

**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**

STATEMENT OF REVIEW UNDERTAKEN DURING 2003/4.

Statement COC/04/S3 – September 2004

Introduction

1. 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. The Committee on Carcinogenicity was asked by the Department of Health in 1999 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 was dieldrin, for which new epidemiological data had become available at the time of that review. The main conclusions of the 1999 review are given below;

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.

2. The Committee was aware of a number of research investigations that were either planned or had been instigated at the time of the 1999 review and agreed to review relevant publications in the scientific literature at some point in the future. A large number of publications have become available and it is now timely to review the evidence.

Introduction to current review

3. The Committee considered a review paper presented to its 22 September 2003 meeting. Further review papers and tabulated summaries of epidemiology studies were considered at the 6 November 2003 and 1 April 2004 meeting. All papers can be accessed through the COC internet site (either via links from agendas or in the section entitled papers).
4. During the review process, members agreed that it was important to consider all of the epidemiology studies together rather than focus on studies published after the last review in 1999. However no additional relevant information has been retrieved on lindane (γ -hexachlorocyclohexane, γ -HCH) since the 1999 review. The COC concluded in 1999 that there was no rationale that γ -HCH could be associated with breast cancer. A summarised tabulation of the studies available at the time of the review has been published as an Annex to this statement. A summary of the main results from epidemiology studies has been presented in a number of graphs which are also available as an Annex to this statement. The tables and graphs present information for DDT (and its isomers and metabolites), β -hexachlorocyclohexane (β -HCH) and dieldrin.
5. The Committee was aware that none of the OCIs included in this review are approved for use in pesticide formulations in the U.K.
6. The Committee agreed in 1999 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. The format of the statement agreed in 1999 presented a review of the biological plausibility that OCIs may be

associated with an increased risk of breast cancer and then a review of the available epidemiology for each OCI under consideration. The conclusion reached for each of the OCIs under consideration in 1999 took account of the potential for an oestrogenic response *in-vivo*, the evidence for persistence in humans and the available epidemiological investigations. The Committee agreed that the format of the current statement should adopt the same procedure used for the 1999 review. Thus a brief overview of the proposed hypothesis that OCIs maybe associated with an increased risk of breast cancer is given below;

Overview of hypothesis that OCIs may cause breast cancer

7.
 - 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 replacement¹,
 - ii) there is some evidence available to suggest that some of the OCIs under consideration may have weak oestrogenic activity²⁻⁷,
 - iii) these OCIs have been shown to induce tumours (predominantly of the liver) in experimental animals⁸,
 - iv) these OCIs persist in the environment and exposure of the population has occurred mainly via the diet.^{4,9}

Consideration of biological plausibility.

8. 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?

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

9. A tabulation of the Committee's assessment of the evidence for oestrogenic activity of the OC insecticides under consideration is given overleaf. The new data published since the 1999 COC review provided additional information on the *in-vitro* oestrogenic effects of β -HCH^{37,38} and DDT isomers/metabolites³² and evidence to show that dieldrin had no effect on human placental aromatase activity *in-vitro*³⁵. An *in-vivo*

study with dieldrin showed that very high lethal doses administered to rats did alter oestrogen metabolism³⁶. However the Committee concluded that the data from this latter study were irrelevant with regard to assessment of the very low levels exposure experienced by the general population.

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. ^{5,10} (ca 40,000 x weaker than oestradiol)	No data available.	Yes ^{5,10,37,38} Data suggest a number of mechanisms possible but relevance to <i>in-vivo</i> situation is uncertain.	Uterotrophic effects documented in rats and mice. ^{11,12}	Regard as a weak <i>in-vivo</i> oestrogen. Mechanism unknown
Lindane	No evidence of oestrogenic activity ^{7,13}	Effects noted in MCF-7 cells ^{14,15} 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. ¹⁷⁻²⁰ No evidence of uterotrophic effect in reproduction studies in rats and mice ²¹	Considered not to have <i>in-vivo</i> oestrogenic activity.
DDT isomers/metabolites (in particular p,p' DDE)	Evidence of weak oestrogenic activity. ^{4,22,32} (ca 1000 x weaker than oestradiol)	Effects noted in MCF-7 cells ^{14,15} but other investigators have been unable to identify xenoestrogens using this test system. ¹⁶	Yes ^{10,22-24} relevance to <i>in-vivo</i> situation is uncertain.	Oestrogenic effects in rodents reported with certain DDT isomers (e.g. o, p' DDT p, p' DDT, and o,p' DDD) ⁴ but not with p,p' DDE ⁴	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 effect on human placental aromatase activity. ³⁵	Yes ³⁹ relevance to <i>in-vivo</i> situation is uncertain.	No evidence of uterotrophic effects in a number of studies in either rats or mice ^{27,30,32} High oral doses given to rats (equivalent to LD50) induced cytochrome P450 enzymes and altered oestrogen metabolism. ³⁶	Does not to have <i>in-vivo</i> oestrogenic activity Effects on oestrogen metabolism at lethal oral doses is irrelevant to consideration of environmental exposure.

10. The Committee reaffirmed the conclusions reached in 1999 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*. The Committee reaffirmed its conclusion that there was no plausible reason for including lindane as a xenoestrogen for examination in epidemiological studies of breast cancer.
11. The Committee concurred with its conclusion reached in 1999 that in comparison to other potential sources of exposure to oestrogenic substances (e.g birth control regimes, post-menopausal hormone therapy, flavenoids in foods⁴⁰) that OCIs represent an extremely small proportion of the potential oestrogenic burden.

Is there any evidence for synergistic effects?

12. The Committee undertook a detailed review of the potential for synergism between OCIs during the 1999 review. 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 and published in 1996 which concerned mixtures of dieldrin with endosulfan or methoxychlor.^{41,42} The authors subsequently retracted their data in 1997 after they were unable to replicate the original experiments.⁴³ Many other research groups were unable to repeat the finding of synergism using a number of *in-vitro*^{20,21,24,31} and *in-vivo* tests.^{4,24,31} The results of the available experiments suggested, at most, an additive effect. The Committee also considered a claim by one group of authors⁴⁴ 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.
13. A further six papers, retrieved since 1999, report the findings of a number of *in-vitro* studies using mixtures of OCIs or mixtures of OCIs with other xenoestrogens.⁴⁵⁻⁵⁰ These studies used yeast or mammalian cell lines and a variety of different reporter systems for measuring activation of oestrogen receptors and were relatively complex in design particularly as dose-response effects for a range of combinations of chemicals under test were investigated. A separate investigation investigated the potential interactions of xenoestrogens but did not include any of the OCIs under consideration in this statement.⁵¹ Most of these studies found no evidence for interaction between OCIs or between OCIs and other xenoestrogens.^{45,46,48,49} The Committee noted several studies from one research group based at the School for

Pharmacy, London had reported significant interactions between xenoestrogens *in-vitro* using either a recombinant yeast system⁵¹ or human breast cancer cells (MCF-7 cells)⁵⁰ which were evident when individual xenoestrogens were included in a mixture at concentrations below the No-observed concentration level when tested individually. The Committee considered that the results obtained in these latter experiments were consistent with an additive effect. A further study which used activation of luciferase linked to oestrogen-receptor activation in T47D breast cancer cells reported evidence for an additive effect between dieldrin and endosulfan.⁴⁷

14. One recently published *in-vivo* study using the immature rat uterotrophic assay has been published which investigated mixtures of seven well established xenoestrogens at dose levels where individual chemicals were ineffective found a uterotrophic response when the mixture was tested. Further investigations by the authors confirmed that the observed response was below that predicted by simple addition of the observed or predicted activities.⁵²
15. The Committee was aware that a Working Group of its sister Committee, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) had undertaken a detailed consideration of the risk assessment of mixtures of pesticides and similar substances and a report was published on 15 October 2002.⁵³
(<http://www.food.gov.uk/science/ouradvisors/toxicity/reports/cocktailreport>) The Working Group on Risk Assessment of Pesticides and similar substances (WiGRAMP) considered the available evidence regarding all toxic endpoints including endocrine disruption effects such as oestrogenic effects. The overall conclusion of all the available evidence is given below;

“Several studies claim to have identified synergistic interactions of some mixtures. However, for the most part, these studies have been inadequately designed and based on incomplete understanding of the concepts involved, but a few well designed studies have demonstrated both synergistic and antagonistic interactions, as well as additive effects in mixtures, usually at high concentrations or high experimental exposure levels, which are probably unrepresentative of exposure doses.”

15. The information available to the Committee regarding OCIs is consistent with the conclusion reached in 1999 that there is 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 possibility of a simple additive effect cannot be excluded but at the likely exposure levels for the OCIs concerned this will represent a negligible risk of any oestrogenic effect *in-vivo*.

Do these compounds persist in breast tissue?

16. 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 In 1999, the COC reviewed the available evidence from surveys of concentrations of OCIs in human adipose tissue or milk from a number of different sources including U.S.A. and countries in Europe. The most complete and appropriate data on adipose tissue concentrations of OCIs in the U.K. had been published by the Pesticides Residues Committee (formerly the Working Party on Pesticides Residues, WPPR) (<http://www.pesticides.gov.uk/committees/PRC/prc.htm>) The data collected from the early 1960s up to 1997 by the PRC which is retabulated below for ease of reference, indicated that body burdens of OCIs have been decreasing.
17. The results published by the Pesticides Residues Committee 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}

Table 2: 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)

18. No new information has been retrieved since the 1999 review . However since it is evident that tissue levels of OCIs were declining, and none of these chemicals is approved for use in pesticide formulations in the U.K. and they have also been subjected to widespread restrictions on use in other countries, it would be appropriate to conclude that concentrations in human adipose tissue and milk have continued to decline.

Conclusions about Biological Plausibility

19. The Committee concluded that the OCIs 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. The possibility of an additive effect of OCIs could not be discounted. However as OCIs are of low potency and occur at low concentrations, it is most unlikely that the effect of current exposures individually or collectively will significantly add to total oestrogenic burden in women and will not present any significant risk with regard to breast cancer.

Epidemiology

20. In 1995 when the Committee first reviewed the subject of organochlorine insecticides and the potential association with breast cancer, 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).⁶²⁻⁶⁷ In 1999 a further eight additional epidemiological studies had been published,⁶⁸⁻⁷⁵ which considerably increased the number of women studied (for p,p, DDE this was estimated to be around 1500). By January 2004 (the deadline for this statement), over 80 estimates of odds ratios/relative risks had been documented from a wide range of epidemiological investigations using different study designs involving both prospective and retrospective approaches, and analyses of OCIs in blood, serum or adipose tissue in women. A number of these investigations have also included an evaluation of hormone receptor status of breast cancer as part of the assessment⁷⁷⁻¹⁰⁸ However most of these studies have examined DDT or its metabolite p'p'DDE whilst relatively few have reported data for dieldrin and β -HCH and none for lindane (γ -HCH). One meta-analysis of 22 investigations of the potential association between p'p'DDE and risk of breast cancer has been published.⁷⁶ It is not possible to provide a narrative summary of all these studies in this statement. A tabulated summary and graphical representation of the main results from the studies are appended to this statement as separate Annexes. The overall conclusions reached by the Committee on each OCI are given below.

DDT (and isomers/metabolites p'p'DDE)

- i) In 1999, the Committee concluded that overall, there was no convincing evidence from epidemiology studies for an elevated relative risk of breast cancer in association with DDT (as measured by p, p' DDE). With regard to DDT, the available studies are overwhelmingly negative apart from one prospective cohort study⁸⁶ and one retrospective case-control study⁸⁰. With regard to p'.p'DDE a number of positive studies have also been published.^{65,73,95,96,103} The Committee considered the meta-analysis study of published studies investigating the association between p'p'DDE and risk of breast

cancer had been adequately undertaken and the summary risk estimate of 0.97 (95% CI 0.87-1.09) suggested there was no evidence for an association.¹¹⁰ Overall the Committee considered there was no compelling evidence that DDT or its metabolite p,p'DDE were associated with an increased risk of breast cancer.

Dieldrin

ii) In 1999 the Committee noted that there was relatively little epidemiological data on dieldrin. Overall, the Committee concluded there was no convincing evidence from epidemiological studies for an elevated relative risk of breast cancer associated with dieldrin. There have been relatively few studies published since 1999 on the potential association between dieldrin and risk of breast cancer. Hoyer and colleagues have reported positive findings in a number of analyses.^{72,87,88} However the COC has previously stated there are methodological problems with these studies which prevent definite conclusions from being drawn.¹⁰⁹ Thus overall the Committee consider there are no convincing data available regarding an association between dieldrin and risk of breast cancer.

(It was not appropriate to calculate an overall estimate of the strength of association from the available data)

β-HCH.

iii) In 1999 the Committee concluded that there was very little epidemiological information available on β-HCH and its possible association with breast cancer. The studies available at that time had all provided negative findings. None of the studies retrieved for the current review reported statistically significant positive findings.^{77,82,86,92,100,103} Thus overall there is no evidence to associate β-HCH with an increased risk of breast cancer.

Lindane (γ-HCH)

iv) In 1999, the Committee noted there was very little epidemiological information on the potential association between lindane and risk of breast cancer. The available studies did not suggest an association. The Committee concluded that it was 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. There have been no additional epidemiological investigations retrieved. There is therefore no evidence to associate lindane with an increased risk of breast cancer.

Overall conclusion

21. The Committee noted the hypothesis that OCIs might increase the risk of breast cancer by virtue of their claimed oestrogenic effects (**para 2**). The Committee reaffirmed conclusions reached in 1999 namely;
- a) 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, which entail much higher exposures to oestrogens (**para 7-11**)
 - b) there is no convincing evidence of oestrogenic synergy in mammals between different OCIs or OCIs with other xenoestrogens. The possibility of a simple additive effect cannot be excluded but at the likely exposure levels for the OCIs concerned this will represent a negligible risk of any oestrogenic effect in-vivo. (**para 15**).
 - c) 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 18**).
22. The following overall conclusions were reached.

DDT (and isomers and metabolites p'p'DDE)

There is evidence that DDT and some of its isomers/metabolites such as p'p'DDE have weak xenoestrogenic activity in-vivo. Concentrations of p'p'DDE in human fat have been declining for decades. There is extensive epidemiological data on the potential for an association between DDT its isomers and metabolites such as p'p'DDE and increased risk of breast cancer. 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 does not have any oestrogenic activity in-vivo. There is evidence to show that concentrations in human fat are decreasing. There is no convincing epidemiological evidence for an association between dieldrin and increased risk of breast cancer. However the available epidemiological evidence on dieldrin and risk of breast cancer is limited and it is suggested that the relevant literature on dieldrin is kept under review.

β-HCH

β-HCH should be regarded as having weak *in-vivo* oestrogenic activity. There is evidence from investigations undertaken in the

UK for a decline in β -HCH concentrations in human fat samples after 1982/3. The available epidemiological studies do not suggest any evidence for an association between β -HCH and increased risk of breast cancer. Overall the available data do not suggest that environmental exposure to β -HCH is a cause for concern as a risk factor for human breast cancer.

Lindane

Lindane (γ -HCH) does not have any in-vivo oestrogenic activity. It is not approved for use as a pesticide in the U.K. Exposure is likely to be negligible. The Committee have previously concluded that there is no biological rationale for including lindane in any epidemiology studies on risk of breast cancer. The Committee concluded there is no reason to undertake any further reviews of the association of this chemical with increased risk of breast cancer.

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