

COMMITTEE ON THE CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

BREAST CANCER RISK AND EXPOSURE TO ORGANOCHLORINE INSECTICIDES: CONSIDERATION OF THE EPIDEMIOLOGY DATA ON DIELDRIN, DDT AND CERTAIN HEXACHLOROCYCLOHEXANE ISOMERS

Introduction

1. A number of articles in the scientific literature and general media have suggested that prolonged exposure to certain organochlorine insecticides (OCIs) may cause breast cancer. In 1995, the COC reviewed the available epidemiological studies on three chemicals (DDT and isomers/metabolites, and the hexachlorocyclohexane isomers γ -HCH (lindane) and β -HCH. The Committee agreed that the available evidence indicated no clear association. It was felt, however, that the matter should be kept under review. It is in this context that the Committee on Carcinogenicity was asked by the Department of Health to review the relevant information on four organochlorine insecticides (OCIs) in respect of the potential for an association with breast cancer. The additional chemical included in this statement is dieldrin, for which new epidemiological data have recently become available. However, it should be noted though, that only one of the OCIs considered by the Committee, namely lindane, is currently used in the UK, whilst pesticidal uses of the other chemicals considered were phased out over a decade ago.¹

Overview of hypothesis that OCIs may cause breast cancer

2. The Committee agreed that a number of observations and assumptions had led some observers to suggest the hypothesis that OCIs and other organochlorine compounds may be associated with an increased risk of breast cancer. These could be summarised as follows;

i) many of the known or proposed risk factors for breast cancer are related to endogenous or exogenous hormones (in particular oestrogen). These factors include age at first birth, at menarche, and at menopause, and obesity, parity and use of oral contraceptives and hormone replacement²,

ii) there is some evidence available to suggest that the OCIs under consideration may have weak oestrogenic activity³⁻⁸,

iii) these OCIs have been shown to induce tumours (predominantly of the liver) in experimental animals⁹,

iv) these OCIs persist in the environment and exposure of the population has occurred mainly via the diet.^{5,10}

3. The Committee reviewed the evidence that dietary exposure to environmental levels of these OCIs might induce an oestrogenic response *in-vivo* through the consideration of three questions, namely;

i) Do these OCIs have oestrogenic activity *in-vivo* and if so what is their potency relative to other sources of oestrogens?

ii) Is there any evidence for synergistic effects?

iii) Do these compounds persist in breast tissue?

4. The Committee used the information from this review to draw conclusions on the biological plausibility of the hypothesis that OCIs may cause breast cancer. The Committee then evaluated the available epidemiological investigations for evidence of an association between the four OCIs considered in this review and breast cancer. Final conclusions on

each of these OCIs took account of the potential for an oestrogenic response *in-vivo*, the evidence for persistence in humans and the available epidemiological investigations.

Do these OCIs have oestrogenic activity in-vivo and if so what is their potency relative to other sources of oestrogens?

5. A tabulation of the Committee's assessment of the evidence for oestrogenic activity of the OC insecticides under consideration is given below:

Table 1: Assessment of oestrogenic activity of OC insecticides

OCI	Evidence of oestrogenicity <i>in-vitro</i> through effects on			<i>In-vivo</i> data	Conclusion
	i) Oestrogen receptors	ii) Oestrogen metabolism	iii) or by other mechanisms		
β-HCH	Evidence of very weak oestrogenic activity. ^{6,11} (ca 40,000 x weaker than oestradiol)	No data available.	Yes ^{6,11}	Uterotrophic effects documented in rats ^{12,13} and mice.	Regard as a weak <i>in-vivo</i> oestrogen. Mechanism unknown
Lindane	No evidence of oestrogenic activity ^{8,14}	Effects noted in MCF-7 cells ^{15,16} but other investigators have been unable to identify xenoestrogens using this test system. ¹⁷	No data available.	Difficult to interpret but equivocal evidence for oestrogenic and anti-oestrogenic effects in rats. ¹⁸⁻²¹ No evidence of uterotrophic effect in reproduction studies in rats and mice ²²	Considered not to have <i>in-vivo</i> oestrogenic activity.
DDT isomers/metabolites (in particular p,p' DDE)	Evidence of weak oestrogenic activity. ^{5,23} (ca 1000 x weaker than oestradiol)	Effects noted in MCF-7 cells ^{15,16} but other investigators have been unable to identify xenoestrogens using this test system. ¹⁷	Yes ^{11,23-25}	Oestrogenic effects in rodents reported with certain DDT isomers (e.g. o, p' DDT p, p' DDT, and o,p' DDD) ⁵ but not with p,p' DDE ⁵	Regard some DDT metabolites and isomers as weak <i>in-vivo</i> oestrogens. Several mechanisms possibly involved.
Dieldrin	Evidence of very weak oestrogenic activity in the majority of studies ca 10,000 -50,000 less potent than oestradiol ^{8,26-32}	No data available	No data available	No evidence of uterotrophic effects in a number of studies in either rats or mice ^{27,30,32}	Considered not to have <i>in-vivo</i> oestrogenic activity

6. The Committee agreed that the evidence supported the conclusion that β-HCH and DDT (in particular some metabolites and isomers) could have weak oestrogenic activity *in-vivo* which most probably occurs by several different mechanisms. Members agreed that

dieldrin appeared to have weak oestrogenic activity *in-vitro*, but no evidence of an effect had been documented *in-vivo* in a number of studies in rats and mice. There was no convincing evidence that lindane had oestrogenic activity *in-vivo*.

7. The Committee agreed that it was important to compare the evidence for oestrogenic activity of the OCIs under consideration with other potential sources of exposure to oestrogenic substances. Members were aware that Dr Safe from the USA (Texas A&M University) had published estimates of total oestrogenic potency (i.e. oestrogenic equivalents EQs).³³ Thus although there were reservations regarding the use of these calculated data (as the method of determining EQs was based on *in-vitro* studies) it was agreed that the results presented a useful comparison of the relative importance of the sources of potential oestrogens to which women might be exposed.³³ The tabulated information from Dr Safe's paper (reproduced below as table 2) show that organochlorine xenoestrogens contribute a very small proportion of the potential total oestrogenic burden.

Table 2. Estimated mass balance of human exposures to environmental and dietary oestrogens and anti-oestrogens

Source of oestrogen	Oestrogen equivalents (µg per day)
Morning after pill	333,500
Birth control pill	16,675
Post-menopausal therapy	3,350
Flavonoids in foods (1,020 mg/day x 0.0001)	102
Environmental organochlorine oestrogens (2.5 x 0.000001)	0.0000025

(Abstracted from Safe H (1995). *Environmental Health Perspectives*, 103, 346-351.)

Is there any evidence for synergistic effects?

8. The evidence for synergism between xenoestrogens, and in particular in respect of OCIs, arose from the results obtained in *in-vitro* experiments undertaken by one research group in the USA mainly involving mixtures of dieldrin with endosulfan or methoxychlor.^{34,35} The authors subsequently retracted their data after they were unable to replicate the original experiments.³⁶ Many other research groups were unable to repeat the finding of synergism using a number of *in-vitro*^{21,24,25,32} and *in-vivo* tests.^{5,25,32} The results of these more recent experiments suggest, at most, an additive effect. There is thus no evidence to support the view that low levels of mixtures of xenoestrogens induce a biologically significant oestrogenic effect in mammals by acting synergistically. The Committee considered recent claims by one group of authors³⁷ regarding evidence of synergism between certain xenoestrogens and concluded that any significant synergistic interactions in mammals should have been identified by the available published experiments.

Do these compounds persist in breast tissue?

9. The observation that residues of certain OCIs persist in adipose tissue leading to bio-accumulation which might result in continuous exposure of breast tissue to weak oestrogenic substances has been cited as an essential part of the hypothesis that such compounds may cause breast cancer.³⁶ Many research groups have measured levels of OCIs in human adipose tissue or in human milk samples.³⁸⁻⁴³ The results published by the UK Working Party on Pesticide Residues (WPPR) show that p, p' DDE, and β-HCH can be detected in samples of fat or milk from most individuals studied whilst dieldrin was detected in fewer individuals. Lindane was infrequently found in human fat (3%) and milk (1.8%) samples, mainly at low levels (i.e. only one human fat sample contained > 0.01 mg/kg). The available literature shows that lindane is more rapidly metabolised and eliminated in mammals⁴⁴ than other OCIs such as dieldrin⁴⁵ and thus one possible explanation for the low frequency of detectable lindane residues in humans could be due to its metabolism.^{38,39}

10. The WPPR results support the conclusion that the mean concentration of p, p' DDE and dieldrin in human fat samples has been decreasing for several decades. There is no evidence from the WPPR survey for a decrease in the mean concentration β -HCH in human fat up to 1982/3. However, the mean concentration β -HCH in human fat was substantially lower in samples taken in 1995-7 in comparison to the mean concentration of this chemical reported in human fat samples taken in 1982/3. In other surveys, a significant reduction in adipose tissue concentrations of β -HCH was reported in the USA⁴³ between 1970-1983 but not in a separate study undertaken in the Netherlands during 1968-1986.⁴¹

Table 3: Concentrations of OC insecticides in human fat

OC	Mean concentration (mg/kg) in human fat. (Percentage of first reported residue level)				
	1963/4	1969-71	1976/7	1982/3	1995-7
Dieldrin	0.26 (100)	0.16 (61.5)	0.11 (42)	0.08 (30.7)	0.02 (7.6)
p,p'DDE	2.0 (100)	1.8 (90)	2.1 (100)	1.3 (65)	0.71 (35.5)
β -HCH	No Data	0.28 (100)	0.27 (96.4)	0.31 (110)	0.12 (42.8)

Conclusions on biological plausibility

11. Regarding the specific chemicals under review, the Committee agreed that there was sufficient evidence to support the contention that some of the DDT metabolites and isomers and β -HCH had weak oestrogenic activity *in-vivo*, but dieldrin and lindane should not be regarded as having *in-vivo* oestrogenic activity. However, taking into account the low frequency of detectable levels of lindane in samples of human fat and milk, there appeared to be no convincing reason for including lindane as a xenoestrogen for examination in epidemiological studies of breast cancer.

12. The Committee concluded that the xenoestrogens considered, were, at most, very weak *in-vivo* oestrogens and agreed that there was no evidence of any synergistic effects between these chemicals. The impact of exposure to oestrogenic chemicals would be the product of oestrogenic potency and bioavailability. As OCIs are of low potency and occur at low concentrations, it is most unlikely that the effect of current exposures will represent a significant risk of breast cancer. Members were aware that other review groups²⁵ had reached a similar conclusion and noted that some recent methodological research had been published to identify appropriate biomarkers of total oestrogenic body burden from environmental sources.^{46,47,48}

13. The Committee agreed that it would be appropriate if further investigations of the potential association between xenoestrogens and breast cancer concentrated on the evidence for risks associated with the effects of the total exposure to xenoestrogens.

Epidemiology

14. In 1995, the available epidemiological data on breast cancer and exposure to OC insecticides were limited, comprising 6 case-control studies which investigated a total of 301 women with breast cancer using a variety of exposure analyses (in serum, plasma and breast adipose tissue).⁴⁹⁻⁵⁴ Only one of these studies used a prospective design.⁵⁴ All six studies investigated DDT (measured as the metabolite p, p' DDE), with an equal number of positive and negative associations reported between p, p' DDE and the risk of breast cancer. The two investigations that considered β -HCH gave conflicting results, but no clear association was found. The two studies that considered lindane in breast tissue found no difference in lindane levels between cases and controls. There was no evidence of an association between the concentration of dieldrin in breast tissue and breast cancer in the one limited study before 1995 where dieldrin was measured.⁵⁰

15. Since 1995, eight additional epidemiological studies have been published,⁵⁵⁻⁶² which have considerably increased the number of women studied. Thus the total number of women

with breast cancer studied with respect to p, p' DDE has now risen to over 1500. A brief description of these studies and their results is given in table 4 below. The conclusions reached by the Committee with regard to the epidemiological data are given below and in paragraph 17

Table 4: Epidemiological studies of organochlorine insecticides and breast cancer published after 1995

Study (Reference no)	Description	Results/Comment
Lopez-Carrillo L et al (1997) ⁵⁵ (Mexico)	Hospital based case-control investigation. (n= 141 cases and controls)	No evidence for an association between serum p, p' DDE concentrations and risk of breast cancer. Age-adjusted Odds ratio for serum DDE concentrations comparing lowest tertile to middle and upper tertiles were below 1.
Hunter DJ et al (1997) ⁵⁶ (U.S.A.)	Prospective investigation based on 121,700 nurses enrolled 1976. Blood samples provided by 32,836 (1989-90). Study based on 240 women with breast cancer (up to June 1992) and 240 matched controls.	No evidence for an association between plasma p, p' DDE and risk of breast cancer. The median concentration of DDE in cases was below that of controls.
van't Veer P et al (1997) ⁵⁷ (Germany, Netherlands, N.Ireland, Switzerland, Spain)	Multicentre case-control investigation. (n= 374 cases, and 374 population/hospital controls).	No evidence for an association between subcutaneous fat concentrations of p, p' DDE and risk of breast cancer. Mean concentrations of p, p' DDE in needle aspirates of buttock fat were lower in cases compared with controls at all study centres.
Guttes S et al (1998) ⁵⁸ (Germany)	Analysis of p, p' DDT p, p' DDE and α -, β -, γ -HCH breast tissue samples from 45 women with breast cancer and 20 with benign breast disease at two centres.	After age adjustment a significant increased p, p' DDE concentration was documented in breast cancer patients (p= 0.017 by analysis of covariance). A slightly lower mean β -HCH concentration was reported in cases. Lindane (γ -HCH) was only detected in 3/65 samples ($\geq 1\mu\text{g}/\text{kg}$).
Hoyer PA et al (1998) ⁵⁹ (Denmark)	Prospective investigation based on 7712 women enrolled in Copenhagen Heart Study in 1976. 268 women developed breast cancer up to end of 1993. Analyses based on serum samples from 240 cases and 477 controls.	Dieldrin was associated with a significantly increased dose-related risk of breast cancer (adjusted odds ratio for highest tertile of exposure =2.05 (95% CI 1.17-3.57)). β -HCH showed a slightly, but not statistically significant increase in odds ratio. No association was seen for a further 16 organochlorine pesticides studied (including lindane (γ -HCH) and p, p' DDE). The Committee considered the result with dieldrin may have been a chance finding in view of the large number of statistical comparisons (46) undertaken in this study.
Olaya-Conteras P et al (1998) ⁶⁰ (Colombia)	Hospital based case-control investigation. (n= 153 cases, 153 controls).	After adjustment for confounding factors a significant increased odds ratio for serum p, p' DDE concentration and breast cancer was reported for the highest tertile of exposure (OR = 1.95 (95% CI 1.11-1.32)).
Dorgan JF et al (1999) ⁶¹ (Colombia)	Prospective investigation based on 7224 women who donated a blood sample to the Missouri Breast Cancer Serum Bank between 1977/87. 105 cases identified at end of 1989, but there was no follow-up of at least 70% of cohort beyond 1982/3. Analyses based on 105 cases and 208 controls but the criteria for matching for 17 cases were relaxed.	No evidence for an association between total DDT (or p, p' DDT or p, p' DDE), β -HCH, dieldrin, lindane (γ -HCH) or for a further 13 other organochlorine insecticides was found.
Moyish KB et al (1998) ⁶² (U.S.A.)	Case-control study of 154 post-menopausal breast cancer cases and 192 post-menopausal community controls.	No evidence for an association between serum concentrations of p, p' DDE and risk of breast cancer.

16. The Committee was aware that a large number of epidemiological investigations were being conducted, mainly in the USA, under the sponsorship of the National Cancer Institute (NCI) and National Institute for Environmental Health Sciences (NIEHS); these studies would yield additional data over the next few years. It was agreed that completed published studies should be evaluated at a future meeting. Members considered that it would be valuable if such studies included an estimation of total body burden of environmental xenoestrogens as well as an analysis of individual chemicals. The Committee was also aware that it was likely that technological improvements will in the future enable the detection of lower levels of OCIs in tissue samples, although this would not necessarily imply that such concentrations would be associated with any harmful biological effect.

Conclusions: Epidemiology

17. The Committee agreed that the following conclusions regarding the epidemiological data for the OCIs reviewed in this paper could be drawn on the basis of the available evidence.

DDT There is considerably more epidemiological data now than in 1995 on environmental exposure to DDT and its isomers and metabolites and a possible association with breast cancer. All of the eight studies⁵⁵⁻⁶² published since 1995 investigated p, p' DDE, but only two^{58, 60} relatively small retrospective studies found evidence for an association between p, p' DDE and increased risk of breast cancer. Overall, there is no convincing evidence from epidemiology studies for an elevated relative risk of breast cancer in association with DDT (as measured by p, p' DDE).

Dieldrin There is very little epidemiological information available on dieldrin and its possible association with breast cancer. Of the two recent studies published after 1995, which considered this insecticide, one found no evidence for an association⁶¹ and the other found a positive association⁵⁹, which was considered likely to be a chance finding. Overall, there is no convincing evidence from epidemiological studies for an elevated relative risk of breast cancer associated with dieldrin.

β -HCH There is very little epidemiological information available on β -HCH and its possible association with breast cancer. Of the three recent studies published after 1995 which considered β -HCH^{58,59,61}, none reported a statistically significant association with increased risk of breast cancer.

Lindane There is very little epidemiological information available on lindane (γ -HCH) and its possible association with breast cancer. Of the three recent studies published after 1995 which considered lindane^{58,59,61}, none found evidence for an association with increased risk of breast cancer. The available evidence for environmental exposure to lindane suggests that body burdens of this chemical are very small, being undetectable in most individuals. It is therefore unlikely that further epidemiological investigations of breast cancer based on assessment of levels of lindane in adipose tissue, blood, or breast tissue would provide additional relevant information.

Overall conclusion

18. The Committee evaluated the hypothesis that OCIs might increase the risk of breast cancer by virtue of their claimed oestrogenic effects (**para 2**). The Committee concluded that the oestrogenic effects (if any) of these xenoestrogens were likely to be small in magnitude, especially compared with those of oral contraceptives or HRT^{2,33}, which entail much higher exposures to oestrogens (**para 7 and tables 1 and 2**). Moreover, the Committee concluded that there was no convincing evidence of oestrogenic synergy in mammals between different OCIs (**para 8**). There is also evidence that concentrations in human fat of the OCIs

considered in this statement are decreasing in humans which provides some additional reassurance with regard to any potential risk of breast cancer (**para 10, table 3**). The Committee agreed, that further investigations of the potential association between xenoestrogens and breast cancer should concentrate on the evidence for risks associated with the effects of the total exposure to xenoestrogens (**para 13**).

19. The Committee was aware of further epidemiological research on the OCIs considered in this statement and agreed that the relevant reports should be reviewed when published. Regarding the specific chemicals under consideration (i.e. DDT (and isomers/metabolites), dieldrin, β -HCH, and Lindane), the Committee came to the following overall conclusions, on the basis of the available information.

DDT Some DDT isomers and metabolites should be regarded as having weak *in-vivo* oestrogenic activity. The stable metabolite p, p' DDE, a marker for exposure to DDT, can be found in samples of fat from most individuals. There is however, good evidence from investigations undertaken in the UK that concentrations of p, p' DDE in human fat samples have been declining for several decades. There are now 14 epidemiological studies which have considered p, p' DDE using both case-control and prospective study designs. There is no convincing evidence for an association with an increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to DDT (and isomers/metabolites) is a cause for concern as a risk factor for human breast cancer.

Dieldrin Dieldrin is not considered to have *in-vivo* oestrogenic activity. There is thus no rationale to consider that exposure to this chemical should be associated with an increased risk of breast cancer. There is good evidence from investigations undertaken in the UK that concentrations of dieldrin in human fat samples have been declining for several decades. There is no convincing evidence from the five available epidemiological studies for an elevated risk of breast cancer in association with exposure to dieldrin. Overall the available data do not suggest that environmental exposure to Dieldrin is a cause for concern as a risk factor for human breast cancer.

β -HCH β -HCH should be regarded as having weak *in-vivo* oestrogenic activity. β -HCH can be found in samples of fat from most individuals. There is evidence from investigations undertaken in the UK for a decline in β -HCH concentrations in human fat samples after 1982/3. There is no convincing evidence from the five available epidemiological studies for an elevated risk of breast cancer in association with exposure to β -HCH. It is recommended that the published literature on this chemical should be kept under review

Lindane Lindane (γ -HCH) is not considered to have any *in-vivo* oestrogenic activity. There is thus no rationale to consider that exposure to this chemical should be associated with an increased risk of breast cancer. The available evidence for environmental exposure to lindane suggests that body burdens of this chemical in the UK are very small, being undetectable in most individuals. None of the five available epidemiological investigations found evidence for an association with breast cancer. Overall the available data do not suggest that environmental exposure to lindane is a cause for concern as a risk factor for human breast cancer.

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