Dieldrin and Breast Cancer: a Literature Review

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Introduction

This literature review was undertaken in 2007 by six graduate medical students at the Australian National University, supervised by Drs Colin Butler and Gillian Hall, in association with Doctors for the Environment Australia. It is hoped that this work will provide a basis to facilitate and stimulate further exploration of the possible relationship between human-produced molecules, now commonly found in both the food chain and the tissue of humans, and disease, including cancer. This study focuses on a tiny facet of that larger issue, that between the organochlorine compound dieldrin and breast cancer.

Dieldrin is an organochlorine pesticide that was widely used in the 1960s and 1970s. Like other organochlorines, dieldrin is a persistent pollutant. Despite a great reduction in its use, dieldrin residues still persist in the environment, food and people. Exposure to dieldrin at high levels has been shown in both humans and animals to have numerous toxic effects including neurotoxicity and hepatocarcinogenicity. There is also substantial evidence that dieldrin has oestrogenic effects.

Of particular relevance for this paper is concern that a causal link may exist between dieldrin and breast cancer. Dieldrin is stored primarily in fatty tissues. In breast feeding women an important route of dieldrin excretion is via the breast milk, resulting in lower dieldrin levels in women who breast-feed (or express milk). This paper will explore the possible link between dieldrin and breast cancer. In particular it will examine whether the breast cancer-protective effect of breast-feeding, especially among younger mothers and those who feed for a prolonged time,[1] may operate in part by decreasing a woman's burden of dieldrin, and perhaps other carcinogenic molecules. The possible effects of dieldrin contaminated breast milk on the breast-fed infant are also discussed.

Dieldrin: a pesticide and pollutant

The era of the organochlorine pesticides started with the discovery in the 1930s that DDT (chemical name 4,4'-(2,2,2-trichloroethane-1,1-diyl) bis-chlorobenzene, originally **d**ichloro-**d**iphenyl-**t**richloroethane) had a broad spectrum of insecticidal properties, with relatively low toxicity to mammals, low cost, and good stability and persistence.[2] In the following years, many other organochlorine pesticides, including aldrin, dieldrin, gamma lindane and endrin were introduced. Dieldrin and aldrin were produced by Shell Chemical from 1948. In both the environment and *in vivo* aldrin is rapidly converted to dieldrin, so these two organochlorines are usually discussed together.[3]

Dieldrin and aldrin are crystalline lipophilic solids, with low solubility in water (refer to Appendix 1) In biological tissues, they accumulate in lipids, and in soils they bind to soil particles. They both evaporate slowly. Aldrin readily undergoes epoxidation to dieldrin in the environment via the action of sunlight and bacteria.[3] Dieldrin is a stable and persistent molecule. Organochlorine pesticides, including dieldrin, are stable in the environment, and bioaccumulate.

Regulation of the use of dieldrin

Organochlorines and other chemicals were originally discovered in the 1930s for use as insecticides and pesticides. DDT became famous worldwide in 1939 after its use in overcoming a typhus infestation in Naples.[4] The use of organochlorines increased during the 1950s and peaked in the 1970s. The use of organochlorine pesticides in Australia was

dramatically lowered between the mid 1970s and the early 1980s. The first restrictions on the use of dieldrin and related chemicals in Australia were introduced in 1961-2, with registration required for their use on produce animals, such as cows and chickens.[4] This coincided with increasing concerns worldwide about the long-term effects of persistent pesticides. The publication of *Silent Spring* (a widely read and highly influential popular account of the environmental and health effects of pesticides) by Rachel Carson in 1962 was a key driving force in raising this concern.[5] The phase-out process was driven by government bans and deregistration, in turn promoted by changing public perceptions that food containing residues of these chemicals was less acceptable and possibly hazardous to health.(4)

Throughout this time continuous pressure was maintained by relevant committees, for example the Technical Committee on Agricultural Chemicals (TCAC), to reduce approved organochlorine use. By 1981 the use of dieldrin worldwide was limited to sugarcane and bananas and these uses were deregistered by 1985.[4] In 1987 a nation-wide recall system was put into place and in December of that year the government prohibited all imports of these chemicals into Australia without express ministerial approval.(4) In 1994, the National Registration Authority for Agricultural and Veterinary Chemicals (NRA) published *Use of organochlorines in termite control*, recommending the phase-out of organochlorines used in termite control upon development of viable alternatives.(4) The same year, the Agriculture and Resource Management Council of Australia and New Zealand (ARMCANZ) decided to phase out remaining organochlorine uses by 30 June 1995, with the exception of the Northern Territory.[4] In November 1997 the use of all organochlorines other than mirex was phased out in Australia. Remaining stocks of mirex are to be used only for contained baits for termites in plantations of young trees in the Northern Territory until stocks run out, which is expected in the near future.

The recognition of negative impacts on health has stimulated the implementation of multiple legislative policies in regards to the use and disposal of organochlorine pesticides. For example, the Environment Protection (Marine) Policy 1994 became operational in May 1995 in South Australia.[6] It dictated the acceptable concentration of toxicants such as dieldrin in marine waters and the manner in which these levels must be tested and tried.

Momentum against organochlorine and similar molecules continued to grow internationally, leading, to negotiations which matured as the Stockholm Convention on the use of Persistent Organic Pollutants (POPs).[7] POPs are defined as hazardous and environmentally persistent substances which can be transported between countries by the earth's oceans and atmosphere. All POPs (including dieldrin) bioaccumulate in the fatty tissues of humans and other animals. The Stockholm Convention banned twelve POPs, nicknamed “the Dirty Dozen” (see Appendix 2). This took force on 17 May 2004. Australia ratified the Convention only three days later and became a Party to it in August that year.[7]

Well before this, Australia had been well advanced in meeting the measures agreed upon under the Convention. Production, import and use of aldrin, chlordane, DDT, dieldrin, Hexachlorobenzene (HCB), heptachlor, endrin, and toxaphene are not permitted in Australia.[4] Production and import of Polychlorinated biphenyls (PCBs) are not permitted in Australia, with the phase-out of existing PCBs being managed under the National Strategy for the Management of Scheduled Waste.[8] This strategy also addresses how Australia will manage HCB waste and organochlorine pesticides.

Legislation in Australia on the import, use and disposal of dieldrin and other organochlorines has been extensive and covers mainly environmental and potential health impacts on the population (refer to Appendix 3).

Pharmacokinetics of dieldrin

Dieldrin and aldrin are absorbed by inhalation, oral intake and through the skin. Both aldrin and dieldrin are lipophilic. Absorption is believed to be by passive diffusion, with subsequent transport in the lipid fraction of the blood.[9] Once absorbed, aldrin is converted rapidly to dieldrin. This conversion is mediated by monooxygenases in the liver,[10] lungs[11] and skin.[11, 12] After absorption, dieldrin is rapidly taken up by the liver, then redistributed to be stored primarily in fat.[9,13-16]

Dieldrin is metabolised further in the liver, for example by hydroxylation to 9-hydroxydieldrin.[17] There is also evidence suggesting that a prostaglandin synthetase system may be involved in the metabolism of dieldrin.[9,11]

Dieldrin is excreted in bile, faeces, urine[18] and breast milk.[19,20] The relative importance of these routes is unclear. The data on dieldrin excretion in bile, faeces, and urine are derived from rats given aldrin orally. The daily dieldrin output in the bile and faeces was roughly ten times the output in the urine.[18] The excretion of dieldrin in milk by dairy cows fed dieldrin (0.11 to 2.32 mg per kilogram of body weight) ranged from 1.7-13.1 parts per million (ppm) in fat-corrected milk.[20] There are limited data concerning the half life of dieldrin in humans. However there is consensus that it is prolonged, and probably over one year. One study, undertaken in 1969, estimated this as 369 days.[21]

Human exposure to dieldrin

Despite its widespread ban in industrialised nations, dieldrin has persisted in the environment, resulting in ongoing human exposure. The lipophilic nature of organochlorines means they tend to concentrate in the food chain and therefore animals at the top of the food chain, including man.[22] Routes of exposure include ingestion of contaminated animal derived food products, or ingestion of food grown in dieldrin contaminated soil. Humans can also be occupationally exposed to the pesticide or even absorb it through household air.[9, 23] The global nature of food trade and travel puts all people at risk of dieldrin exposure, even those living in areas with low levels of proximal environmental contamination.

Studies have identified a number of risk factors for high average body burdens of organochlorines. These include living on farms, being non-white, male, older, or poor.[24] A vegetarian diet may be protective, in at least some settings.[25]

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) set the acceptable daily intake (ADI) of dieldrin at 0.1 µg/kg body weight.[26] It has been estimated that levels of intake exceed this in some developing countries, for example, the average daily intake in India in the early 1990s, was estimated to be 19 µg/person.[27] This is more than 30 times the recommended dose.

Measurement of dieldrin in humans

Measuring dieldrin levels in humans is a useful way of surveying its distribution, and can identify at-risk groups. Measurement of dieldrin levels is also important for investigating the role of the pesticide in various diseases. As dieldrin accumulates in fat, it is often measured in

adipose tissue, serum or breast milk. Techniques for determining dieldrin levels are complex and involve gas chromatography coupled with electron capture detection.[9]

There are advantages and disadvantages to using different tissue samples for measuring human dieldrin levels. Although serum has a relatively low fat content when compared with breast milk or adipose tissue, it is a useful medium in which to measure dieldrin levels, as it can be collected relatively non-invasively.[28]

Breast milk is also relatively non-invasive to obtain, and has been used since the 1970s to study human dieldrin levels.[29] Limitations to studies using breast milk include a lack of standardised methodology between studies, small study populations, and selection bias towards women likely to have been exposed to high levels of the pesticide.[30] Further, breast milk can only measure dieldrin levels in a subset of the population (women of child-bearing age). Adipose tissue contains up to 30 times more dieldrin than breast milk and up to 140 times more dieldrin than blood.[31]

Numerous studies have found that dieldrin levels increase with age.[28,32,33] This probably reflects bioaccumulation of the chemical within individuals over a lifetime. The levels in humans vary with the race of the subjects. These variations are likely to reflect a difference in levels of exposure.[34]

Several studies have been conducted in Australia to ascertain the levels of dieldrin in breast milk. Dieldrin was found in 100% of samples from Western Australia[35] in 1993 and in 40% of samples from a study of 23 Victorian women in the following year.[36] Disturbingly, these studies found that 88-90% of subjects had dieldrin levels in breast milk which were higher than the WHO acceptable daily intake (ADI) for infants. However, more recent studies, one from Western Australia and another from Victoria, have suggested that dieldrin levels have peaked and are now falling.[37, 38] By 2002 only a few samples of adipose tissue and breast milk in WA had detectable levels of dieldrin (refer to Table 1).[38]

***Table 1*:** Comparison of median and interquartile (IQR) of dieldrin levels in human adipose tissue,[a], Western Australia, 1970-2002 (adapted from[38]).

Year of Sampling:	*Dieldrin: median (IQR)*
1970[b,c]	0.19
1988[d]	0.30 (0.20 – 0.45)
1991[c]	0.04 (0.01 – 1.10)
2002	0.01 (0.01 – 0.01)

[a] Tissue concentration as mg/kg of extractable fat.
[b] IQR not available
[c] Source:. [35]
[d] Source:[39]

In Australia, dieldrin levels in breast milk have fallen from several hundred ng/g lipid in the 1970s to 10-20 ng/g lipid more recently (refer to Table 1 and Figure 1). This decline in dieldrin levels likely reflects the decreasing levels of the pesticide in the environment since its use was banned. However, the rate of decline has slowed, reflective of the persistent nature of dieldrin. This may also reflect continued global use of dieldrin, with consequent potential exposure in Australia from imported and offshore sources.

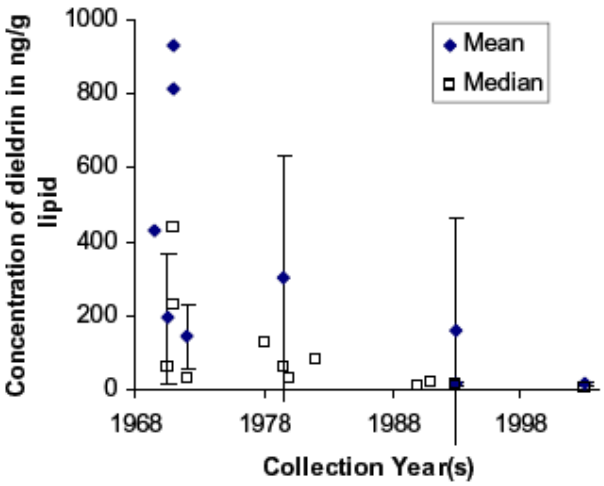

Figure 1 – Historic trends in the concentration of dieldrin in human milk samples from Australia.[29]

In the United Kingdom a marked decline in dieldrin levels in breast milk has occurred since the 1960s.[40] A recent study in Denmark found levels of dieldrin in breast milk to be between 0.77-35.5 ng/g lipid.[41] Similar levels have been found in other industrialised nations, such as Canada, Germany, Sweden and Japan. However levels remain much higher in nations such as Kenya where the use of dieldrin is reported as continuing[30] even though Kenya has also ratified the convention

The effects of dieldrin on humans

Exposure to dieldrin can cause both acute and chronic adverse consequences for humans and other mammals. Acute exposure results in symptoms such as headache, dizziness, nausea and vomiting, muscle twitching and convulsions.[42] Small quantities of dieldrin have a low acute toxicity. The median lethal dose (LD50) of dieldrin in rats is 46 mg/kg and that of Aldrin is 39 mg/kg.[43] The bioaccumulation of dieldrin can have important chronic consequences, including stimulation of the nervous system, hepatocarcinogenicity, renal toxicity, oestrogenic effects leading to cancers, altered fertility, and birth defects, and involvement in the aetiology of Lewy body diseases. To undertake a full review of the pharmacodynamics of these effects is outside the scope of this paper. We will discuss neurotoxicity and oxidative stress, immunological effects, and oestrogenicity.

Mechanisms of action

Neurotoxicity

Neurotoxicity is the primary effect of acute or chronic exposure to high doses of aldrin or dieldrin, leading to hyperexcitation and generalised seizures. It is probably the result of oxidative stress.

Oxidative Stress

Oxidative stress resulting from dieldrin or aldrin exposure can have a variety of other adverse effects. Oxidative stress leads to mitochondrial dysfunction, protein aggregation and apoptosis. In specific areas of the brain, oxidative stress can lead to Parkinson's disease. Pesticides are likely to be causally involved in the aetiology of Parkinson's disease and may also be a cause of Lewy body disease. In mice studies, oxidative stress has been linked to hepatocarcinogenicity. However, the results of such studies cannot reliably be extrapolated to humans. It is evident that many of the adverse effects of dieldrin exposure are brought about by oxidative stress; interestingly, antioxidant supplementation has been shown to prevent dieldrin-induced cellular changes.[44] However, evidence that anti-oxidant supplements can improve human health (rather than when consumed *in situ* as part of a varied diet) is much more limited. In fact, the reverse may be true.[45]

Immunological effects

It has been suggested that POPs, including dieldrin, may be responsible for the dramatic rise in allergy related illness.[38] Low level persistent organic pollutant exposure has been linked to decreased type-1 reactions and increased type-2 reactions which may promote allergic disease.[46] It has also been shown that oestrogenic environmental pollutants enhance the degranulation of mast cells by physiological oestrogens.[46] However, Noakes *et al.* (2001) showed that allergic disease is still increasing despite a decrease in the exposure to dieldrin and other persistent organic pollutants.[38] There are also claims that POPs may be causally associated with diabetes.[47]

Oestrogenic effects

Chlorinated hydrocarbons (including dieldrin and aldrin) are endocrine disruptors, with oestrogenic properties.[34] This xeno-oestrogenicity is thought to be the mechanism of their oncogenic effects.[34] Although the known xeno-oestrogens have a much lower oestrogenic potency than oestradiol,[48] humans may be exposed to more than one xeno-oestrogen, which may act synergistically.[49] Xeno-oestrogens are thought to be a cause of endometriosis, as well as breast, testicular, and prostate cancers.(50-52) One study found that fat tissue samples from boys operated on for cryptorchidism contained higher levels of pesticides than similar samples from a control population of boys operated on for other reasons.[53] Carenno *et al.* have suggested that exposure to persistent organochlorines have long-term effects on their fertility and reproductive tracts in males.[54] The potential association between dieldrin exposure and breast cancer will be discussed separately later.

Contradicting this are studies which have shown that dieldrin is weakly oestrogenic at best.[48, 55, 56] Others have failed to shown any oestrogenicity.[49, 55, 57]

Dieldrin and Breast Cancer

Breast cancer is the second most frequent cancer in the world[58] and the leading cause of global cancer mortality in women.[1] The incidence of breast cancer in Australia has steadily increased from 5,318 cases in 1983 to 12,027 cases in 2002 (i.e. at a rate higher than population increase or ageing). The 2006 publication, *Breast Cancer in Australia*, by the National Breast Cancer Centre and the Australian Institute of Health and Welfare predicted that there would be 13,261 women diagnosed with breast cancer that year and almost 15,000 cases in 2011 (refer to Table 2).[59] Ascertainment bias - earlier detection of breast cancer due to new technologies and screening methodologies - especially via the National Breast Cancer

Screening Mammography Program, BreastScreen Australia, explains part of this increased incidence. The target population for screening is women aged 50-69 years. The greatest increase in breast cancer rates was observed in the 60-64 year age group, where the incidence rate (per 100,000 women) increased from 216 in 1992 to 334 in 2002. An increase in the incidence rate of breast cancer was also found in the 65-69 year old age from 264 to 362 per 100,000 for the same time periods. Earlier detection has also meant that some cases are detected before they have become invasive, and are therefore curable. It is also possible that some cases of breast cancer are now diagnosed which would never have become invasive.

In Australia a woman's risk of dying from breast cancer before the age of 85 has decreased from 1 in 29 in 1983 to 1 in 36 in 2004. The age-standardised death rate for breast cancer has also dramatically decreased from 31 deaths per 100,000 women in 1990 to 23 deaths per 100,000 in 2004. In 2004, 2,641 women and 20 males died from breast cancer.[59]

The best-known risk factor for breast cancer is considered to be exposure to excessive oestrogen. Established mechanisms for this include early menarche, nulliparity, late conception, late menopause and hormone replacement therapy (HRT).[60] Many of these factors have increased in Western countries, and the recent reduction in HRT in the US and elsewhere has been credited for a recent and welcome decline in the incidence of post menopausal breast cancer.[61]

The increasing trend in the incidence of breast cancer, including, perhaps among younger women(1) is unlikely to be fully explained by changes in these known risk factors, nor by improved screening, leading to the hypothesis that there are other environmental factors still to be identified. Other evidence in support of this hypothesis is the significant international differences in the incidence of breast cancer,as well as the shift of risk seen among many migrants.[58, 62]

In this context, it is unsurprising that the widespread use of organochlorine compounds has been hypothesized as an explanation. Suspected POPs include dieldrin, DDT, chlordane and lindane.

***Table 2*:** Incidence of breast cancer in Australia, 1983 to 2002 and projections to 2011

	1983	1987	1992	1997	2002	2006[a]	2011[a]
				New cases			
Breast cancer (females)	5,318	6,680	8,022	10,175	12,027	13,261	14,818
Breast cancer (males)	43	56	47	71	84	106	122
				Age-standardised rate (number per 100,000 population[b])			
Breast cancer (females)	80.0	91.1	98.1	111.3	116.8	117.3	117.3
Breast cancer (males)	0.8	0.9	0.7	0.9	0.8	1.0	1.0

(a) AIHW projections.

(b) Standardised to the 2001 Australian standard population.

Source: National Cancer Statistics Clearing House, AIHW.

How might dieldrin cause breast cancer?

The mechanism by which dieldrin may increase the risk of breast or uterine cancer has two leading hypotheses: by oestrogenic or immunological effects. These mechanisms could also act synergistically. High levels of organochlorines in contaminated fish have been shown to depress natural killer cell numbers.[63] These cells are crucial in immunological defense against the early stages of cancer.[24]

However, there is a contradictory and sometimes controversial literature concerning the oestrogenicity of dieldrin. The most frequently cited evidence for the oestrogenicity of dieldrin is the positive response documented in the E-SCREEN assay, which measures cell proliferation in an oestrogen-dependent MCF-7 breast tumour cell line. This study found dieldrin was oestrogenic, but only at the highest concentration tested (10 µM). This demonstrates a potency of dieldrin comparable to that of DDT, but six orders of magnitude lower than that of oestradiol.[48]

Researchers have not been able to demonstrate an oestrogenic uterotropic response to dieldrin in *in vivo* tests using immature rat or mouse uteri.[57, 64] The ability of dieldrin to displace titrated oestradiol from oestrogen receptors has been demonstrated, although only at low levels of oestradiol, in some,[64, 65] but not all animal studies.[49, 57] However, it has been argued that these competitive ER-binding assays may not reflect the true ability of dieldrin to compete with oestradiol for oestrogen receptors due its lipophilic nature and low aqueous solubility.[55] Studies using fluorescence polarization (FP), a method which measures the ability of a chemical to displace a high-affinity fluorescent ligand from purified, recombinant human oestrogen receptor, have shown that dieldrin has some capacity to inhibit binding of oestradiol to purified human oestrogen receptor. However this capacity is low, with oestradiol binding inhibited less than 25% at the maximal dieldrin concentration tested of 2×10^{-5} µM, oestradiol binding was inhibited less than 25%.

One study has demonstrated that dieldrin may act as an antiandrogen. Dieldrin induced a 30% inhibition of tritiated 5dehydrotestosterone binding to rat prostate androgen receptor.[57]

It is extremely unlikely that a woman would be exposed to only one organochlorine in isolation. Human and wildlife are simultaneously exposed to a variety of chemical residues, which coexist in the fat and body fluids, hence it is likely that they may become bioavailable in combination and act synergistically.[48] There is limited evidence for a synergistic effect of mixed oestrogenic chemicals. It was found using the E-SCREEN assay that a mixture of 10 oestrogenic chemicals including dieldrin produced significant oestrogenic effect at concentrations 10-fold lower than those required to produce an oestrogenic effect when given alone.[48] Another study by Arnold *et al.*, reported in Science in 1996, found combinations of environmental chemicals including dieldrin, endosulfan and toxaphene produced oestrogenic effects 1000 times that of the chemicals in isolation.[49] However, this report was later withdrawn after the researchers failed to replicate their earlier results.[49]

Evidence for a causal relationship between dieldrin exposure and breast cancer

The evidence for an association between dieldrin exposure and breast cancer risk has been mixed. The issue is extremely difficult to study epidemiologically, and is fraught with problems of measurement, lag effects and ethics. A number of studies have reported higher concentrations of certain organochlorine pesticides, including dieldrin in the blood or adipose

tissue of breast cancer patients than in controls while others have reported similar levels in cases and controls. However, since the incubation of breast cancer is thought to be lengthy – probably decades – the concentration of any chemical at the time of diagnosis does not necessarily correlate with that at the time of cancer initiation This is crucial information if exposure to that chemical is genuinely causal.

An ingenious prospective nested case-control study by Danish researchers published in 1998 provided some important insights into the issue of a variety of organochlorine compounds and the causation of breast cancer.[66] Its strengths included a prospective design, a long follow-up and well-characterised participants, who were selected independently of risk of developing breast cancer from a well-defined homogeneous population that represented a fifth of the background population in the study area. Measurement of organochlorine concentrations for most women was based on blood samples taken several years before the diagnosis of breast cancer, which had been done in only one previous study.

The researchers studied a population of 7,712 women enrolled in the Copenhagen City Heart Study. Serum samples were obtained from participants from 1976 to 1978. In 1996-1997, researchers analysed serum samples from 240 women who had developed invasive breast cancer and 477 matched breast cancer-free controls for levels of kepone, dieldrin, *o,p´*-DDT, *p,p´*-DDT, ß-hexachlorocyclohexane, and several PCB congeners. Controls and cases were matched for age, date of examination, and vital status at the examination. Data were obtained on potential confounding factors including weight, height, number of full-term pregnancies, alcohol consumption, smoking, physical activity, menopausal status, household income, marital status, and education. Dieldrin was detected in 78% of all women enrolled in the study, with median levels at 24.4 ng/g lipid. No relationship with breast cancer was detected for the serum levels of several PCB congeners, DDE or DDT, or ß-hexachlorocyclohexane. However, this was not the case for dieldrin.

Women with the highest quartile of dieldrin had double the risk of breast cancer compared to women in the lowest quartile (OR 2.25, 95% CI 1.32-3.84, *p* trend = 0.003). Relative risks remained unchanged (OR 2.05, 95% CI 1.17-3.57, *p* trend = 0.01) when adjusted for confounding factors (number of full-term pregnancies and weight).

A subsequent study using the same cohort of Danish women also found that past exposure to dieldrin affected the risk of developing breast cancer and survival post-diagnosis.[67] Researchers obtained serum from 195 women with breast cancer who provided blood samples during the two collections in 1976-1978 and 1981-1983. These samples were analysed for dieldrin levels. The Causes of Death Registry from the Danish National Board of Health was the source of information for the causes and dates of death. Those with the highest blood dieldrin levels from the 1976-1978 blood collection had significantly higher risks of dying than those with the lowest levels [relative risk (RR) 2.78, 95% CI 1.38-5.59, *p* trend < 0.01; highest quartile compared to lowest quartile]. When the analysis was performed using an average of the blood dieldrin levels from the two collections, the association was even stronger, with a 5-fold higher risk of dying in women from the highest compared to the lowest quartile (RR 5.76, 95% 1.86-17.92, *p* trend < 0.01). In both analyses, relative risks were adjusted for number of positive lymph nodes, tumour size and grade.

In contrast, an American prospective cohort study found an association between hexachlorobenzene and breast cancer, but not with dieldrin.[68] Blood samples were donated by 7,224 women in this cohort from 1977 to 1987. During a follow-up period of up to 9.5

years, 105 women developed breast cancer; each was matched to two controls based on age and date of blood collection. Dieldrin was detected in serum at levels above the limit of detection in 56.2% of the cases and in 61.8% of the controls. The relative risk of breast cancer in relation to serum dieldrin levels was not significantly different when the highest quartile was compared to the lowest quartile (RR 0.6, 95% CI 0.3-1.3, $p = 0.38$). Dieldrin was detected in a lower proportion of samples, and follow up was significantly shorter.

An ecological study was conducted in 1993 in rural Victoria to examine the association between dieldrin contamination as measured in breast milk samples and breast cancer incidence.[37] Standardised incidence ratios (SIR) for breast cancer from 1983 to 2002 were calculated for the 11 rural regional areas of Victoria. The study found that the region most contaminated with organochlorine pesticides showed an elevated SIR of 1.10 (95%CI, 1.03–1.17), but also found two other regions with lower organochlorine contamination levels also had an elevated SIR. The study did not find any significant correlation between organochlorine contamination and the age-standardised rate of breast cancer across all regions.[37] Refer to Table 5, Appendix 3.

Two studies have found an association between breast cancer and blood levels of organochlorines other than dieldrin. A Belgian study compared blood levels of total DDT and HCB in samples collected from 158 women at the time of breast cancer discovery, with levels in samples from 250 presumably healthy controls.(19) Mean levels of total DDT and HCB were significantly higher for breast cancer patients than for controls. No differences in serum levels of total DDT or HCB were found between oestrogen receptor positive and oestrogen receptor negative patients with breast cancer.[69] A Mexican case control study found that high levels of exposure to DDE as detected by serum levels may increase women's risk of breast cancer, particularly postmenopausal women.[70]

Other studies have reported similar levels of organochlorines in cases and controls. An American prospective investigation of breast cancer and organochlorine exposure found no evidence for an association of breast cancer risk with DDE or PCB levels in the blood nor with their elimination half-lives.[71] A nested case control study in which included 382 women with pre- or post-menopausal breast cancer had similar findings.[72]

In almost all of the studies evaluating the association between environmental chemicals such as dieldrin or other organochlorines, the samples taken for the detection of the chemical only provide a snapshot of exposure. While some studies have had more than one sample of tissue over time,[66, 71, 73] most are just a one-off sample.[34] As dieldrin is a bioaccumulant, it has been suggested that one-off samples can be accurate biomarkers of exposure.[34] However, this does not take into consideration the fact that some women may have a faster metabolism of dieldrin, excrete more through breast milk, have had rapid weight loss, increased parity, or decreased exposure over time. Moreover the half-life for dieldrin elimination is estimated to be only 369 days;[21] thus a woman's entire exposure history is impossible to ascertain.[37] These factors make it difficult to make conclusions on the relationship of dieldrin exposure to breast cancer risk on the basis of current evidence. Without further research with larger sample sizes, it cannot be said that is not statistically significant or just due to small sample sizes.

Carcinogenesis is a complex and multi-step process where it is hypothesised that multiple non-lethal insults act cumulatively over time to bring about dysregulation of cells. The

development of breast cancer in most women is probably multifactorial, with no one exposure accounting solely for the process.

If exogenous hormones raise the risk of breast cancer then exposed women should have increased incidence of the disease. In the case of exposure to dieldrin it appears that this question will be difficult to prove or disprove. This has been the case for other exogenous hormones. For example very high doses of diethylstilboestrol (DES) given to pregnant women were shown to cause an increased incidence of clear-cell adenocarcinoma of the vagina and cervix in daughters exposed *in utero.*[74] For many years this was thought to be the only risk associated with high-dose DES. However, after 20 years of follow up, researchers discovered that the mothers themselves had a 35% increase in breast cancer risk.[75] This example illustrates both the long latent period between exposure and appearance of disease symptoms[22] and the need for well designed studies with long follow-up periods, such as the Hoyer study, in evaluating the relationship between dieldrin and breast cancer risk.

Apart from a long latent period between exposure and the appearance of symptoms, there may be other reasons why demonstrating a link between exposure to hormones or substances with hormone-like action and breast cancer may be difficult. Several reasons have been proposed which may be relevant to dieldrin: i) Hormone abnormalities may be transient and only present at crucial inductive times; ii) Small and therefore difficult-to-detect differences in hormone levels may become determinant if maintained over a long period of time; iii) End organ sensitivity is as important as hormone levels; and iv) Cancer promotion is dependent upon particular fractions or combinations of hormones and tissues rather than circulating levels.[22]

Areas highlighted for future research include women with a genetic susceptibility to breast cancer.[34, 71] The effects of OCPs and dieldrin on these women require further investigation with larger sample sizes, and preferably with several tissue samples over a longer period of time. Some studies have indicated that there may be a race effect of OCP exposure and breast cancer, with African American women at higher risk of breast cancer.[34, 71] The effects of dieldrin in these populations are still uncertain and therefore will also require further investigation.

In 1994 Newcomb *et al.* showed that a history of lactation was in fact a protective factor in pre-menopausal breast cancer, suggesting that there was excretion of carcinogens in the breast milk.[76] In women, lactation is the single most effective pathway of organochlorine excretion, thereby providing a putative protective effect due to elimination.[24] The next question though, is whether or not that risk of breast cancer is then passed onto the nursing infant.

Effects of dieldrin on the infant

Infants can be exposed to dieldrin *in utero* via the placenta, postnatally as a result of breast-feeding and later through the food that they eat. During pregnancy and lactation, there is increased mobilisation of fat stores, leading to increased levels of dieldrin in the maternal blood stream and exposure of the infant to the pesticide.

Placental transfer of dieldrin

In a study of Nicaraguan mothers published in 2001, dieldrin was found in nearly 20% of cord blood samples.[77] In 2007 Shen *et al.* found dieldrin in the placenta of Finnish and Danish mothers, 1.35 and 2.55ng/g lipid respectively, thus implying that the exposure starts from the time of conception.[77, 78] It has been found that perinatally, foetal blood contains higher levels of dieldrin than maternal blood (1.22mg/kg vs. 0.53mg/kg) and that dieldrin levels are higher in the placenta (0.8 mg/kg) than the uterus (0.54 mg/kg).[9, 79] The proportion of adipose tissue is low in the foetus until the later stages of pregnancy thus indicating that although they may be exposed via the cord blood and placenta, they do not have the same ability to store the organochlorines as adults.[78] Shen *et al*. also suggested that the infant got a greater exposure to dieldrin from the breast milk than through the placenta.[78]

Transfer of dieldrin through breast milk

As previously mentioned, dieldrin accumulates in breast milk, and there is certainty that dieldrin is passed onto the infant via the breast milk. Studies of breast milk have shown that the levels of OCPs, dieldrin and other environmental contaminants decrease with the duration of lactation and the number of pregnancies;[28, 36] therefore the level of exposure to infants in subsequent pregnancies is that what you mean? It was unclear is likely to be less. However, the longer a child is breastfed, the higher the exposure of the child and their level of dieldrin.[78] While this may be beneficial to the mother, what is the risk to the child? Studies looking at life time total exposure of OCPs and PCBs showed that 12% and 14% for males and females respectively was acquired just from being breast fed for 16 months. The other large proportion of exposure came from eating large amounts of dairy products as a toddler.[80] An Australian study published in 1993 found dieldrin in all samples taken, and in 90% of cases the level was above the WHO ADI guidelines.[35] As already mentioned, these levels had decreased to almost undetectable levels by 2002.[38] However, the long term effects of this high exposure to dieldrin on the children breastfed during the late 1980s and early 1990s has not been investigated. It would be interesting to do a follow up study of these children to see what the health implications have been and the rates of breast cancer. Although dieldrin levels in breast milk have been declining since they were first measured in the 1970s, the chemical still contaminates breast milk of Australian mothers, and levels should continue to be monitored as exposure to the pesticide can have negative consequences for the infant.

Impact of dieldrin on the infant

The effects of OCPs on infants are still not fully understood, but OCP exposure has been linked with a number of adverse outcomes including cryptorchidism[41] and other developmental problems. Przyrembel *et al.* believe that OCPs that cross the placenta are more likely to affect the cognitive function and physical development of the child than OCPs that the infant is exposed to postnatally.[81] A study in 1998 by Pantadin found that children with high levels of PCBs exposure *in utero* did have lower birth weights and reduced postnatal growth up to three months of age, however, more studies need to be carried out to test this hypothesis.[80] There have also been some suggestions that the levels of OCPs and other pollutants may be altering the gender ratio and resulting in more females being born.[82]

Conclusion

Despite the relatively convincing evidence from Høyer *et al.*[66] that an association between dieldrin and breast cancer does indeed exist, subsequent studies have been inconclusive. There are several plausible factors that are likely to have contributed to this doubt. These include insufficient lengths of follow up, insufficient tissue samples to account for the bioaccumulation of dieldrin, individual variation in the rate of metabolism of dieldrin, varying levels of excretion of dieldrin in the breast milk and finally the long half life makes it very difficult to determine the actual exposure to dieldrin. For these reasons we cannot claim that reducing the dieldrin load via breast-feeding is a major mechanism to explain the reduction in risk of breast cancer which we know does occur to women who breast feed, especially if such feeding is prolonged and starts fairly early in the reproductive life of the woman.

Although it is clear that dieldrin does pass into the breast milk and the short-term effects on the infant are known, the long-term effects for an infant exposed to dieldrin are still unknown. Furthermore, the effect on the infant's subsequent risk of breast cancer is an area which requires more research. Finally, while we applaud the banning of the "dirty dozen" POPs in terms of public health, there are many other substances still in widespread use which have uncertain health consequences. Where possible it is desirable to limit human exposure to these substances, some of which may act similarly to dieldrin, or in synergy with it.

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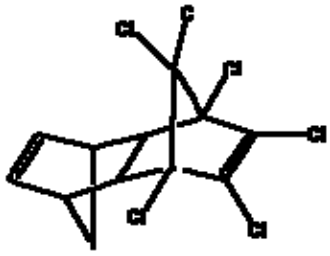
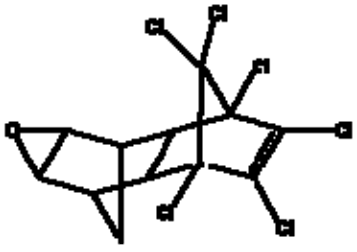
APPENDIX 1:

The chemical nature and physical properties of dieldrin

Figure 1: Chemical Structure of Aldrin and Dieldrin http://ntp.niehs.nih.gov/ntp/htdocs/structures/2d/TR021.gif



Aldrin $C_{12}H_8Cl_6$



Dieldrin $C_{12}H_8Cl_6O$

Table 3: Physical and Chemical Properties of Aldrin and Dieldrin (adapted from U.S. Dept of Health & Human Services, 2002, http://www.atsdr.cdc.gov/toxprofiles/tp1-c4.pdf)

Property	Aldrin	Dieldrin
Molecular weight	364.91	380.91
Colour	White (pure); tan to brown (technical Grade)	White (pure); light brown (technical grade)
Physical state	Crystalline solid[b]	Crystalline solid[b]
Melting point	104–105.5 ºC c; 49–60 ºC (technical grade)c	176–177 ºC c; 95 ºC (technical grade)d
Boiling point	Decomposes[e]	Decomposes[e]
Density	1.6 g/L at 20 ºC[f]	1.75 g/L at 25 ºC[f]
Odor	Mild chemical odour[e]	Mild chemical odour[e]
Odor threshold: Water Air	No data 0.017 mg/kgc	No data 0.041 mg/kgc
Solubility: Water at 20 ºC Organic solvents	0.011 mg/L[g] Very soluble in most organic solvents[b]	0.110 mg/L[g] Moderately soluble in common organic solvents except aliphatic petroleum solvents and methyl alcohol[b]
Partition coefficients: Log Kow Log Koc	6.50[h] 7.67[i]	6.2[c] 6.67[i]
Vapor pressure: at 20 ºC at 25 ºC	7.5x10-5 mmHg[b] 1.2x10-4 mmHg	3.1x10-6 mmHg[b] 5.89x10-6 mmHg[j]
Henry's law constant: at 25 ºC	4.9x10-5 atm-m3/mol[k]	5.2x10-6 atm-m3/mol[k]
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	Nonflammable[f]	Nonflammable[f]
Conversion factors	1 ppm=14.96 mg/m3 at 25 EC, 1 atm	1 ppm=15.61 mg/m3 at 25 EC, 1 atml
Explosive limits	Stable[f]	Stable[f]

All information obtained from HSDB 2001a or 2001b unless otherwise noted.
[b]Budavari et al. 2001
[c]Verschueren 2001
[d]Hayes 1982
[e]NIOSH 1997
[f]Weiss 1986
[g]Bus and Leber 2001
[h]Hansch et al. 1995
[i]Briggs 1981
[j]Grayson and Fosbraey 1982
[k]Guerin and Kennedy 1992
[l]EPA 1987a

APPENDIX 2: "The dirty dozen"

Aldrin – A pesticide applied to soils to kill termites, grasshoppers, corn rootworm, and other insect pests.

Chlordane – Used extensively to control termites and as a broad-spectrum insecticide on a range of agricultural crops.

DDT – Perhaps the best known of the POPs, DDT was widely used during World War II to protect soldiers and civilians from malaria, typhus, and other diseases spread by insects. It continues to be applied against mosquitoes in several countries to control malaria.

Dieldrin – Used principally to control termites and textile pests, dieldrin was also used to control insect-borne diseases and insects living in agricultural soils.

Dioxins – These chemicals are produced unintentionally due to incomplete combustion, as well as during the manufacture of certain pesticides and other chemicals. In addition, certain kinds of metal recycling and pulp and paper bleaching can release dioxins. Dioxins have also been found in automobile exhaust, tobacco smoke and wood and coal smoke.

Endrin – This insecticide is sprayed on the leaves of crops such as cotton and grains. It is also used to control mice, voles and other rodents.

Furans – These compounds are produced unintentionally from the same processes that release dioxins, and they are also found in commercial mixtures of PCBs.

Heptachlor – Primarily employed to kill soil insects and termites, heptachlor has also been used more widely to kill cotton insects, grasshoppers, other crop pests, and malaria-carrying mosquitoes.

Hexachlorobenzene (HCB) – HCB kills fungi that affect food crops. It is also released as a byproduct during the manufacture of certain chemicals and as a result of the processes that give rise to dioxins and furans.

Mirex – This insecticide is applied mainly to combat fire ants and other types of ants and termites. It has also been used as a fire retardant in plastics, rubber, and electrical goods.

Polychlorinated Biphenyls – These compounds are employed in industry as heat exchange fluids, in electric transformers and capacitors, and as additives in paint, carbonless copy paper, sealants and plastics.

Toxaphene – This insecticide, also called camphechlor, is applied to cotton, cereal grains, fruits, nuts, and vegetables. It has also been used to control ticks and mites in livestock.

APPENDIX 3

Australian legislation and regulations controlling the use of dieldrin.

Table 4: Legislation and Regulations implemented by the Australian Government in regards to Dieldrin and other POPs.

Legislation	Website address
Agricultural and Veterinary Chemicals (Administration) Act 1992	http://www.austlii.edu.au/au/legis/cth/consol_act/aavca1992511/
Agricultural and Veterinary Chemicals (Administration) Regulations 1995	http://www.austlii.edu.au/au/legis/cth/num_reg_es/aavcr1995n28647.html
Customs Act 1901	http://www.austlii.edu.au/au/legis/cth/consol_act/ca1901124/
Customs (Prohibited Exports) Regulations 1958	http://www.austlii.edu.au/au/legis/cth/consol_reg/cer1958439/
Customs (Prohibited Exports) Regulations 1956	http://www.austlii.edu.au/au/legis/cth/num_reg_es/cear200442004n244573.html
Environment Protection and Biodiversity Conservation Act 1999	http://www.austlii.edu.au/au/legis/cth/consol_act/epabca1999588/
Product Stewardship (Oil) Amendment Regulations 2003 (no 1)	http://www.austlii.edu.au/au/legis/cth/num_reg_es/psar200312003n47518.html
Hazardous Waste (Regulation of Exports and Imports) Act 1989	http://www.austlii.edu.au/au/legis/cth/consol_act/hwoeaia1989548/

Table 5: Summary of number of breast cancer cases and dieldrin exposure from three studies.

Study	Yr dieldrin measured	Location	Max f/up (years)	Pop studied	Breast Ca cases	Av level (ng/gm)	Dieldrin detection	Cancer diagnosis
Høyer	76-78	Denmark	(19-20)?	7712	240	24.4	78%	1978-1998(?)
Dorgan	77-87	Missouri	9.5	7224	105	?	56-60%	?1986-1996
Khanjani	?	Victoria				>29 ppb		1983-2002

Referenced from: (37, 66)

GLOSSARY OF ABBREVIATIONS

ADI – Acceptable daily intake
AIHW – Australian Institute of Health and Welfare
DDT – Dichloro-Diphenyl-Trichloroethane, chemical name 4,4'-(2,2,2-trichloroethane-1,1-diylbis-chlorobenzene
DES – Diethylstilboestrol
FP – Fluorescence polarization
HCB Hexachlorobenzene
HRT Hormone replacement therapy
OCPs Organochlorine pesticides
PCPs Polychlorinated biphenyls
POPs Persistent organic pollutants
SIR Standardised incidence ratios WHO World Health Organisation

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