures to which the respondent is aware. Potential bias in assessment is a major concern quite apart from the possibility of the respondent being unaware of exposures. Objective measures of exposure, such as biomarkers in biological samples, potentially avoid these issues but raise a different series of questions. In particular, the choice and sensitivity of the assays needs to be understood and appreciated.

Several studies measuring DDE, the main persistent metabolite of DDT, from biological samples, have been carried out to investigate this hypothesis. These studies can be classified into the following three groups according to the types of study and biological samples taken: (i) case-control studies with fat tissue samples, (ii) case-control studies with serum samples, and (iii) nested case-control studies within cohorts.

The majority of the case-control studies using fat samples for the measurement of DDE seem to yield an inverse association with breast cancer. The first case-control study using fat samples for the measurements was reported in 1976, but no association was found (26). Subsequently, over a dozen studies have been published, and figure 1 (27–30) includes the odds ratios for selected studies that provided data to assess the highest versus the lowest exposure comparisons. It has been suggested that investigations assessing the DDE in fat tissue are more temporally informative than those using serum samples because levels of the chemicals in fat tissue can indicate the long-term exposure of people. However, there are certain limitations to all previous studies. First, the reports, particularly those before 1997, had a low number of cases, namely, less than 50. Second, persons with benign breast tumors, which potentially have common risk factors, were used as controls in some studies. Third, many studies failed to control for important factors, such as lactation history, socioeconomic status, and body mass index. Furthermore, these studies, except the earliest study, were conducted in the United States and Europe. Evidence from these studies does not support an association between breast cancer and DDE.

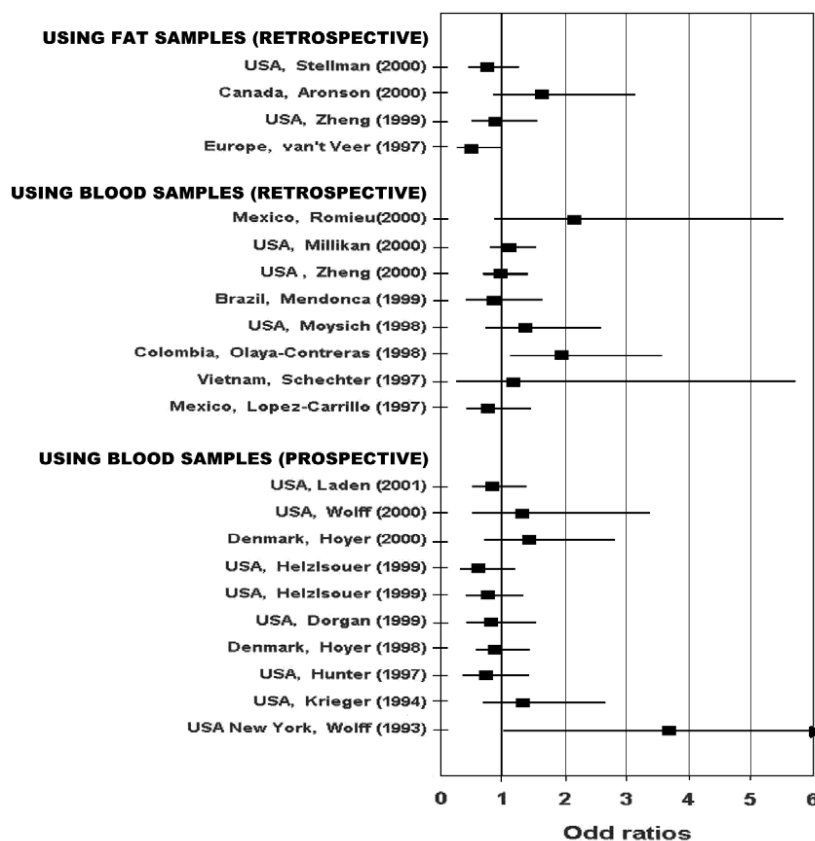


Figure 1. Plot of the odd ratios of the associations between breast cancer and DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)].

Case-control studies using blood samples for measuring DDT and its metabolites were also undertaken in some countries, including the United States (21, 18, 31), Mexico (32, 25), Colombia (24), Vietnam (33), and Brazil (34). The studies allowing a highest versus lowest comparison are also presented in figure 1.

The third group of studies measured serum DDE levels in blood samples that were collected in existing cohort investigations. These studies had advantages in that blood samples were taken before the development of the cancer; therefore, it is unlikely that having breast cancer could have affected the levels of the compound and selection bias should be reduced. Among the 10 original studies, the first study published in 1993, by Wolff and his colleagues, found that levels of DDE were significantly related to breast cancer risk with a significant trend (OR 3.68, 95% CI 1.01–13.50) despite the relatively small number of women with breast cancer (58 cases) (17). Among the nine later studies, a study from Denmark (35), using a repeated measure of the chemicals, observed some suggestion of a positive association. The rest of the studies were conducted in the United States and did not observe any significant associations (13, 16, 20, 36–39). There was an attempt to increase the power of the study by pooling individual data from five nested case-control studies conducted in the United States to derive the overall estimate of the

association (40). This pooled analysis comprising 1400 cases and 1642 controls did not find a relationship with quintiles of the serum concentration of DDE. The odds ratio from this pooled analysis, together with summary results from the aforementioned studies, are also shown in figure 1.

Thus only a small number of case-control studies measuring DDE in blood samples out of a larger group of studies has revealed an increased risk of breast cancer for the highest level of DDE. Of particular note is that five of eight studies that collected blood samples from developing countries, such as Mexico, Brazil, Colombia, and Vietnam, showed elevated risk. These studies had higher concentration levels of DDE and also a much greater gradient between low and high exposure categories than those from the United States. For selected studies, table 1 shows the quantitative estimates from studies in different settings. The combined odd ratios for each group of studies are small, however, and not statistically significant, and the results should therefore be interpreted with caution.

In summary, the nested case-control study and case-control study using fat samples to measure DDE levels gave odd ratios of less than one, while a case-control study measuring the chemicals in blood samples yielded odd ratios of more than one, particularly in areas of higher exposure. In conclusion, it is suggested that

Table 1. Case-control study with blood samples. [OR = odds ratio, 95% CI = 95% confidence interval, DDE = 1,1-dichloro-2,2-tris(p-chlorophenyl)]

Author	Year of study	Population	Cases	Controls	OR ^a	95% CI ^{a,b}	DDE levels in controls		Ratio of DDE ^a
							Mean	SD	
Schechter et al, 1997 (33)	1994	Vietnam	21	21	1.14	0.23–5.68	16.67 ng/ml	4.14	3.68
Lopez-Carrillo et al, 1997 (32)	1994–1996	Mexico	141	141	0.76	0.41–1.42	505.46 ng/g	567.22	2.10
Moysich et al, 1998 (17)	1986–1991	New York (United States)	154	192	1.34	0.71–2.55	10.77 ng/g	10.64	2.17
Olaya-Contreras et al, 1998 (24)	1995–1996	Bogota (Colombia)	153	153	-	1.10–3.52 ^c	2.50 ng/ml	3.60	14.07
Mendonca et al, 1999 (34)	1995–1996	Rio de Janeiro (Brazil)	177	350	0.83	0.40–1.6	4.8 ng/ml	..	5.85
Millikan et al, 2000 (21)	1993–1999	North Carolina (United States)	748	659	1.09	0.79–1.51	760 ng/g ^d 1690 ng/g ^e	1200 1700	2.65 ..
Romieu et al, 2000 (25)	1990–1995	Mexico City (Mexico)	120	126	2.16	0.85–5.50 ^f	2510 ng/g	..	3.01
Zheng et al, 1999 (31)	1995–1997	Connecticut (United States)	475	502	0.96	0.67–1.36 ^g	456.2 ng/g ^h	..	2.24

^a For of highest versus lowest categories.^b Combined odds ratio (random-effect model): 1.12 (95% CI 0.90–1.39), test for heterogeneity P=0.281.^c P-trend 0.09.^d White subjects.^e African-American subjects.^f P-trend, 0.06.^g P-trend, 0.58.^h Geometric means.

further studies should be conducted in populations with a wide range of exposure including high levels. Assessment of a wider range of organochlorine pesticides and combinations together with other sources of estrogenic chemicals are also needed to gain a better understanding of the potential risks.

Genetic susceptibility and other factors that may modify effects. It is well established that the etiology of breast cancer is multifactorial and includes both host and environmental factors. Between 5% and 10% of the cases of female breast cancer can be ascribed to the inheritance of mutations in the high penetrance genes BRCA1 and BRCA2 (41–43). In addition, studies have suggested the existence of common predisposition genes conferring more moderate risks. These genes will rarely give rise to large breast cancer families but are likely to have a much greater overall impact on the incidence of breast cancer and are likely to act in conjunction with environmental risk factors, including exposure to organochlorine pesticides. For example, enzyme detoxification polymorphisms have been identified that may modify the association between breast cancer risk and exposure to organochlorine pesticides (44–47). Characterization and further assessment of how these genetic factors may modify risk is a major area of ongoing investigation (48).

Current status for breast cancer. To date, for breast cancer, several studies have particularly assessed the role of DDT and its metabolites, and the majority has shown no strong associations with breast cancer per se (49). In general the studies that show an effect tend to be from situations of higher exposure or may have co-factors that also exert an effect (50). An evaluation of other

endocrine-disrupting pesticides and chemicals and combinations of such is still required.

Prostate cancer

For prostate cancer, concern exists, as rates are increasing and are also influenced by hormonal factors. Much less systematic investigation of possible endocrine-modulating effects has been undertaken for this cancer type. Earlier studies, however, did monitor the health of workers employed in both the production and application of pesticides, herbicides, and fungicides. Such investigations were set up partly as routine monitoring of such workers and partly in response to allegations of possible excess of prostate cancer in farming groups (51–61). Studies of groups employed in the manufacture and application of these chemicals are normally limited by two main problems. First, given that these groups are directly concerned with these chemicals, the likelihood that these groups have taken and followed safety advice limiting their exposure is greatest, and therefore actual exposure may be low. Second, the numbers of persons involved in such production and application is relatively small. The power of such studies is therefore normally relatively limited.

Examples of early epidemiologic studies, such as that by Wang & MacMahon (62) examined a cohort of 16 126 male professional pesticide applicators prospectively and did not identify any cases of prostate cancer.

Kay (63) conducted a review of the early work prior to the appreciation of a possible endocrine action of some pesticides based on 175 papers concerning the carcinogenic potential of various pesticide materials. The review showed that many pesticidal chemicals have at least low levels of carcinogenic activity for labo-

ratory species, that chemicals of low cancer-producing potential have a major effect on spontaneous tumor incidence, and that some carriers and vehicles of pesticidal chemicals are carcinogenic and co-carcinogenic in humans. However, the review concluded that the results necessitate the conduction of well-planned epidemiologic investigations of pesticide-exposed persons at the occupational level, where maximal exposures can be expected to occur.

Several more-recent epidemiologic studies have been conducted to ascertain the mortality associated with the production and application of herbicides and other agrochemicals. These studies have found both positive and negative associations. Overall the evidence to date is inconclusive. Other more-recent studies have started to consider endocrine-mediated action for prostate cancer, but to date no convincing evidence of an effect has been found.

Concluding remarks

For breast cancer, a group of pesticides that mimic estrogen pose a credible new risk as these organochlorine pesticides may interact with both a woman's endogenous estrogen profile and the distribution of body fat (breast in particular) and breast cancer type (non-BRCA1/2, postmenopausal, estrogen-receptor positive) (15). DDT and its metabolites have so far been the most extensively investigated in this regard because they are not only bio-accumulative but also persistent in the environment, although the use of DDT has been banned in the United States and Europe for two decades. It is still being used in some developing countries for the vector-control of communicable diseases, and it has a high volume of production, more than 1000 tonnes per year. The importance of interactions with other factors remains disputed. More recently, other widely used pesticides have also been considered for a possible role, but data on such from human populations is more limited [COM (1999) 706] 14 June 2001, Brussels. "Communication from the Commission to the Council and the Parliament on the implementation of the Community Strategy for Endocrine Disrupters—a range of substances suspected of interfering with the hormone systems of humans and wildlife"(11.2)]. Such investigations are required, however, to allow a full and considered assessment of the role of this wide group of chemicals to be made.

For prostate cancer much fewer data are available. Furthermore, the mechanisms by which pesticides could adversely affect prostate cancer have been less substantiated. Nevertheless, a small number of cohort studies has suggested elevated prostate cancer rates in farming groups. The role of endocrine-disrupting pesticides remains unclear for this cancer, however.

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