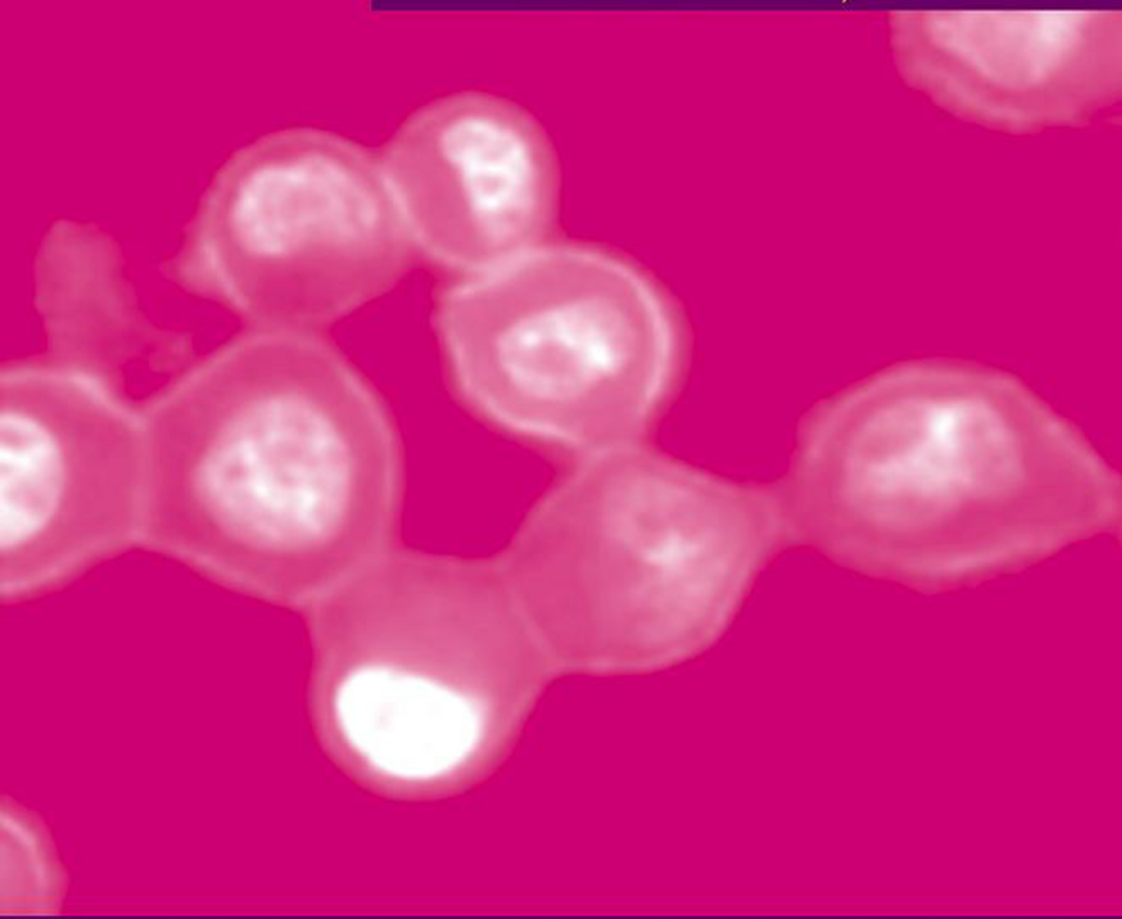
PESTICIDES & BREAST CANCER
A WAKE UP CALL

MERIEL WATTS, PHD



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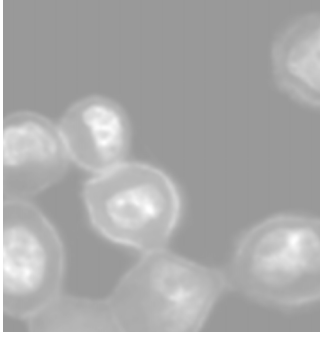

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PESTICIDE ACTION NETWORK ASIA & THE PACIFIC

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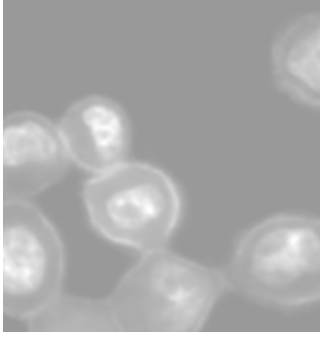

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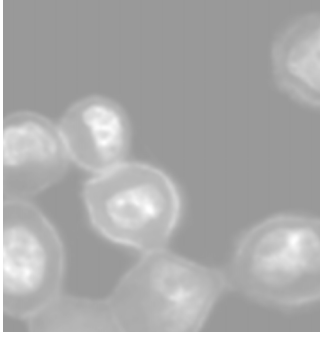
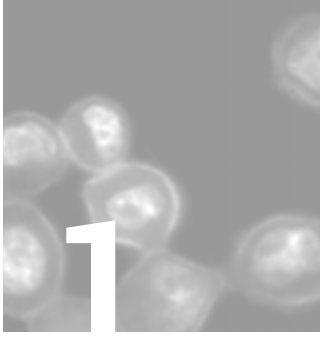


The focus of this book is on breast cancer in the wider Asia Pacific region, an area generally underrepresented in the scientific literature on breast cancer. Almost all epidemiological studies have been carried out in the US or Europe. Yet breast cancer is escalating in the Asia Pacific region—in fact New Zealand has one of the highest incidence rates in the world. In many of the developing countries of the region there are serious problems with pesticide use, and many women are grossly overexposed to them. Yet where are the epidemiological studies?

Despite this focus on the Asia Pacific region, most of the material in the book, especially that showing how 98 pesticides, plus one adjuvant and two contaminants, may be implicated in the global breast cancer epidemic, is applicable to all countries that use pesticides.



1 INTRODUCTION

Poisoning from exposure to pesticides is a problem the world over, but most especially in developing countries and most especially for women. Acute poisoning kills, maims or debilitates many millions of women each year.

There is no accurate data on the true extent of the effects of pesticides: often symptoms are not recognised by either victims or medical personnel as resulting from pesticides, and underreporting is endemic in all countries but especially in poorer nations where few workers have access to medical personnel. In Central America the under-reporting rate has been documented as 98 percent (Murray et al 2002). Estimates of acute poisoning of agricultural workers range from 1-5 million (UNEP 2004), through 25 million in developing countries alone (Jeyaratnam 1990) to 50-100 million (Kaosa-ard & Rerkasem 1999). These figures do not include poisonings resulting from household or public authority use, non-agricultural occupational exposures, or 'bystander' exposure; nor do they include chronic effects such as cancer. An estimated 99 percent of acute poisoning deaths are believed to occur in developing countries (WHO 1990).

Women account for more than 50 percent of the agricultural labour force in Asia (IFAD 2002). In Bangladesh, Cambodia, China, India, Lao PDR, Viet Nam, and India more than 70 percent of women are employed in agriculture, with this figure rising to 98 percent in Bhutan and Nepal. In the Pacific Islands women's engagement in agriculture varies from a low of 1-3 percent in the atoll countries like Kiribati and Marshall Islands, to a high of 80 percent in Vanuatu, 84 percent in Papua New Guinea, and 85

percent in the Solomon Islands. In Australia the figure is only 4 percent and in New Zealand 6 percent (Balakrishnan & Fairbairn-Dunlop 2005).

They are severely over-exposed to pesticides, especially women in the Asian countries.

No attempts have been made to estimate how many of these women are affected by chronic poisoning caused by exposure to pesticides. How many suffer and die from breast cancer to which pesticides have contributed will probably never be known.

Women in poorer developing countries are much more vulnerable to exposure to pesticides than other agricultural workers for many reasons, including lesser control over their ability to avoid pesticides, and greater susceptibility to the effects of those pesticides. Women in developing countries are the ones most affected by economic policies rooted in structural adjustment programmes, WTO trade rules, privatisation of community resources, and other equally discriminatory programmes of the global economic agenda driven by the giant transnational corporations and the western G8 governments. These polices have resulted in the intensifying of corporate control over land and agricultural inputs. They have caused increasing displacement of women in agriculture, increasing unemployment and loss of skills; and loss of women's control over the seeds that have for centuries been their domain and conferred their status in society, thus even further eroding their control over their own lives. Women who were once self-sufficient farmers have become displaced menial workers in the most marginal positions in the workforce, driven further into poverty. Women comprise an estimated 70 percent of the world's 1.3 billion absolute poor. The number of rural women living in poverty has almost doubled in the last 20 years (Holla 2005).

Many of these women have been driven into the plantation sector or into other forms of corporate cash cropping (such as floriculture) where their exposure to pesticides has increased dramatically. In some countries women make up 85 percent or more of the pesticide applicators on commercial farms and plantations, often working whilst pregnant or breastfeeding. There are an estimated 30,000 women pesticide sprayers in Malaysia alone. They spray pesticides, and frequently highly toxic ones like paraquat, on average 262 days per year. Eighty percent of the spraying is carried out with leaky hand-held spray equipment. Because of their poverty, an incentive of only 50 cents extra per day offered by the management is enough to encourage women to spray (Joshi et al 2002).

Even if they do not directly apply the pesticides, women work and raise their children in a toxic environment—mixing the pesticides, weeding while they are being applied, washing out the pesticide containers, or harvesting the pesticide-doused crops. They wash pesticide-soaked clothing and store pesticides in their homes—there is nowhere else to store them. In Chile there are at least two reported poisoning epidemics amongst women working in recently sprayed fields: in 1996, 58 of 64 reported poisonings were women; and in 1997, of the 120 reported poisonings 110 were women, nearly all employed in the flower industry (Wesseling et al 1998).

Data collected from developing countries show that women's exposure to pesticides is significantly higher than is formally recognized, and that pesticide poisonings are greatly underestimated for women. Given that most episodes of acute pesticide poisoning appear to escape the attention of medical authorities—and this is more recognisable than chronic effects—it is not surprising that so little is known about the relationship between exposure to pesticides and breast cancer. A study that tracked the pesticide usage of 50 Viet Namese farmers for one year found that they suffered 54 moderate poisonings per month, but only two cases per month were treated at the local health centre (Murphy et al 2002).

These problems are compounded by gender biases in epidemiology (London et al 2002). Most researchers looking at links between cancer and farming have concentrated on male farmers (Miligi & Settimi 2003), and as will become evident in Chapter 4 there have been very few epidemiological studies investigating a potential link between exposure to pesticides and breast cancer, especially those pesticides in current usage.

Women's greater vulnerability to pesticides is also overlooked in the toxicological risk assessment of pesticides (London et al 2002). Women's higher proportion of body fat provides a greater reservoir for fat-loving pesticides, some of which are known to be hormonally active and/or carcinogens, and are associated with breast cancer. Women may also absorb pesticides through their skin more easily than men—dermal absorption of the organochlorine lindane has been found to be three times greater for women than for men (Pesticides Safety Directorate 1999). And once there, fat-loving pesticides may reside in the body longer in women than in men (Hardell 2003). Women's higher level of hormonally sensitive tissues make them more vulnerable to the effects of pesticides, especially those that are hormonally active known as endocrine disruptors. These pesticides are capable of effecting profound changes on hormonally sensitive tissues—

such as breast tumours. Increased fat exchange, for example during pregnancy and lactation, together with the cyclic nature of hormonal changes, add to that greater sensitivity (Howard 2003).

Lastly, where there is poverty there is malnutrition, and especially for women for they are the ones that eat last, the least and the left-overs. Malnutrition can enhance the adverse effects of pesticides. Low levels of dietary protein enhance vulnerability to organophosphate insecticides (Pronczuk de Garbino et al 2003). Low levels of dietary protein are also known to increase the toxicity of diuron, a known mammary carcinogen (Boyd & Krupa 1970). The toxic effects on liver, kidneys and muscle tissue of a mixture of monocrotophos, hexachlorocyclohexane (HCH) and endosulfan were aggravated by malnourishment in laboratory tests (Benjamin et al 2006)—and HCH and endosulfan are also associated with breast cancer. Malnutrition leads to weakened immune systems. Malnutrition of the pregnant woman leads to underdevelopment of the unborn child, paving the way for chronic ill health later in life (James 2006). These effects can contribute to an increased risk of breast cancer.

As women's poverty and marginalisation has deepened, so has their exposure to pesticides increased. At the same time, that poverty has also increased their vulnerability to the pesticides, and to the development of chronic diseases such as breast cancer.

Not surprisingly the corporate economic agenda that has driven women into this position in the first place, has also failed to do anything to stop the escalating epidemic of breast cancer to which pesticides are undoubtedly contributing. The corporates have certainly contributed to the breast cancer research programme—but usually only in ways designed to enhance their own returns from the sale of screening equipment and expensive drugs. Whilst billions of dollars are being poured into an attempt to develop a vaccine against breast cancer, these corporates are contributing almost nothing to preventing breast cancer from occurring in the first place. With the vast majority of breast cancer thought to be caused by environmental and lifestyle factors (less than 10 percent is due to inherited genetic mutations), this is an eminently preventable disease. But most government breast cancer programmes, driven by the self-interest of drug companies and specialist medical sectors, continue to focus on understanding the genetic factors that underlie less than 10 percent of breast cancer cases, on early detection, and on treatment with increasingly expensive and sophisticated drugs like Herceptin. For example the USA's National Breast Cancer

Awareness month was founded and sponsored by Zeneca Chemicals, which ironically earns millions from sales of carcinogenic pesticides such as acetochlor on the one hand and, now as Astra Zeneca from the breast cancer treatment drug tamoxifen (which is itself carcinogenic) on the other hand (Cancer Prevention Coalition undated). Zeneca was a subsidiary of ICI chemicals. Zeneca/ICI pesticides that increase the risk of breast cancer included lindane, permethrin, cypermethrin and captan. Zeneca also purchased the largest for-profit chain of cancer treatment centres in the US, Salick Health Care Inc (Sherman 2000), neatly assuring profits from both the causing and the curing of breast cancer, as well as massaging their corporate image.

As Dr Devra Davis (2000), a Senior Adviser to the World Health Organisation, put it:

> ***"investments in controlling and studying avoidable environmental contributions to cancer remain scandalously low . . . fuelled by a sophisticated disinformation campaign of the tobacco industry—just confirmed by the WHO—we wasted 50 years debating the importance of cigarettes. We cannot afford to make the same mistake again."***

Pesticides that are carcinogenic, disrupt hormones, or in other ways disrupt the development of the mammary gland, are a significant environmental factor that contributes to the global breast cancer epidemic—one that has long been ignored. Numerous laboratory studies show that animal mammary carcinogens and pesticides which mimic oestrogen, or otherwise disrupt natural hormones, may be increasing breast cancer risk (Davis et al 1993; Wolff et al 1996; Snedeker 2001; Birmbaum & Fenton 2003; Brody & Rudel 2003; Evans 2006). Pesticides can also contribute to breast cancer by undermining the immune system, interfering with intercellular communication, and interfering with metabolic activities. Whilst increasing (but still insufficient) attention is now being paid to some industrial and household chemicals—such as phthalates, bisphenol A, polyvinyl chloride (PVC), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and dioxin—as known, probable, or possible causes of breast cancer (e.g. Evans 2006), scant attention is being paid to the role of pesticides. Generally only the organochlorine insecticides like DDT have been linked with breast cancer. But this review has, conservatively, identified 98 pesticides, plus one adjuvant and two contaminants, as potentially increasing the risk of breast cancer to a greater or lesser extent. Most of these, unlike the organochlorines, are still in widespread use in many countries.

A number of these pesticides are found as residues in women's breast milk, indicating exposure, not only to the women, but also to the newly-born child transferred in breastmilk. However this ***does not*** mean that breastfeeding should be replaced with bottle-feeding. Breastfeeding should be maintained because, despite the residues, it confers health benefits on both the infant and the mother. For example, it reduces the risk for mothers of developing uterine and breast cancer, especially for those women with the BRCA1 susceptibility gene, and especially premenopausal breast cancer (e.g. Zheng et al 2000c; Hejar et al 2004; Freund et al 2005; Leung & Sauve 2005; Kim et al 2007). Additionally having been breastfed reduces the risk of premenopausal but not postmenopausal breast cancer (Martin et al 2005). It is widely acknowledged that breastfeeding confers substantial benefits on babies, in the form of vital nutrients, growth factors and immunological components passed from the mother to baby, especially in the first few months of life. Breastfeeding reduces the risk of postneonatal death (Chen & Rogan 2004). It reduces the incidence and severity of infections, helps prevent the development of allergies, obesity, hypertension and insulin-dependent diabetes mellitus, and enhances cognitive development (Leung & Sauve 2005). Breastfeeding significantly develops the bonding process between mother and child, and helps prevent Sudden Infant Death Syndrome (Gordon et al 1999; McVea et al 2000). Breastmilk is the cheapest and best available food for newborn infants: it provides complete nutrition for the first six months and many benefits thereafter for the first two years and more of the child's life. This is vital for all infants but especially those in households that do not have enough to eat and where women and children are often nutritionally deprived. Therefore, in spite of concerns regarding chemical contamination, the advice from scientists and health professionals is to continue breastfeeding (Leung & Sauve 2005).

The solution to the problem of transferring residues to the infant is not to stop the breastfeeding but to stop the contamination of the breast milk in the first place, by stopping the use of the pesticides. In March 2004, the World Alliance for Breastfeeding Action (WABA) and the International POPs Elimination Network (IPEN) issued a joint statement (WABA & IPEN 2004), which acknowledged that:

> ***"The contamination of breastmilk is one symptom of the environmental contamination in our communities. Responsibility for this problem belongs to the industrial sources of contamination, not to breastfeeding women."***

Most of the pesticides implicated in breast cancer are still in common use because of the prevailing regulatory failure to access up-to-date independent scientific research, and to apply the precautionary principle. Instead regulators invariably rely on toxicological data provided by the pesticide manufacturers as 'proof' that a pesticide is 'acceptable' because it doesn't identify effects such as breast cancer. This regulatory approach, and national and international chemicals policy, is underpinned by an increasingly widely-applied paradigm of 'science-based' decision-making. 'Science-based' decision-making is erroneously taken to mean quantitative risk assessment, and proof of a causal link between a pesticide and an 'unacceptable' effect before action should be taken to remove that pesticide. In the words of Dr Janette Sherman, Adjunct Professor in the Department of Environmental Sciences, Western Michigan University in Kalamazoo, this "grant[s] to chemical companies the right to claim their product 'innocent' until proven guilty beyond the shadow of a doubt" (Sherman 2000). The burden of proof then falls on the community and those who work in the public interest to prove that a pesticide *does* cause unacceptable effects such as breast cancer. Decision-making based on quantitative risk assessment and the need for causal proof is in fact really politically-based, not science-based, because it implicitly places more importance on the commercialisation of pesticides than it does on the community's health. A precautionary approach is more thorough and more 'scientific' than the standard risk assessment process because it requires recognition of the limitations of science, such as uncertainty about the chronic effects from ongoing low-dose exposure to mixtures of chemicals; recognition of the lack of knowledge about casual links; recognition of the value judgements involved in risk assessment; and attention to other factors involved, such as the availability of less harmful alternatives.

The current situation is a no-win situation for the community. Chronic effects are complex and difficult to link back to pesticide exposure and, especially, to prove. They usually arise from ongoing low-dose exposures to pesticides that do not result in acute poisoning, thus the real effects of that exposure often lie below the radar. As breast cancer can have a very long latency period, linking its onset to an original pesticide exposure is extraordinarily difficult. Thus studies that do show a link between pesticide exposure and breast cancer, or laboratory studies that show a pesticide can cause mammary tumours in rodents, should never be dismissed, simply because other studies do not. Conversely, studies that fail to find a link between exposure to a pesticide and breast cancer, do not exonerate that

pesticide. It is imperative that we apply the precautionary principle to these findings, and dramatically reduce women's exposure to pesticides that may be contributing to the escalating global epidemic of breast cancer.

2

INCIDENCE OF BREAST CANCER

2.1 GLOBAL PREVALENCE

Of the 10 million new cases of invasive cancer worldwide each year in males and females combined, approximately 10 percent are breast cancer, which makes it the second most common site of cancer after the lung (Parkin et al 2001).

But breast cancer is by far the most common form of cancer in women throughout the world, and the leading cause of cancer death amongst women (Althius et al 2005).

An estimated 1.15 million women got breast cancer, and 411,000 died from it, in 2002 (Parkin et al 2002, 2006), and the incidence rate continues to climb in all age groups (Brody & Rudel 2003). There are an estimated 4.4 million women alive who have had breast cancer diagnosed within the last 5 years (Parkin et al 2006). Whilst there has been a minor decrease in the mortality rate from the disease in some countries, the tragic reality is that there is still an increasing number of women dying from breast cancer each year.

Men can also develop breast cancer, although the incidence rate is very low compared with women and male breast cancer is regarded as a rare disease. It accounts for less than 1 percent of all breast cancer (Pappo et al 2005).

The *reported* incidence rate for breast cancer varies enormously between countries. Reported rates are highest in the USA, Europe, New Zealand, Canada and Australia, and lowest in Asia and Africa. Using the age-

standardised incidence rates reported by the International Agency for Research on Cancer (IARC 2002), the country with the lowest incidence is Mozambique (3.9 cases per 100,000 population) and the highest is the USA (101.1). Other countries with high rates—over 90 cases per 100,000 population—are Belgium (92), France (91.9), New Zealand (91.9), Israel (90.8), and Iceland (90.0). [refer Table 1].

Mortality from breast cancer parallels incidence: it is reported to be highest in the countries with the highest incidence rates, lowest in Latin America and Asia (Althuis et al 2005).

This apparently huge regional variation in breast cancer incidence may not be all it seems: it is likely that there is substantial under reporting in many developing countries—for some of the same reasons that hinder the collection of accurate poisoning statistics. Many poor rural women simply cannot afford to go to doctors, so their breast cancer may never be recorded. Additionally not all countries have adequate breast cancer registries even for those cases that do get seen by a doctor. Not surprisingly then, it has been observed that the introduction of breast screening results in a rise in the *reported* incidence rate of detected breast cancer (Fakhro et al 1999). So countries in which health structures and services are inadequate, and in which breast screening and follow-up is lacking or insufficient, may in fact have a significantly higher rate of breast cancer than the currently available statistics reveal. In referring to cancer statistics in the Arab states, Safi (2002) put forward additional reasons for an apparently lower incidence rate: "there is always a tendency not to register cancerous fatalities to avoid autopsy of the bodies, and statistical book-keeping is not yet well established and regular". Therefore it is advisable not to place too much emphasis on the differences in reported incidence rates between countries.

Other explanations offered for the regional variation include disparities in lifestyle and hereditary factors (Althuis et al 2005). The role of hereditary factors has been somewhat supported by findings such as those of Kerlikowske et al (2005), who reported that the rate of invasive breast cancer per 1000 mammography screenings in the USA was 45 percent lower for Chinese than for white women, aged 50 to 69 years, and 29 percent lower for Filipino than for white women. This supports earlier findings reported by Krieger et al (1994) that, in the US, "the age-adjusted incidence of breast cancer is approximately 30% higher among white women compared with black women and 40% higher among black women

compared with Asian women". However Ziegler et al (1993) also found that breast cancer incidence rates amongst Asian women increase dramatically when they migrate to the USA—"Asian-American women born in the West had a breast cancer risk 60% higher than Asian-American women born in the East", and "migrants who had lived in the West for a decade or longer had a risk 80% higher than more recent migrants"—lending support to the view that environmental and/or lifestyle factors are implicated in the higher rates, as well as genetic factors.

In terms of lifestyle factors, it has been suggested that the traditional diets common in Asian countries, which are rich in soy products, fish and vegetables and low in diary products that concentrate lipophilic contaminants such as DDT, may provide some protection against breast cancer (Davis et al 1998). For example, genistein (found in soy) and curcumin (in turmeric) have been shown to inhibit the growth of human breast cancer cells, leading some to suggest that "combinations of natural plant compounds may have preventive and therapeutic applications against the growth of breast tumours induced by environmental estrogens" (Verma et al 1998). The evidence regarding soy, however, is conflicting, inconclusive and controversial (Bouker & Hilikiva-Clarke 2000; Michels et al 2007). Another lifestyle factor that may also influence variations is the propensity for women in high-income countries to have fewer children than those in low-income countries—and having children is regarded as being protective against breast cancer. Lower life expectancy in developing countries also probably accounts for a significant part of the difference since breast cancer incidence is still substantially higher in postmenopausal women.

2.2 GLOBAL TRENDS

Breast cancer incidence is increasing almost everywhere: over the period from the 1970s to the 1990s reported breast cancer incidence rose 30-40 percent in most countries, with the most marked increases among women aged 50 years or older (Althuis et al 2005). The incidence of male breast cancer has increased by 26 percent in the last 25 years in the US (Giordano 2005).

However, although the incidence rates continue to climb in 'western' countries, they are climbing more rapidly in 'non-western' nations (Althuis et al 2005; Parkin et al 2006).

- Whilst the global increase in incidence rate is about 0.5 percent annually, in China it is 3-4 percent, and "not much less elsewhere in eastern Asia" (Parkin et al 2006).
- Kono et al (2005) reported a rapid increase in years of potential life lost to breast cancer in Japan, increasing 5 fold over the fifty years from 1950 to 2000, and recommended the development of preventative strategies to reduce the rapid increase in breast cancer.
- Mortality from breast cancer in Kazakhstan has been rising steadily, and this increase accelerated in 1995-1997 (WHO 1999).
- Rising incidence rates have been observed in Hong Kong (Parkin et al 2006).
- There has been a striking recent increase in breast cancer in Taiwan, coupled with a relatively young median age (45-49 years) at diagnosis. Whereas the increase in the incidence rate in the USA slowed down between 1980 and 1999, in Taiwan it continued to escalate, with the incidence rates of Taiwanese women born after the 1960s approaching that of Caucasian Americans (Shen et al 2005).
- In India, the incidence of breast cancer is rapidly increasing, with an estimated 80,000 new cases diagnosed annually (Sinha et al 2003). The incidence of breast cancer increased by 40 percent between 1965 and 1985 (Saxena et al 2002). This is thought to be at least in part due to increased life expectancy: in recent years life expectancy in India increased from 32 years to 63 years in just one decade (Dinshaw 2004).
- In Singapore, the increase in incidence of breast cancer was reported to be 5.7 percent per year among premenopausal women and 3.9 percent per year among postmenopausal women by 1992 (Chang 2000).
- In Hawaii, the breast cancer incidence rate increased by 42 percent compared with less than 20 percent over the same time period for areas of mainland USA such as San Francisco Bay area, Detroit and Seattle (Allen et al 1997).

Explanations given for these striking increases in breast cancer rates include westernisation of diet, increasing life expectancy, increasing sedentary lifestyle in urban areas, radiation, alcohol—and increased use of pesticides (Allen et al 1997; Chang 2000; Shen et al 2005; Dinshaw 2004).

Some reviewers have linked this trend to synthetic chemicals, noting that

"the increasing incidence of breast cancer has paralleled the proliferation of synthetic chemicals since World War II" (Evans 2006). Pesticide use began in earnest post-World War II in western countries, with dramatic increases in use first of organochlorines, then of organophosphates, and more recently in synthetic pyrethroid insecticides: there is evidence that all of these may be implicated in the global increase in breast cancer. Strikingly, these pesticides did not come into prominence in Asian countries until the excesses of the Green Revolution (1970s-80s), during which pesticide usage soared, and after which breast cancer rates began to follow suit.

2.3 PREVALENCE IN ASIA AND THE PACIFIC

Breast cancer is the most common cancer for women in many countries in the region, such as Sri Lanka and Thailand, although in others it is second to cervical cancer, e.g. Fiji, India and Indonesia (Chandra 2000; WHO 2005).

There is huge regional variation, with New Zealand topping the list for age standardised incidence rates (91.9), with Israel (90.8) and Australia (83.2) not far behind.

The lowest *reported* incidence rates are in East and South Central Asia, averaging 20.6 and 21.8 cases per 100,000 women respectively. However there is a major exception, and that is Pakistan. Pakistan has an incidence rate of 50.1 cases per 100,000 women—well in excess of comparable countries such as Afghanistan (26.8), Sri Lanka (23.6), Nepal (21.8), India (19.1), and Bangladesh (16.6). Why? It cannot be explained away by a nationwide screening service or a westernised lifestyle. According to Professor Zeba Aziz (2006), Professor of Oncology at the Allama Iqbal Medical College, Lahore, there are no population-based cancer registries in Pakistan except for the Karachi Cancer Registry, which has a figure of 56.6 cases per 100,000, for the city of Karachi, for the period 1995-1999. This may suggest that the relatively low figures throughout many parts of rural Asia are an artefact of a lack of a breast cancer registry as well as diagnosis. The true magnitude of the breast cancer problem in rural Pakistan, as well as the rest of rural Asia, is unknown, although it is the most common cancer in women throughout Pakistan, and an unusually high proportion of cases occur in women under 40 (Liede & Narod 2002).

The city of_Manila in the Philippines also has a world age-standardised rate (ASR) greater than 50 per 100,000, joining Karachi as the highest in

the Asian region (Parkin et al 2006). China has seen a greater rise in incidence rate in rural women, although the rates are still lower than for urban women.

Very little information is available about breast cancer rates in the Pacific Islands, although what does exist indicates rates generally higher than in Asia, with Guam topping the list at 50.4 cases per 100,000 women (ASR), and Papua New Guinea having the lowest recorded rate (17.3).

The global breast cancer rates reported in Table 1 do not include the Pacific island of Hawaii, as it is officially part of the United States. However the American Cancer Society provided the following estimates for Hawaii, for 2004 (CPC 2004):

- 750 new cases of breast cancer would be diagnosed among women in Hawaii.
- 140 women would die of breast cancer in Hawaii.

The average annual age-adjusted death rates for breast cancer per 100,000 persons by race, 1997–2001, were as follows (CPC 2004):

	Hawaii	US National
Overall	19.7	27.0
White	25.9	26.4
Black	-	35.4
Hispanic	33.5	17.2
Asian/Pacific Islander	17.7	12.6
American Indian/Alaska Native	-	13.6

These figures show that, although the overall death rate from breast cancer is lower in Hawaii than mainland USA, it is higher for Asians, Pacific Islanders and Hispanic people. No explanation is given.

Additionally the global statistics do not contain a figure for the Gaza Governorates. Professor Jamal Safi (2002), of the Al-Azha University, provided an age-adjusted incidence rate of 19.3 per 100,000 for female breast cancer and 0.1 for male breast cancer, for the period 1990-1999. Breast cancer accounted for 34 percent of all cancer cases in women.

GLOBOCAN 2002:

The following data is sourced from the GLOBOCAN 2002 database developed by the International Agency for Research on Cancer (IARC 2002), using incidence data from national cancer registries and mortality data from other national registrations. The quality of the data varies considerably. The data covers the entire national population or is based on samples from selected regions.

Cancer data are always collected and compiled some time after the events to which they relate, so that the most recent statistics available are always 'late' by varying degrees. GLOBOCAN 2002 presents estimates for the year 2002. However, although the populations of the different countries are those estimated for the middle of 2002, the disease rates are not those for the year 2002, but from the most recent data available, generally 2-5 years earlier. Incidence and mortality rates by age group (0-14,15-44,45-54,55-64,65+) were estimated for as many countries as possible. The numbers of cases and deaths are computed by multiplying the estimated rates by the year 2002 population estimates for the corresponding country.

These estimates are based on the most recent incidence, mortality and survival data available at IARC, but more recent figures may be available directly from local sources.

Because the sources of data are continuously improving in quality and extent, estimates may not be truly comparable over time and care should be taken when comparing these estimates with those published earlier. The observed differences may be the result of a change in the methodology and should not be interpreted as a time trend effect.

Incidence = the number of new cases of breast cancer per year, expressed as either the absolute number of new cases or as a rate per 100,000 persons.

Mortality = the number of deaths per year, expressed as either an absolute number of deaths or as a rate per 100,000 persons.

Crude rate = the number of new cases of breast cancer per year divided by the number of people in the population at risk, expressed as an annual rate per 100,000 persons at risk.

ASR (age-standardized rate) = a summary measure of a rate that a population would have if it had a standard age structure. Standardization is necessary when comparing several populations that differ with respect to age because age has such a powerful influence on the risk of cancer. The most frequently used standard population is the world standard population. It is also expressed per 100,000. The ASR (world standard) is calculated using the 5 age-groups 0-14,15-44,45-54,55-64,65+. The result may be slightly different from that computed using the same data categorised using the traditional 5 year age bands.

Table 1: Breast cancer incidence and mortality rates in Asia and the Pacific

	INCIDENCE			MORTALITY		
COUNTRY	**Cases**	**Crude Rate**	**ASR(W)**	**Deaths**	**Crude Rate**	**ASR(W)**
World	***1,151,298***	***37.4***	***37.4***	***410,712***	***13.3***	***13.2***
Highest ASR - USA	209,995	143.8	101.1	42,913	29.4	19.0
Highest CR - Sweden	6,583	148.1	87.8	1,516	34.1	17.3
Lowest Cr & ASR - Mozambique	236	2.5	3.9	170	1.8	2.8
ASIA						
East Asia	***167,525***	***22.9***	***20.6***	***47,866***	***6.5***	***5.8***
China	126,227	20.1	18.7	36,630	5.8	5.5
Japan	32,245	49.6	32.7	9,178	14.1	8.3
Korea, N	2,388	21.3	20.4	517	4.6	4.4
Korea, S	5,511	23.5	20.4	1,201	5.1	4.4
Mongolia	64	5.0	6.6	31	2.4	3.5
SE Asia	***58,495***	***21.8***	***25.5***	***26,818***	***10.0***	***11.8***
Brunei	28	17.4	20.6	12	7.5	9.0
Cambodia	1,032	14.7	21.5	453	6.5	9.5
Indonesia	25,208	23.3	26.1	10,881	10.1	11.3
Lao	217	7.8	10.9	94	3.4	4.7
Malaysia	2,974	26.2	30.8	1,292	11.4	13.5
Myanmar	4,117	16.8	20.2	1,800	7.3	8.9
Philippines	13,051	33.5	46.6	7,582	19.5	27.1
Singapore	1,213	59.0	48.7	394	19.2	15.8
Thailand	5,282	16.3	16.6	1,980	6.1	6.3
Viet Nam	5,268	13.1	16.2	2,284	5.7	7.1
S. Central Asia	***13,3802***	***18.0***	***21.8***	***67,165***	***9.0***	***11.1***
Afghanistan	2,021	17.8	26.8	874	7.7	11.7
Bangladesh	7,735	11.1	16.6	3,376	4.9	7.3
Bhutan	170	15.7	21.8	74	6.8	9.6
India	82,951	16.5	19.1	44,795	8.9	10.4
Iran	4,742	13.5	17.1	2,039	5.8	7.4
Kazakhstan	3,447	41.9	38.7	1,687	20.5	18.7
Kyrgyzstan	522	20.4	23.0	258	10.1	11.5
Nepal	1,835	15.6	21.8	799	6.8	9.6
Pakistan	25,719	35.6	50.1	11,194	15.5	22.0
Sri Lanka	2,180	23.2	23.6	948	10.1	10.3

Table 1: Breast cancer incidence and mortality rates in Asia and the Pacific

	INCIDENCE			MORTALITY		
COUNTRY	**Cases**	**Crude Rate**	**ASR(W)**	**Deaths**	**Crude Rate**	**ASR(W)**
S. Central Asia						
Tajikistan	304	9.9	13.2	135	4.4	6.2
Turkmenistan	349	14.1	17.9	155	6.3	8.5
Uzbekistan	1,755	13.7	17.3	789	6.2	8.2
W Asia	***25,163***	***26.1***	***33.3***	***10,738***	***11.2***	***14.3***
Armenia	1,162	59.8	51.6	561	28.9	24.5
Azerbaijan	1,295	31.6	31.5	557	13.6	13.7
Bahrain	91	32.4	40.2	40	14.3	17.7
Cyprus	349	87.7	67.2	157	39.4	29.6
Georgia	1,901	70.1	51.8	1,003	37.0	25.1
Iraq	2,497	21.0	31.7	1,081	9.1	13.9
Israel	3,382	106.3	90.8	978	30.8	24.0
Jordan	509	20.4	33.0	223	8.9	14.6
Kuwait	194	23.2	31.8	83	9.9	14.0
Lebanon	816	44.4	52.5	362	19.7	23.4
Oman	100	7.8	13.2	43	3.4	5.8
Qatar	53	25.6	33.3	23	11.1	14.6
Saudi Arabia	1,563	15.5	24.7	677	6.7	10.9
Syria	2,177	25.9	44.8	955	11.4	19.9
Turkey	6,729	19.9	22.0	2,970	8.8	9.7
United Arab Emirates	179	19.5	24.1	77	8.4	10.5
Yemen	1,795	18.0	35.1	787	7.9	15.6
PACIFIC						
New Zealand	2,330	120.0	91.9	670	34.5	24.5
Australia	11,176	114.1	83.2	2,667	27.2	18.4
Melanesia	***474***	***14.5***	***22.2***	***220***	***6.8***	***10.5***
Fiji	104	25.5	31.2	48	11.8	14.5
Papua New Guinea	261	10.8	17.3	118	4.9	8.0
Solomon Islands	39	16.8	29.8	17	7.3	13.9
Vanuatu	16	15.9	24.0	7	6.9	11.1
Micronesia	***99***	***38.0***	***50.4***	***47***	***18.0***	***23.6***
Guam	35	44.9	50.4	16	20.5	23.6
Polynesia	***84***	***28.2***	***34.2***	***38***	***12.8***	***15.8***
Samoa	20	26.5	34.2	9	11.9	15.8

3

WHAT CAUSES BREAST CANCER?

The wellbeing of humans is intricately interrelated with the environment in which we live and function—the physical, social and psychological/spiritual environment—such that good health can be seen as a state of harmony between a person and her/his broader environment, and illness as a result of the disruption of that harmony. Many things bring about that disharmony—such as toxic synthetic chemicals that cause cancer, immune system dysfunction, endocrine disruption, reproductive abnormalities, developmental anomalies, degenerative diseases, and other states of ill-health in both animals and humans. Inappropriate consumption of tobacco and alcohol, recreational drugs, and inessential pharmaceuticals also disrupt our environment. So do social factors like colonisation, corporate globalisation, structural adjustment programmes, and aggressively imposed development, all of which result in a lack of safe drinking water, nutritious food and clean air for many people. So do the various forms of social control and manipulation that distort and destroy the psyche/spirit, leaving people disempowered, oppressed, silent and defeated in the midst of social injustice. So may the mutant organisms, potentially infectious virus vectors, antibiotic resistant genes, allergenic novel proteins, and other as yet unknown side effects of genetically modified organisms especially in agriculture. (Quijano 2006)

All these factors may play a role in the genesis and/or development of breast cancer. In this review only one, very important, aspect of this total environment will be reviewed: pesticides. Breast cancer is a complex, multi-faceted disease and the role of pesticides needs to be understood in the broader context of disruption of the human environment. Pesticides are

part of the disruption of the social and psychological environments especially in Asian countries where they have often been forced on poor, powerless farmers, as a conditionality of credit, or through farmers being coerced into buying pesticides by the promise of riches or the lure of otherwise unachievable prizes—such as the Syngenta advertising campaign in Thailand that provided buyers of paraquat with the chance to win a motorcycle or even a truck. Pesticides are also part of the environment in terms of depriving many users of safe drinking water, nutritious food (when staple foods are replaced by cash crops) and clean air. In this review, however, the focus has been considerably narrowed—to only the ways in which pesticides might directly interfere with DNA, the endocrine and immune systems, or other physiological processes. But first, a look at the mainstream understanding of the factors that contribute to breast cancer is necessary.

3.1 CONTRIBUTING RISK FACTORS

A number of factors are regarded by mainstream science and medicine as contributing to the risk of breast cancer, but they do not account for the majority of cases.

Inherited breast cancer susceptibility genes—notably the genes BRCA1 and BRCA2, which confer a 60-80 percent lifetime probability of breast cancer—are thought to underlie fewer than 10 percent of breast cancer cases (Davis et al 1998). These genes do not cause breast cancer, but they do increase the vulnerability of women to carcinogens and other factors that promote breast cancer. A study of women with high-risk BRCA1 and BRCA2 genetic variations showed that 24 percent of women born before 1940 were diagnosed with breast cancer by age 50, compared with 67 percent of women born later, indicating that non-genetic influences do affect women at high genetic risk (King et al 2003).

It has been estimated that more than 80 percent of breast cancer is associated with environmental factors that include exposure to contaminants, lifestyle and diet (Charlier & Dejardin 2007). Exposure to ionising radiation (e.g. x-rays, uranium, nuclear waste) is a clearly established environmental cause, with exposures early in life imparting greater risk than exposures later in life (Brody & Rudel 2003).

However, factors affecting the ovarian hormones oestrogen and progesterone, and particularly the cumulative lifetime exposure to

oestrogen, are regarded as the best-established contributing risk factors for breast cancer. The mammary gland is a complex organ that undergoes continuous change under the influence of cyclic hormonal stimulation from birth to senescence (Bradlow et al 1995; Cabello et al 2001). Breast development in particular depends on a complex interplay of oestrogen, progesterone and other growth factors (Davis et al 1998). Several epidemiological studies have shown that breast cancer risk is strongly linked to elevated serum levels of the free, bioavailable endogenous 17*beta*-oestradiol hormone (Toniolo et al 1995; Berrino et al 1996; Dorgan et al 1996).

Some lifestyle factors that affect the ovarian hormones, and are believed therefore to increase breast cancer risk, include:

- reproductive characteristics such as early menarche (before age 12), late menopause (after age 55), no pregnancies, late age at first full-term pregnancy, short lactation;
- pharmaceutical hormones: both oestrogen only and oestrogen-progesterone hormone replacement therapy increase breast cancer risk and recent, but not long-term, use of oral contraceptives is associated with higher risk;
- alcohol use, lack of physical activity, diet low in fibre and vitamin D;
- low premenopausal body mass index, higher body mass index and weight gain after menopause, advancing age.

(Davis et al 1998; Zheng et al 2000c; Snedeker 2001; Brody et al 2005).

But all these factors, including inherited genes, are thought to underlie less than 50 percent of the cases of breast cancer that actually occur, and the remaining more than 50 percent of cases are regarded as being unexplained (Brody & Rudel 2003; Evans 2006).

There is now significant international concern that some of the estimated 70,000 synthetic chemicals in our environment today may be making a major contribution to that 'unexplained' more than 50 percent of breast cancer cases. Some chemicals have been identified as either mammary carcinogens or likely to be contributing to breast cancer because of their influence on naturally occurring hormone levels—chemicals such as flame retardants, pharmaceuticals, solvents, dyes, benzene, polycyclic aromatic hydrocarbons, bisphenol A and phthalates which are used in plastics,

parabens, styrene, mercury, and pesticides. The strongest evidence of a link exists for polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) (Brody et al 2007); and organochlorine insecticides like DDT (Davis et al 1998; DeBruin & Josephy 2002; Birnbaum & Fenton 2003; Brody & Rudel 2003; Evans 2006)—largely because they have been the focus of research. Many pesticides known from laboratory studies to cause mammary tumours in rodents have been poorly, if at all, studied from a human breast cancer perspective.

As noted earlier, the increasing incidence of breast cancer, and other cancers, has paralleled the global proliferation of synthetic chemicals since World War 1 (Evans 2006). As developing countries industrialise and, significantly, take up industrial agricultural practices their breast cancer rates escalate, climbing towards those of the already chemicalised societies of the western world. Many chemicals, including pesticides, persist in the environment, accumulate in body fat, and can now be found residing in the breast tissue of women the world over. Coyle (2004) concluded that pesticide exposure in combination with genetic pre-disposition, age at exposure, and hormonal milieu has a cumulative effect on breast cancer risk. Liechenstein et al (2000) also made the link between the late onset of breast cancer—over 78 percent of breast cancer cases occur in postmenopausal women—and the long latency periods typically associated with chemical carcinogenesis in humans.

3.2 HOW PESTICIDES ARE INVOLVED IN BREAST CANCER

There is a growing body of epidemiological evidence, backed by laboratory studies, linking exposure to pesticides with breast cancer (see Chapter 4). Because of the many factors involved in breast cancer it is not possible to arrive at an absolute determination of a cause and effect relationship between individual pesticides and breast cancer. What can be done though is to identify how pesticides might be involved and on that basis which pesticides are likely to be increasing the risk of breast cancer in the context of multiple contributing causes.

There are a number of ways in which pesticides may be instrumental in the breast cancer epidemic, including:

- As *mammary carcinogens.* Cancer initiation may arise by a number of different mechanisms—such as mutations in a gene including tumour

suppressor genes, chromosomal damage, DNA damage, covalent bonding with elements of the cell (particularly nuclear elements), disruption of the mitochondrial membrane potential, and formation of free radicals that cause oxidative stress and DNA damage leading to cancer. The presence of DNA adducts is an indicator of covalent bonding and of free radicals. Any pesticides that cause these effects—and there are many that do—can potentially cause the initiation and development of breast cancer cells. Pesticides that are associated, to a greater or lesser extent, with the increased incidence of mammary tumours in rats and/or mice include alachlor, captafol, clonitralid, 2,4-D, DBCP, dichlorvos, endrin, ethalfluraline, ethylene dibromide, ethylene dichloride, ethylene oxide, folpet, malathion, mancozeb, oryzalin, parathion, paraquat, PFOS, propylene dichloride, sulfallate, and toxaphene.

- As *tumour promoters,* i.e. promoting the growth of breast cancer cells and hormonally sensitive tumours—this is the primary effect of oestrogen in breast cancer. Pesticides that promote the growth of breast cancer cells include allethrin, chlordane, chlordecone, cypermethrin, deltamethrin, dicofol, DDT, dieldrin, endosulfan, fenarimol, fenvalerate, heptachlor, lindane, methoxychlor, monocrotophos, omethoate, permethrin, sumithrin, and the adjuvant nonylphenol.

- By affecting *mammary gland development* in ways that increase susceptibility to carcinogens or hormonally active agents, such as by increasing the number or density of terminal buds also called terminal end buds (the least mature ductal structures in the mammary gland and the most susceptible to carcinogens)—for example atrazine, DDT, endosulfan, malathion, methoxychlor, and permethrin.

- By compromising the *immune system* and affecting a women's defences against cancer—for example DDT, chlordane, endosulfan, and heptachlor reduce the ability of Natural Killer T-cells to destroy tumour cells (Reed et al 2004); or suppressing the tumour necrosis factor-alpha which regulates immune cells—for example atrazine.

- By interfering with *communication between cells*. 'Gap junctions' are intercellular plasma membrane channels that allow inter-cytoplasmic movement of small molecules such as nutrients, ions and secondary messengers between neighbouring cells. 'Gap junction intercellular communication' (GJIC) plays an essential role in the regulation of cell

proliferation and differentiation, and hence the growth of tumours (Ke et al 2005). Pesticides that affect GJIC—such as chlordecone, cypermethrin, DDT, deltamethrin, fenvalerate, heptachlor, lindane, permethrin, and toxaphene—may affect cancer risk (Wandji et al 1998; Bounias 2003).

- By disrupting the *endocrine system* in ways other than promoting tumours or affecting the development of mammary gland tissue (see below).
- Other mechanisms may also be involved—for example *intrauterine growth retardation* has been shown to increase susceptibility in later life to breast cancer (Sanborn et al 2004); and a particular genetic form (or polymorphism) of the cytochrome P450 enzyme CYP1A1 has been associated with increased risk of breast cancer in premenopausal women with high serum levels of DDT (Li et al 2006a).

3.2.1 Endocrine disruption

Some scientists and many regulators take a narrow view of the role of pesticides (and other chemicals) in cancer, acknowledging only those which actually initiate the formation of cancer cells. However the importance of pesticides that act as promoters of breast cancer cell development and the spread of tumours, or affect the development or susceptibility of mammary tissue—in particular the hormonally active chemicals, otherwise known as endocrine disruptors—can no longer be ignored.

Oestrogen and progesterone affect breast cancer risk by affecting rates of cell proliferation in the breast or by supporting the growth of oestrogen-dependent breast tumours. Oestrogen levels in breast tumours can be 10 times higher than in normal circulation, in postmenopausal women (Fan et al 2007). Similarly hormonally active pesticides that affect breast cell proliferation by acting as oestrogen mimics, or by disrupting hormonal pathways leading to enhanced breast cell proliferation, can also play critical roles in the development of breast cancer (Snedeker 2001). There is strong evidence from *in vitro* laboratory tests that oestrogen-mimicking chemicals promote the growth of human breast cells in laboratory conditions, just as natural oestrogen does (e.g. Soto et al 1991, 1994, 1995; Korach & MacLachlan 1995; Shelby et al 1996; Zava et al 1997).

There are many ways in which pesticides disrupt the natural hormonal system, including:

- mimicking oestrogen, binding to and activating the oestrogen receptor, which then increases (upregulates) the oestrogen-dependent transcription of target genes and promotes breast cancer cell proliferation and tumour growth—e.g. chlordane, chlordecone, DDT, heptachlor, lindane;
- binding to a hormone receptor but not activating it and preventing it being normally activated, e.g. androgen receptor antagonists—fenarimol;
- stimulating the manufacture of more oestrogen receptors;
- binding to proteins in the blood that transport natural hormones, thus altering the amount of natural hormone that can circulate;
- increasing the activity of aromatase, an enzyme complex that catalyzes the final rate-limiting step in the conversion of androgens to oestrogens and so contributes to oestrogenic activation of oestrogen receptors—e.g. atrazine, chlordane, cypermethrin, DDT, pirimicarb, propamocarb, simazine, triphenyltin;
- increasing expression of growth factors, especially TGF-alpha (transforming growth factor) which increases cell division in breast cancer cells; and IGF-1 (insulin-like growth factor) which stimulates the growth of breast cancer cells and their invasiveness;
- binding with growth factor receptors;
- interfering with metabolic processes involved in the breakdown of natural hormones, e.g. cytochrome P450 enzyme complex, the same enzyme complex that breaks down xenobiotics such as pesticides; e.g. chlordane; heptachlor;
- suppressing melatonin or interfering with prostaglandins (see below);
- stimulating the release of prolactin (see below).

(Davis et al 1997; Badawi et al 2000; Coumoul et al 2001; Europa 2005; Holloway et al 2005; Guillette 2006; Mukherjee et al 2006; Eliassen et al 2007; Hsu et al 2007)

The European Union has identified 87 pesticides that are known to cause, or suspected of causing, endocrine disruption (EC 2001, 2004; PAN UK 2005). Not all of these will necessarily affect breast cancer risk. But those that have oestrogenic effects will.

Oestrogen

The naturally occurring oestrogen, oestradiol, is synthesised from testosterone (an androgen) by the enzyme aromatase in the ovary, placenta, breast and other tissues. Oestradiol and oestrone (the other natural oestrogen) are removed from the body by metabolic conversion to inactive water-soluble molecules that are then excreted in urine or faeces. They are metabolised predominantly via hydroxylation (inserting an atom of oxygen and an atom of hydrogen), which yields a number of hydroxyestrones and hydroxyestradiols ('hydroxys' for short here), including, 2-, 4- and 16-hydroxys such as 2-hydroxyestrone, 4-hydroxyestrone, and 16-hydroxyestrone:

- 2-hydroxys are weakly antioestrogenic, non-genotoxic, help cells fix themselves, and inhibit the growth of breast cancer cells.
- 4-hydroxys are similar to oestradiol in ability to bind to and activate oestrogen receptors, can damage DNA, are carcinogenic, and are associated with human breast cancer.
- 16-hydroxys also activate oestrogen receptors, are tumorogenic, genotoxic, increase unscheduled DNA synthesis, cause cell proliferation, and enhance breast cell growth.

A number of different cytochrome P450 enzymes catalyse this metabolism. Pesticides—such as DDT, 2,4-D, endosulfan and lindane—that interfere with these enzymes to increase the levels of 4-hydroxys and 16-hydroxys, and decrease the 2-hydroxys, may contribute to breast cancer (Bradlow et al 1995; Zhu & Conney 1998).

The other metabolic pathways (sulfonation, glucuronidation, and methylation) for oestradiol and oestrone produce a number of different metabolites, some of which are also implicated in the growth of breast cancer cells. Sulfonated oestrogens have no ability to bind to oestrogen receptors but, because they can release unconjugated oestrogen in breast cells, they are thought to be an important source of oestrogen in breast cancer cells, as may be the metabolites resulting from the metabolic pathway of glucuronidation. Conversely, 2-methoxyoestradiol inhibits the growth of breast cancer cells. Therefore pesticides that induce the enzymes that catalyse glucuronidation and sulphonation, or conversely inhibit the enzymes that catalyse methylation, may also contribute to the growth of breast cancer tumours.

Thus the mechanisms involved in the endocrine control of breast cells are complex and there are a number of opportunities for pesticides to influence the development and progression of breast cancer. The understanding of the real impacts of endocrine disrupting pesticides is still in its infancy. Although some were noted as long ago as 1950, when DDT was shown to cause smaller testes and arrested development of secondary sex characteristics in male chicks (Burlington & Lindeman 1950), it is only very recently that their implications for breast cancer began to be revealed. In 1988 Drs Ana Soto and Carlos Sonnenscheim identified that nonylphenol was leaching out of plastic laboratory test plates and causing the proliferation of human breast cancer cells in culture (Colborn et al 1996; Soto et al 1991). Nonylphenol is used as an inert ingredient in pesticide formulations or as an adjuvant when a pesticide is applied. It is now clearly established as an endocrine disruptor that mimics oestrogen. Nonylphenol stimulates the cytochrome P450 enzymes to increase production of the oestrogenically active product oestriol formed by the 16-hydroxy pathway, and it has been shown to increase mammary cancer incidence by this mechanism (Acevedo et al 2005).

Since then a large number of pesticides have been identified as having oestrogenic and other endocrine effects. Commonly, laboratory tests (assays) using an oestrogen receptor (ER) alpha gene were used to identify oestrogenic chemicals. However, the discovery of a second oestrogen receptor (ER beta), which is activated by different chemicals (Kojima et al 2004), means that earlier tests on pesticides that fail to show oestrogenicity should not be taken as evidence that the pesticide does not have this potential. Japanese researchers Kojima et al (2004) tested 200 pesticides for their oestrogenic and androgenic activity on oestrogenic receptors in hamster ovarian cells. They found 51 pesticides or pesticide metabolites to have oestrogenic effects including 34 that were also antagonistic to androgens. Predominant amongst these were organochlorine and organophosphate insecticides. Another 29 pesticides exhibited anti-androgenic effects alone. The authors expressed concern about potential additive and synergistic effects resulting from exposure to these pesticides.

Prolactin

Pesticides that increase prolactin, a hormone primarily associated with lactation, may also be implicated in breast cancer, as there is gathering evidence to confirm the role of increased levels of prolactin in the development and growth of breast tumours and a critical role in mammary

gland development (Welch & Nagasawa 1977; Tomblyn et al 2005; Hankinson 2005-2006; Eliassen et al 2007; Greendale et al 2007). Prolactin is integrally linked to growth factors (which are hormones)—any change in one affects the other—that in turn are linked to the 'tumour factor'. Stevens et al (1994) reported that the herbicide simazine caused an increase in breast tumours in rats. Although the rats did not have elevated levels of oestrogen they did have elevated levels of prolactin. Other pesticides that can stimulate the release of prolactin include atrazine, chlordane, chlordecone, dieldrin, endosulfan, *o',p'*-DDE, methoxychlor, methomyl (Mahgoub & El-Medany 2001), quinalphos, and the adjuvant nonylphenol.

The chemical industry, in defence of atrazine, has argued that prolactin release although implicated in mammary carcinogenesis in rats is of "low relevance to humans" (O'Connor et al 2000). However it is known that prolactin increases the motility of human breast cancer cells (Miller et al 2007), and several studies show a link between elevated prolactin levels and elevated breast cancer risk in humans (e.g. Eliassen et al 2007; Hankinson 2005-2006). In fact, Oakes et al (2007) asserted that high levels of prolactin confer a two-fold increase in the risk of breast cancer, and that prolactin "acts directly on the mammary epithelial cells to increase cell proliferation in pre-invasive lesions, resulting in more neoplasia and acceleration of the transition to invasive carcinoma".

Androgens and progesterone

The role of androgens in breast cancer remains to be unequivocally established (Davis et al 1997), and the role of progesterone is controversial (e.g. Russo & Russo 1998; Gizard et al 2005; Medina 2005); so, therefore, is the role of androgen disrupting pesticides, as well as the role of progesterone disrupting pesticides such as Roundup, Monsanto's well known formulation of the herbicide containing the active ingredient glyphosate (Walsh et al 2000a).

However, as androgens are the precursors of oestrogen, it is reasonable to assume that pesticides that affect them may contribute to breast cancer. Kelce & Wilson (1997) asserted that strong anti-androgens such as the fungicide vinclozolin, are implicated in the increasing incidence of breast cancer. As reported above, Kojima et al (2004) found 63 pesticides that have anti-androgenic effects, including 34 that also have oestrogenic effects. The remaining 29 pesticides have not been included in this review, but much more consideration needs to be given to the potential role of

anti-androgens in breast cancer. They include linuron, which like vinclozolin, has been shown to cause the permanent development of nipple tissue in male mice (McIntyre et al 2002), indicating a potential influence on the development of mammary tissue.

Melatonin

Melatonin, a hormone produced by the pineal gland, can also play a role: it has strongly anti-oxidant action and has been found to prevent damage to DNA caused by the carcinogenic 17*beta*-estradiol in animal studies (Karbownik et al 2001). It has anti-tumour effects through its influence on the immune system (Arushanian & Beier 2002), by enhancing T-cell expression (Carillo-Vico et al 2005). There are a small number of studies showing that melatonin has a protective effect against the cytotoxic and oxidative effects of a number of pesticides such as chlorpyrifos, paraquat, and phosphine (e.g. Melchiorri et al 1998; Hsu et al 2000; Ortiz et al 2000; Gultekin et al 2006), but none could be found showing which pesticides suppress melatonin. Those that do may also have a role in breast cancer.

Prostaglandins

Lastly, prostaglandins may also have a potential role, though their linking of the endocrine and immune systems—mediating in inflammatory responses, and regulating hormones and cell growth. Pesticides that affect prostaglandins may also affect breast cancer risk.

Thus, the mechanisms by which pesticides might increase the risk of breast cancer through their effects on the hormonal system are varied and complex, and not always immediately apparent. Some potential pathways appear to be not yet fully identified. For example little work seems to have been carried out on the interaction between pesticides and prolactin or melatonin, most work focussing on their direct effects on oestrogen and activation of oestrogen receptors.

For most pesticides, most of the potential mechanisms by which breast cancer risk might be increased—including endocrine and immune effects, effects on gap junction intercellular communication, and even carcinogenic mechanisms—remain unexplored. Until such time as they are fully explored, it is not possible to give a 'clean bill of health' to any pesticide regarding its relationship to breast cancer.

3.2.2 Critical exposures

The timing, duration and pattern of exposure to carcinogenic and endocrine disrupting pesticides are extremely important. There are critical periods during the human life cycle at which the breast is more vulnerable to the influence of such chemicals, and at these times exposure to even very low doses can cause permanent damage (Evans 2006). The critical periods occur particularly at times of rapid cell proliferation (Davis et al 1998; Brody & Rudel 2003). Prenatal, early childhood, menarche, the age of first childbirth, and perimenopause are periods of vulnerability for breast tissue. During these periods there appears to be greater propensity for undifferentiated mammary cells to bind with carcinogens, triggering DNA damage (Brophy et al 2002). Prenatal exposure appears to imprint breast cells making them more sensitive to subsequent exposures to carcinogens and hormonally active compounds (Davis et al 1998). Additionally Cohn et al (2007) demonstrated the vulnerability of females pre-menarche through young adulthood, with their finding of a five-fold increase in the risk of developing breast cancer many years later (median of 17 years to diagnosis) associated with exposure to DDT during the early years of life. The women would have been exposed before the age of 14 and were mostly under the age of 20 when DDT use/exposure peaked.

An epigenetic theory for the foetal origin of breast cancer

Exposure to toxic chemicals during embryonic development can result in chemical modification of the operation of some genes in the offspring, i.e. the DNA itself is not damaged but the way in which the genes are 'turned off' and 'turned on' is affected. This is known as epigenetic inheritance and it suggests an environmental toxin can permanently reprogram an inheritable trait. The effect can last over a number of generations—at least four in studies carried out by Anway et al (2006) using the fungicide vinclozolin on rats.

Hilikivi-Clarke et al (2006) proposed that exposure to carcinogens and hormonally active substances can lead to modifications which result in epigenetic changes to mammary gland development, increasing the susceptibility of epithelial cells to malignancy, for example through higher levels of cancer cell proliferation, or reduced apoptosis (programmed death of cancer cells).

Evidence of effects from foetal and perinatal exposure

A number of chemicals, including the organochlorine insecticide dieldrin, have been found to have carcinogenic effects as a result of prenatal or postnatal exposure in animals (Barton et al 2005). A smaller number of chemicals have been studied for the effect of *in utero* exposure on the subsequent risk of breast cancer, and few of these have been pesticides. However atrazine is one pesticide identified as increasing breast cancer risk with foetal exposure.

- Several studies on prenatal exposure to the herbicide atrazine and its metabolites have revealed effects on mammary gland development in rats that include increased presence of terminal buds and delayed mammary gland development extending the window of sensitivity (Brown et al 1998; Birnbaum & Fenton 2003; Rayner et al 2005; Enoch et al 2006).
- Anway et al (2006) found that embryonic exposure to the fungicide vinclozolin at critical times resulted in breast tumour development in subsequent generations of adult rats.
- Bonner et al (2005a) found that exposure to polyaromatic hydrocarbons around the time of birth is associated with increased risk of postmenopausal breast cancer.
- Mice exposed *in utero* to bisphenol A showed mammary gland development was altered in ways that are associated with the development of breast cancer in rodents and humans: it altered the timing of DNA synthesis in the epithelium and stroma (connective tissue) of the mammary gland, and increased the number of terminal ducts and terminal buds in adults (Markey et al 2001).
- Similarly perinatal exposure to bisphenol A resulted in increased terminal bud density at puberty thus increasing the risk of breast cancer (Munoz-de-Toro et al 2005).
- Intrauterine exposure to the dioxin 2,3,7,8-TCDD in the laboratory resulted in offspring with a proliferation of terminal buds and twice the number of mammary tumours (Brown et al 1998); and interference with the maturation of the mammary gland, increasing the risk of breast cancer (Fenton et al 2002).
- Prenatal exposure to the plasticiser bisphenol A resulted in increased breast tissue susceptibility to carcinogens at puberty (Durando 2007).

- Luebke et al (2006) found that the immature developing immune system is at greater risk of adverse effects from immunotoxic chemicals such as diethylstilbestrol (DES), the dioxin 2,3,7,8-TCDD, and tributyltin oxide.

A number of other studies indicate that prenatal or preconception exposure to ionising radiation, diethylstilbestrol, saccharin, arsenic, various pesticides, flame retardants, solvents, paints, thinners, plastics, cigarette smoke, and synthetic halogenated chemicals, are all linked to the increase of various cancers (Birnbaum et al 2003). In fact Barton et al (2005), in their review of available data, identified more than 50 chemicals causing cancer after perinatal exposure, including the pesticides amitrole, dieldrin, and ethylene thiourea (a breakdown product of dithiocarbamate fungicides that include mancozeb and maneb).

The relevance of these findings is enormous for it demonstrates what has become a critical problem for normal regulatory risk assessment for pesticides: that low dose exposure to endocrine disrupting and/or carcinogenic pesticides during a critical window of development can cause permanent damage and health effects that only become apparent later in life, and can affect subsequent generations. As Colborn (2006) points out, regulatory assessment misses almost all delayed developmental, morphologic and functional damage of foetal origin.

Evidence of foetal exposure

Evidence that the unborn foetus is indeed being exposed to pesticides comes from the findings of pesticide residues in umbilical cord blood and meconium, the newborn infant's first faeces. A study of umbilical cord plasma samples collected from African-American and Dominican newborns in New York (USA) found a staggering 29 active ingredients or metabolites (Whyatt et al 2003)—see Table 2. There is evidence, in Chapter 4, linking 13 of these to an increased risk of breast cancer (two—phthalimide and tetrahydrophthalimide—are metabolites). This means that those unborn children were exposed to a cocktail of at least 12 pesticides (the screen did not include obsolete organochlorine insecticides or 'inerts' or adjuvants) that may increase their risk of breast cancer later in life. All but two of these pesticides have oestrogenic effects and the remaining two are known to cause mammary tumours. These pesticide residues were reported to come from recent use of pesticides in urban areas.

There appear to have been very few studies carried out in the Asia Pacific region on levels of pesticides in umbilical cord blood and infant meconium,

Table 2: Breast cancer pesticides in umbilical cord blood in New York, USA (Whyatt et al 2003)

Pesticide	Epidemiology	Mammary Tumours	Oestrogenic	Carcinogenicity	Other
Triazine herbicides					
atrazine	+	carcinoma	+	+	immune
Pyrethroids					
cis -permethrin			+	+	
trans-permethrin			+	+	+
Organophosphates					
chlorpyrifos			+	+	
diazinon			+	+	
dichlorvos		+	+	+	
malathion	+	carcinoma		+	
methyl parathion			+	+	
parathion		carcinoma		+	
Fungicides					
captan metabolites	[+]			[+]	
captafol metabolites		[+]		[+]	
Other herbicides					
alachlor		+	+	+	
trifluralin			+	+	

as a measure of foetal exposure. However, on the basis of repeated findings of residues in breast milk and serum throughout the region and findings of cord blood and meconium contamination elsewhere, it is highly likely that females in Asia and the Pacific are being exposed *in utero* to a cocktail of pesticides that are implicated here in breast cancer. Various organochlorine insecticides have been found in umbilical cord blood in China, India, Japan, Thailand, Kazakhstan and Kyrgyzstan.[1] The meconium of infants randomly sampled from the nurseries of five hospitals in Manila, Philippines, contained the organochlorines chlordane, DDT, lindane, and pentachlorophenol, as well as the organophosphates chlorpyrifos, diazinon, malathion, and parathion (Ostrea et al 2002).

The residues indicate foetal exposure at a time when the developing female is at her most vulnerable to breast cancer stimulants. Pesticides, particularly organochlorines, that are also prevalent in breast milk (see Chapter 4.2), cause additional postnatal exposure.

1 China (Zhao et al 2007), India (Nair et al 1996), Japan (Fukata et al 2005), Thailand (Asawasinsopon et al 2006), Kazakhstan and Kyrgyzstan (UNEP 2002d).

3.2.3 Low doses and mixtures of chemicals

The issue of low dose exposure is quite straightforward for genotoxic carcinogens: there is no safe level of exposure. The lowest level of exposure can cause a carcinogenic effect (US EPA 1990a; Kowalczyk 1996). Pesticides reviewed here for which there is evidence of genotoxicity include alachlor, aldicarb, atrazine, captafol, captan, chlordane, chlorpyrifos, cyanazine, cyfluthrin, cypermethrin, 2,4-D, DBCP, deltamethrin, diazinon, dichlorvos, endosulfan, EPN, ethion, ethylene dibromide, ethylene oxide, fenarimol, fenvalerate, folpet, isofenphos, lindane, malathion, mancozeb, maneb, methyl parathion, monocrotophos, omethoate, paraquat, parathion, permethrin, phenthoate, phosmet, simazine, sulfallate, toxaphene, trifluralin, and triphenyltin.

However for non-genotoxic carcinogens—which cause cancer through mechanisms such as promotion of cell or tumour growth, peroxisome proliferation, cytotoxicity leading to compensatory cell division, and endocrine disruption—thresholds are believed to exist (Kowalczyk 1996). What those thresholds actually are, is in essence unknown. So various mathematic models are applied by toxicologists to estimate 'acceptable' levels of exposure, based on a positive dose–response relationship: the greater the dose/potency of chemicals the greater the risk of cancer.

The 'non-monotonic' dose-response

Attempts to link breast cancer to exposures to endocrine disrupting chemicals are complicated by the fact that their oestrogenic potency is low compared to that of 17*beta*-oestradiol, the naturally occurring hormone. Yet there is concern about the endocrine disrupting effects if exposures take place at times when levels of endogenous oestrogen are normally low and tissues exquisitely sensitive to it, such as *in utero*, pre-puberty and postmenopause.

Additionally, endocrine disruptors do not obey the normal rules of toxicology, and low levels of exposure, assumed by regulators to be non-toxic, can in fact be of profound importance. This is because endocrine disruptors do not act in the typical positive dose-response manner upon which toxicologists often rely. A positive dose-response means that the higher the dose the greater the effect, but with endocrine disruptors the opposite can happen. Studies have produced dose-response graph shapes that were either low-dose linear; or threshold-appearing; or non-monotonic (e.g. U-shaped or inverted U-shaped) (Melnick et al 2002) meaning that

the strongest effect is felt at a low or medium exposure level, not a high exposure; or a bi-modal response (Bulayeva & Watson 2004) meaning there are some concentrations at which effects do not occur.

Effects have been observed on animals at very low doses in laboratories (Melnick et al 2002; Bulayeva & Watson 2004; Wozniak et al 2005), and on fish at or below the detection limits (EC 2004). They have been observed for prenatal exposure to a number of chemicals (Wadia et al 2007) such as methoxychlor, a mammary carcinogen: prenatal exposure to this organochlorine insecticide produced an inverted U dose-response relationship in terms of the response of adult mice to 17*beta*-oestradiol, with a low dose of methoxychlor increasing uterus weight and a high dose decreasing it (Alworth et al 2002). Fenvalerate provoked mRNA induction in MCF-7 breast cancer cells at very low (nanomolar) levels, but higher exposures were required to cause cell proliferation (Go et al 1999). At very low levels (1 µM) d-trans allethrin was a moderate oestrogen blocker in MCF-7 human breast cancer cells, but at higher levels it provoked breast cancer cell proliferation. At even higher levels it was toxic to the cells. The dose-response curve had the classic inverted U form of a non-monotonic relationship (Go et al 1999).

Methoxychlor, fenvalerate and d-trans allethrin are all still in widespread use, and there is every reason to be concerned that low dose exposure to these hormonally active insecticides may well be contributing to the breast cancer epidemic.

Mixtures

Andersen et al (2002) found that a number of pesticides have at least three to four different ways to potentially disturb sex hormone actions, and they concluded that even if "potencies of the pesticides that react as hormone agonists or antagonists are low compared to the natural ligands, the integrated response in the organism might be amplified by the ability of the pesticides to act via several mechanisms and the frequent simultaneous exposure to several pesticides".

Additionally, women are constantly exposed to a multitude of agents with oestrogenic activity (Gillesby & Zacharewski 1998). Through their attraction to fat (lipophilic) and persistence, many of these 'xenoestrogens' accumulate in adipose tissue, including breast tissue and breast milk, and are present in blood serum. They are likely to interact not only with each other but also with endogenous (natural) oestrogens. Animal studies have

demonstrated that mixtures of oestrogenic chemicals can act together to exert an effect even when the level of each individual chemical is too low (see below). Other studies have shown that endocrine disrupting effects of low doses of pesticides on thyroid hormone levels were consistently a response due to mixtures (Porter et al 1993, 1999).

(a) *Shekhar et al (1997)* found that the effect of *p,p´*-DDT in regulating oestrogen receptor-mediated cellular responses in MCF-7 human breast cancer cells was enhanced when in combination with oestradiol or *o,p´*-DDT (see Chapter 4.2.1 for explanation of types of DDT).

(b) *Payne et al (2001)* found that *p,p´*-DDE, *o,p´*-DDT, *p,p´*-DDT, and *beta*-HCH, acted together to cause proliferation of MCF-7 human breast cancer cells. There were combination effects even when each mixture component was present at levels at or below its individual 'No Observed Effect Concentration' (NOEC).

(c) *Silva et al (2002)* tested the oestrogenic effects of PCBs, benzophenones, parabens, bisphenol A, and genistein on yeast cells. They found substantial mixture effects even though each chemical was present at levels well below its NOEC. They concluded that oestrogenic agents are able to act together to produce significant effects when combined at concentrations below their NOECs, and stated that the traditional focus on the effects of single agents which "ignore the possibility of joint action of oestrogenic chemicals will almost certainly lead to significant underestimations of risk".

(d) *Desaulniers et al (2001)* found that exposure of neonates to a mixture of organochlorines (DDT, DDE, and PCBs) increased susceptibility to chemically induced mammary tumours.

(e) *Soto et al (1994)* administered a mixture of 10 estrogenic chemicals to MCF-7 human breast cancer cells at concentrations 10-fold lower than those required to produce an oestrogenic effect when given alone. They found that the combination resulted in significant cell proliferation.

(f) *Hayes et al (2006a)* examined the effects of four herbicides (alachlor, atrazine, metolachlor, nicosulfuron), three insecticides (cyfluthrin, cyhalothrin, tebupirimphos), and two fungicides (metalaxyl and propiconazole) alone or in combinations, on metamorphosis, time to metamorphosis, and gonadal differentiation in northern leopard frogs. They found that the mixtures had much greater effects than individual pesticides in inhibiting larval growth and development.

Andreas Kortenkamp (2006) summed it up thus:

> ***"breast cancer epidemiology should face the reality of combined exposures and should take account of recent evidence from in vitro models demonstrating that a large number of oestrogen-like pollutants, all present at low levels, can act together to add to the internal oestrogenic load".***

In conclusion, even when adverse impacts of pesticides on health are identified using tests on laboratory animals, the results are often dismissed as being of no relevance to humans, for human exposure is presumed to be at relatively lower levels than those used in laboratories. This is an erroneous conclusion:

(i) Firstly, a dose-response relationship should not be expected with cancer—if a substance is a genotoxic carcinogen there is no threshold for initiation of activity, and they present a health risk at every exposure level (US EPA 1990a; de Ratt et al 1997). Similarly, there is evidence that endocrine disrupting substances do not always follow conventional dose-response patterns and low or moderate doses can cause greater effects than higher doses.

(ii) Secondly, the main reason for the use of high doses in laboratory studies is to increase the chance of observing effects, but this does not necessarily identify the doses that are clinically significant in humans.

(iii) Thirdly, most sample sizes in laboratory studies are too small to accurately identify adverse effects, especially cancer, or to achieve statistical significance—given that the US EPA uses '1 in a million' as the standard for the acceptable risk of developing 'excess' cancer (Margolis 1996), and the usual number of animals used in laboratory test is nothing like a million, perhaps less than two hundred (Rudel et al 2007).

The findings of critical periods of development at which mammary tissue is highly sensitive to very small doses of hormonally active substances, together with the understanding that mixtures of these substances can exert a greater effect than that of individual chemicals, sends a potent message about the exposure of women to these substances: simply, safe levels of exposure cannot be determined, and women—especially pregnant women and prepubescent girls—should not be exposed to any levels of mammary carcinogens or hormonally active pesticides that may increase the risk of breast cancer.

4

MAMMARY CARCINOGENS AND HORMONALLY ACTIVE PESTICIDES

Identifying which pesticides might cause or promote breast cancer is not a simple matter, given the complexity of factors underlying breast cancer, and the notorious difficulty of providing absolute proof of a relationship between a pesticide and a specific health effect. The approach taken here has been to identify those pesticides that, based on available evidence, may increase the risk or severity of breast cancer.

4.1 AN OVERVIEW OF EVIDENCE

In drawing this review together several different types of evidence have been considered.

Firstly, there are the epidemiological studies, comprising occupational and ecological studies, that attempt to identify a link between exposures to pesticides generally and risk of breast cancer. Some studies have shown elevated rates of non-Hodgkin's lymphoma, leukemia, multiple myeloma, soft tissue sarcoma, and cancers of the breast, ovary, lung, bladder, cervix, and sinonasal cavities in women in agriculture or with agricultural exposures (McDuffie 1994).

Secondly, there are the epidemiological studies that attempt to identify a link between specific pesticides and incidence of and/or mortality from breast cancer. These are few and far between, as are studies linking specific pesticides to any cancers. Some studies have linked

- phenoxy acid herbicides or contaminants in them with soft tissue sarcoma and non-Hodgkin's lymphoma

- organochlorine insecticides with soft tissue sarcoma, non-Hodgkin's lymphoma, and leukaemia
- organophosphate insecticides with non-Hodgkin's lymphoma and leukaemia; and
- triazine herbicides with ovarian cancer. (Miligi et al 2006)

Few, if any, of these associations are considered established and causal (Dich et al 1997). Epidemiological links to breast cancer are reviewed throughout this chapter.

Thirdly, there are the *in vivo* and *in vitro* laboratory studies that indicate a pesticide is a mammary carcinogen, a tumour promoter, an endocrine disruptor, or acts in some other way to increase the risk of breast cancer—such as affecting mammary gland development, gap junction intercellular communication, the immune system, prostaglandins, or causing oxidative stress or the formation of free radicals, etc.

These are the standard scientific approaches to obtaining evidence, although frequently only epidemiology and the existence of mammary tumours in laboratory animals are considered. All of these approaches are fraught with difficulties and the resulting evidence is often inconsistent and inconclusive. The validity of results of epidemiology studies can be severely compromised by confounding factors, and by the difficulty of establishing what exposures to pesticides occurred, especially at critical periods of development such as *in utero.* Synergism between chemicals is regularly overlooked.

4.1.1 Problems with epidemiological evidence

The problems with evidence from epidemiological studies can best be illustrated by scrutinising those that focus on DDT. The results of these studies are inconsistent. The conclusion frequently reached by reviewers of these studies (e.g. Snedeker 2001; Calle et al 2002; Lopez-Cervantes et al 2004; Rogan & Chen 2005; Beard 2006; Khanjani et al 2007) is that overall they do not support a link between exposure to organochlorine insecticides such as DDT and breast cancer, or that there is no evidence that DDT causes breast cancer. However that is not the full story.

Levels of residues

It was the early studies, by and large, which found a link between DDT and breast cancer; and it is the more recent studies that have failed to—except in countries such as China (Li et al 2006b) where exposure to DDT is still occurring or is very recent. Here again, where exposure is more recent, links between DDT and breast cancer have been demonstrated. The issue is that the levels of DDT and DDE in blood and breast tissue, in countries in which DDT was banned or severely restricted more than three decades ago, are now significantly lower than they once were (e.g. Charlier et al 2003), in some cases the levels are now only one-tenth what they once were and are too low to identify their real impact on breast cancer (Davis 2002). So, we cannot conclude that a link between DDT exposure and breast cancer does not exist based on recent studies in countries where DDT has been banned for many years; but we can say that studies indicating a link between breast cancer and DDT/DDE residues in blood and breast tissue, in countries where DDT exposure continues, are more meaningful.

Determining Exposure

Brody et al (2005) warn that there is always a strong likelihood of generating "inconclusive negative findings, which are common in case-control studies of hard-to-assess exposures to pollutants in the general population"; and the results of studies that fail to show an association contribute little because "study design limitations mean we cannot conclude from null results that no association exists" (Brody et al 2005).

For example, no one in a study on DDT or DDE can reasonably be considered unexposed—official US government surveys in the late 1970s found detectable levels of DDT and DDE in 100 percent of the more than 1000 samples taken (Sherman 2000)—raising questions about whether there is adequate exposure variability to detect effects. The Cape Cod study, for example, suffered from difficulties in accurately assessing exposure, resulting in ambiguous results (Brody et al 2004). Many studies relied on "self-reports" to determine exposure to pesticides, but this is "at best a weak method of assessing exposure" (Brody et al 2005).

The Long Island Breast Cancer study suffers from both these problems: the apparently 'negative' findings (i.e. failure to establish a link) of this study are often used to discount the link between organochlorines and breast cancer, but the levels of DDE in this relatively recent study were more than

10 times lower than in earlier studies that showed a positive link (Evans 2006). Additionally the controls were inexplicably also drawn from Long Island raising doubts about the credibility of supposed differences in exposure between cases and controls (Sherman 2000).[2]

Other problems

There are many other difficulties inherent in the epidemiological studies that may seriously affect the accuracy of their results:

- Most studies measured DDE rather than DDT. Because DDE is persistent in humans (half-life of 13 years), and only slowly eliminated, it is the most prevalent form of DDT found in body tissue; and so is used as a surrogate for determining past exposure to DDT. However, in most of the negative studies, especially those in the USA where DDT has not been used for many years, the main source of DDE in a woman's tissues would be DDE residues ingested in food, rather than as a metabolite of DDT in the body. As DDE is much less oestrogenic than DDT, this does not accurately reflect a women's exposure to the oestrogenic DDT (Snedeker 2001). An important new study (Cohn et al 2007), based on blood samples taken from American females during the period of highest exposure to DDT (1959-67) revealed a strong statistically significant link between *p,p'*-DDT and breast cancer, but not between *p,p'*-DDE and breast cancer. Thus studies attempting to link levels of DDE with breast cancer may be missing the mark. None of the other American epidemiological studies have evaluated breast cancer risk in rural women potentially exposed to DDT while it was being used, although the Cohn et al (2007) study concluded that the peak exposure to DDT probably occurred during urban insect control programmes and through dietary intake (of DDT, not DDE) rather than rural exposure. The number of published studies in countries still using DDT is very low. One small pilot study in Viet Nam where DDT was used for mosquito control until the late 1980s did not find an association between DDT in serum and breast cancer risk (Schecter et al 1997). However, given the very small number of cases (28), it is possible that such an effect may not show up. Other studies in China (Li et al 2006b) and Mexico (Waliszewski et al 2005), where DDT use was recent and DDT was

2 Long Island, New York: age adjusted breast cancer incidence rates for 62 community groupings were 30% higher than the county (Suffolk) average; and the county average had itself increased by 13% in just 9 years (Sherman 2000).

measured in serum and breast adipose, did show a positive relationship with breast cancer.

- Most studies have not been able to utilise blood or adipose samples taken at or near the time of exposure. Many relied on single or double sampling times near to diagnosis of breast cancer to determine levels of hormonally active substances, yet elevated breast cancer rates are associated with hormonal exposures beginning *in utero* and extending to within 5 years of diagnosis (Brody et al 2005). The time of life when exposures take place is important. As discussed in Chapter 3, mammary tissue is more susceptible to carcinogenesis at certain periods of breast development, especially prenatal and neonatal and during rapid breast cell proliferation in adolescence (Wolf et al 1996; Brody et al 2005). Specifically, serum measures taken near the time of diagnosis may not represent early life exposures or even total lifetime exposure, because recent levels are influenced by variables related to mobilization and excretion, such as weight gain/loss and lactation, and by intake of metabolites in food that have different toxicological properties from the parent compound (e.g. DDE, which is ingested in meat and dairy products, is less estrogenic than the parent compound DDT) (Snedeker 2001; Brody and Rudel 2003). The Cohn et al (2007) study is the first to measure blood levels of DDT in young adulthood, taken during the period of exposure, and it found a statistically-significant five-fold increase in the risk of breast cancer among young American women who were under the age of 14 in 1945 when widespread use of DDT began in the USA and mostly under the age of 20 when that use peaked.

- In most studies organochlorine insecticides were measured in serum, but levels in breast adipose tissue are higher and represent cumulative internal exposure at the target site for breast cancer (Aronson et al 2000). Some studies have suggested that levels in serum correlate to levels in adipose tissue (Snedeker 2001); however Waliszewski et al (2005) maintain that adipose levels reflect a steady state of organochlorine levels in the body whereas blood levels fluctuate, because of differential partitioning of the pesticides in various components of blood, and this biases results.

- Many used controls with benign breast disease rather than healthy women, and there is evidence that women with benign breast disease have a higher risk of developing breast cancer (e.g. Worsham et al 2007). One study that did use non hospital-based controls and in a country

where DDT is still used, did find a significantly higher level of DDE associated with breast cancer (Olaya-Contreras 1998). Additionally Waliszewski et al (2005) found consistently higher levels of organochlorine pesticides in the adipose tissue of women with benign breast tumours than in the adipose tissue of women with malignant breast tumours; and similarly higher levels in malignant breast tumour cases compared with the adipose tissue of non-cancer controls (patients).

control < malignant <benign

If these findings are duplicated, then it throws into question the results of all studies in which women with benign breast disease are used as controls.

- Some had very small sample size (less than 25 women) (Snedeker 2001).
- Some failed to control for potential confounding factors such as multiple chemical exposure, lifestyle factors, genetic, and other environmental influences that could affect breast cancer risk (Jaga & Brosius 1999). The Long Island study failed to control for radiation exposure, and for carcinogenic and hormonally active chemicals used there other than DDT, DDE, chlordane and PCBs. These others included aldicarb, dieldrin, endrin, and parathion (Sherman 2000).
- Sherman (2000) reported a number of flaws in the actual management of the Long Island study, such as insufficient quantities of blood drawn, some samples being left to clot, samples being taken after radiation and/or chemotherapy had begun, and the storing of environmental samples in plastic containers (which may leach chemicals into the samples).
- Some studies showing equivocal results, and one with a strong positive result (Dorgan et al 1999 with regard to HCB), were discounted because of the lack of demonstration of a positive dose-response relationship, yet we know hormone dose-response may be other than positive and that, in fact, lower or medium level exposure may result in a greater adverse effect on oestrogenic activity than a higher level exposure (refer Chapter 3).
- Most studies have involved Caucasian women from the USA, Canada, Europe, and very few from Asia or the Pacific.
- Most USA studies did not differentiate between Asian, white, and African-American women. One study did (Krieger et al 1994) and found

a positive relationship between DDE levels and breast cancer in African-American women, but not in others. When the 150 Asian, white, and African-American breast cancer cases in this negative study were analyzed as three distinct racial/ethnic groups, African-American women and white women had higher organochlorine levels and two to three times more breast cancer.

- Some studies have found that CYP1A polymorphisms of the cytochrome P450 enzyme complex affect breast cancer risk from exposure to DDT (e.g. Li et al 2006a); and that high serum levels of DDT may affect risk in premenopausal but not postmenopausal women (e.g. Li et al 2006b). The 'val' polymorphism of cytochrome P450 1B1 (CYP1B1), which is implicated in the activation of potentially carcinogenic substances and oestrogens, increased susceptibility to breast cancer from exposure to agricultural pollutants (Saintot et al 2004). All these factors may confuse outcomes of studies if they are not taken into account.

- Finally, financial and corporate interests may be an issue especially with critical elements of the study design—some of those organisations funded to carry out the Long Island study had direct financial interests in a radiation laboratory sited there, the Brookhaven National Laboratory (Sherman 2000). The initial design of a study can be critical in determining the outcomes.

In summary, negative findings in epidemiological studies should not be interpreted to mean that particular pesticides do not play a role in breast cancer. Sometimes that role can be glimpsed through analysing other mechanisms. For example Iscan et al (2002) concluded, from measuring levels of organochlorine insecticides and antioxidant enzyme activity in breast tumour and surrounding tumour-free tissue, that "free-radical mediated oxidative stress is, at least partly, associated with some of these [organochlorine pesticide] residues in human breast tumors". As Lopez-Cervantes et al concluded in 2004, "exposure to DDT during critical periods of human development—from conception to adolescence—and individual variations in metabolizing enzymes of DDT or its derivatives are still important areas to be researched in regard to breast cancer development in adulthood".

Epidemiological studies of historically-used persistent pesticides, degraded into various metabolites, may well be too blunt a tool to accurately define the real role of organochlorine insecticides in breast cancer. And they do nothing to elucidate the role of the many other pesticides reviewed here

that may be involved in the global escalation of breast cancer rates given the observations of their effects on carcinogenic, endocrine, immune and other mechanisms important in breast cancer genesis and development. It is critical that epidemiological studies focus on currently used pesticides especially those identified in this review as potentially increasing the risk of breast cancer. Many of these leave no trace in the body soon after exposure; others do and have been measured in umbilical cord blood and infant meconium—yet there are still few real attempts to elucidate their possible role in breast cancer. To date epidemiological efforts have focussed largely on obsolete, or nearly obsolete, pesticides.

4.1.2 Problems with studies on mammary tumours

There are also a number of problems with laboratory-generated data relating to the development of mammary tumours (Rudel et al 2007):

(i) A typical cancer bioassay program using small numbers of animals and high doses in order to detect effects is designed to detect genotoxic effects but is unlikely to detect nongenotoxic carcinogens, such as those that affect mammary gland development or act as promoters, or have transgenerational epigenetic effects (i.e. cause breast cancer in the subsequent generation).

(ii) It cannot be assumed that all chemicals that are carcinogenic in rodents are also carcinogenic in humans and vice versa; or that chemicals that cause mammary tumours in one species have the same target organ in the other. In other words animal tests may falsely identify chemicals as mammary carcinogens for humans, or conversely fail to identify chemicals that are in fact mammary carcinogens in humans.

(iii) Typically the tests are carried out on pubertal animals and are not carried out on younger developing animals which can be very much more sensitive to the effects of chemicals.

(iv) Typically the duration of the studies—usually two years—is too short to identify mammary carcinogens with a longer latency period.

(v) The tests fail to identify the effects of chemical interactions because they test only one chemical at a time.

(vi) There are concerns about inconsistencies in the way in which findings are interpreted: findings of fibroadenomas in rats may be discounted because there is a reasonably high background level in one particular

variety of rats (Fischer rats); discounting these may miss a real carcinogenic effect. There is also a tendency by some to discount benign breast tumours despite evidence of benign tumours progressing to malignant ones; and to discount tumours if the underlying mechanism is not understood in humans.

Rudel et al (2007) commented that

> ***"disproportionate financial resources have been dedicated to supporting arguments that the carcinogenicity in animal studies is due to toxicity that occurs only at high doses or through biological mechanisms that are not relevant to human exposure scenarios (false-positive) with an aim to reduce regulatory constraints and increase public scepticism of the relevance of the animal toxicity studies".***

This charge is clearly evidenced by the situation with atrazine: as described later, in detail, in the section on atrazine, mammary tumours caused by this herbicide were discounted by chemical industry scientists, and subsequently the US EPA, because their underlying mechanism involved prolactin, a mechanism "thought to be of low relevance in humans" (O'Connor et al 2000). This assumption has subsequently been challenged by recent research that indicates prolactin is important in breast cancer development, and may in fact double the risk of breast cancer (Oakes et al 2007).

Rudel et al (2007) continue:

> ***"Conversely, comparable resources are not extended to evaluate how chemical testing and risk assessment as currently practiced may miss critical adverse effects".***

For this reason, and the limitations of the epidemiological evidence, every effort has been made here to include other laboratory-generated data that may elucidate mechanisms underlying the onset, development, and progression of breast cancer and which pesticides might be implicated in this process.

4.1.3 Using the best available knowledge

Most of the information presented in this review is derived from epidemiological or laboratory studies, which are by convention regarded as the scientific norm—and often as the only acceptable type of

information. However, such an approach runs the risk of overlooking other valuable knowledge. There may be case reports (only some of which get written up in scientific journals), direct testimony, anecdotal evidence, and community monitoring reports and participatory research, such as those assisted by Pesticide Action Network Asia and Pacific's Community Pesticide Action Monitoring Programme (CPAM), and Pesticide Quick Response and Surveillance Team (PQRST)(Quijano undated). These programmes have provided reports on the impacts of pesticides on the peoples of Kasargod in India (Quijano R 2002), and of Kamukhaan in the Philippines (Quijano I-I 2002), on former workers at the International Rice Research Institute in the Philippines (Quijano & Quijano undated), and on women plantation workers in Malaysia (Joshi et al 2002). The reports give valuable insight into the actual effects of pesticides as they are used, and hence add significant new information to that provided by formal epidemiological and laboratory studies. Where available such information has been added here to provide a more comprehensive picture.

Community knowledge and experience, and the wisdom engendered by that experience, can provide cautionary information that is not accessible to the positivist science of risk assessment (Watts 2000). This kind of evidence is more usual with acute effects, but an example that is relevant here is that of the paraquat sprayers in Malaysia who, via a community monitoring project, reported adverse effects on their breasts including inflammation (Joshi et al 2002). This finding adds to the small base of knowledge derived from toxicological studies that is relevant to breast cancer, and lends weight to the plausibility of exposure to paraquat as increasing the risk of breast cancer, since we know that inflammation can be a key event in cancer development (Lu et al 2006).

Given the immense burden of breast cancer on women across the world, it is vital that we make best use of the available knowledge, including community knowledge—not least because of the value framework of the conventional science process, which drives what data is collected and how it is interpreted (Watts 2000). It requires provable causal relationships and diminishes the potential implications of uncertainty. It frequently dismisses results that do not conform to a positive dose-response relationship (e.g. Dorgan et al 1999 in finding elevated risk of breast cancer with elevated serum residues of HCB), when in fact one should not be expected, as with genotoxic and endocrine disrupting substances. It dismisses a result as not statistically significant when in fact it may be clinically significant. This is not to say we should dismiss the results of positivist science—indeed that is

primarily what is reported here. What it does mean is that we should incorporate credible community experience where it is available. We need also to reconsider where the burden of proof should lie, looking at the weight of evidence from a broad perspective and then applying the precautionary principle. We should not wait forever to obtain definitive statistical proof, because in the meantime women die unnecessarily.

> ***"Not acting to reduce or control our use of such suspected toxic materials is a form of acting"*** (Davis 2002)

—in this instance against the welfare of women worldwide.

4.1.4 A note about the pesticides reviewed

The pesticides reviewed here were selected on the basis of epidemiological evidence linking them with breast cancer, and/or laboratory data indicating oestrogenic activity or mammary carcinogenicity in animals. These pesticides were then briefly reviewed for other effects that might increase the risk of breast cancer, such as effects on the immune system, gap junction intercellular communication, cytochrome P450 enzymes, oxidative stress, genotoxic potential and for epidemiological evidence of other types of cancer. These latter categories of information, by themselves were not deemed sufficient to identify here a potential breast cancer agent, without the accompanying oestrogenicity or mammary carcinogenicity. This is a conservative approach as oestrogenicity may not be the most important influence of endocrine disruptors on breast cancer, although at present it is deemed to be. So it is quite possible that other pesticides that increase breast cancer risk have been omitted, chief amongst which may be the carbamate insecticide methomyl which increases prolactin secretion at least in male rats (Mahgoub & El-Medany 2001), and the herbicide Roundup which affects progesterone (Walsh et al 2000a) as well as containing the contaminant 1,4-dioxane which causes mammary tumours (IARC 1999b).

The comment in the square brackets after the name of each pesticide indicates the primary type of evidence for breast cancer potential.

4.2 STUDIES LINKING PESTICIDES IN GENERAL WITH BREAST CANCER

A relatively small number of epidemiological studies have been undertaken in an attempt to explore the link between exposures to pesticides generally and risk of various types of cancer, and the resulting

evidence on the relationship between pesticides and cancer tends to be inadequate and contradictory. Cancer risk among women engaged in farming has been particularly poorly investigated. Many studies of cancer and farming do not include breast cancer, and in fact have omitted women altogether, yet announce that they have found no link between pesticides and cancer; or else list cancers other than that of the breast that may be linked to pesticide exposure (e.g. Beard et al 2003; Meyer et al 2003; Bonner et al 2005b; De Roos et al 2005).

Of the few studies that have been carried out on rural women and breast cancer, most have been undertaken in USA or Europe, in conditions that differ markedly from those experienced by rural women in Asia and the Pacific Islands—particularly with respect to the types of pesticides used, the frequency and duration of exposures, the use or non-use of protective clothing and its appropriateness, and the presence of other socio-economic factors that can affect health outcomes (such as malnutrition, lack of access to washing water for removing pesticides on the skin or clothes, etc).

Some of these studies have found a positive link between exposure to pesticides and increased risk of breast cancer, and some have found no link or even a decreased risk of breast cancer. The studies briefly reviewed below all show a positive link between pesticides and breast cancer (those that fail to show such a link are reviewed in Appendix 1).

(a) *Canada – women in agriculture – 2002*
Brophy et al (2002) found a 3- to 9-fold increase in incidence of breast cancer amongst women with a history in agriculture. They compared the lifetime occupational histories of 299 women newly diagnosed with breast cancer and 237 women with other cancers, in Ontario, Canada. They also concluded, after reviewing 36 epidemiological studies, that "population-based studies that provided any adjustment for the 'healthy-worker' effect found evidence of a pesticide-breast cancer association". Farmers have generally been viewed as having above average health with lower rates of total mortality, heart disease and several cancers, thought to be because of reported lower rates of smoking, greater physical activity and possibly healthier diets—hence the healthy-worker effect.

(b) *Canada – women on farms – 2006*
An investigation into the occupations of women who developed breast cancer were 2.8 times more likely to have worked on farms than women who didn't get the disease. The study involved 564 women

from Windsor, Ontario who developed breast cancer between 2000 and 2002 (Brophy 2006).

(c) *Colombia – women in farming – 2000*
Band et al (2000) found significant associations, in both premenopausal and postmenopausal women, between breast cancer and involvement in crop farming and fruit and vegetable production that was likely to have entailed exposure to pesticides. In a matched case-control study, they used a self-administered questionnaire from 1,018 women with breast cancer and 1,020 population controls to collect information on lifetime occupational histories and on known and suspected breast cancer risk factors.

(d) *Poland – 1996*
Kocic et al (1996) found a significant association between occupational exposure to pesticides and breast cancer in a case-control study conducted in 1993-1994 in Poland. It involved 106 female patients with histologically documented breast cancer and matched controls amongst women with mild injuries, hospitalized at the Clinical Centre in Nish.

(e) *Costa Rica – 1999*
In an investigation into cancer incidence and exposure to pesticides in Costa Rica, Wesseling et al (1999) found an increased risk of breast cancer associated with heavy use of pesticides.

(f) *USA – farmers' wives – 2005*
Engel et al (2005) examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina. The women had no history of breast cancer prior to enrolment in the study from 1993 to 1997. By 2000, 309 breast cancer cases were identified. Risk of breast cancer was modestly elevated among women whose homes were closest to areas of pesticide application. There was significant increased risk associated with husband's use of 2,4,5-trichloro-phenoxypropionic acid (2,4,5-TP or silvex). There was also significantly increased risk associated with husbands' use of the organochlorine insecticides aldrin, dieldrin, heptachlor, lindane, chlordane, and toxaphene, but only in Iowa and not in North Carolina and with no dose-response relationship. There was also increased risk associated with husband's use of captan, paraquat, and of organophosphate insecticides especially dichlorvos, malathion, parathion, and chlorpyrifos; however patterns of risk were inconsistent between own use and husbands use, and between states.

All the increased risks associated with own use of pesticides occurred amongst premenopausal women. Risk of breast cancer related to own use of diazinon was significantly higher for women with a family history of breast cancer. However the small number of exposed cases (23) generally precluded firm conclusions.

(g) *USA – residential use – 2006*
Teitelbaum et al (2007) found an association between self-reported residential use of pesticides and breast cancer in a population-based case-control study of 1,508 women newly diagnosed with breast cancer on Long Island, New York, and 1,556 randomly selected, age-frequency-matched controls. There was an association between lawn and garden pesticide use and breast cancer risk, with no identified dose-response; but "little or no association" for "nuisance-pest" pesticides, insect repellants, or products to control lice or fleas and ticks on pets.

(h) *Belgium – potato cultivation – 2001*
Janssens et al (2001) analysed 1998 data on crops, pesticides and cancer statistics. They noted a correlation between mortality from breast cancer and use of defoliants and potato cultivation in Belgium.

(i) *China – 1998*
Petralia et al (1998) found a medium probability of increased incidence of breast cancer with high levels of occupational exposure to pesticides in China.

(j) *USA – women on farms – 2000*
A population-based case-control study (862 cases, 790 controls) of farming and breast cancer, in North Carolina, revealed a possible increased risk of breast cancer in those most likely to be exposed to pesticides—in particular women present in fields during or shortly after pesticide application (80% increased risk), and those who did not use protective clothing. It found no increased risk in women who did use protective clothing. It also found a reduced risk of breast cancer for women living or working on farms but less likely to be exposed to pesticides (Duell et al 2000). This may result from the protective effects of physical activity and Vitamin D generated by sunlight (Sanborn et al 2004), but these protective effects appear to be overcome by the pesticides.

(k) *USA – Mississippi – 2003*
Abdalla et al (2003) used total number of acres planted in Mississippi,

and type of crop, as a "proxy measure" for pesticide exposure. They found evidence of a potential association between pesticide exposure and risk of breast cancer mortality in three areas: Greenville, Corinth and Yazoo. The total number of acres planted was positively and significantly associated with female breast cancer mortality rate, and these associations differed by race and type of crop. The strongest correlation was between breast cancer mortality rate for white women and rice crops planted in Yazoo. Moderate correlations were found between African-American breast cancer mortality rates and total acres planted in Corinth, catfish crops in Greenville and, although not statistically significant, also with total planted acres in Greenville.

(l) *Organochlorine pesticide waste – USA*
O'Leary et al (2004) found an increased breast cancer risk for women residing within one mile of hazardous waste sites containing organochlorine pesticides, on Long Island, New York. They conducted a nested case-control study of 105 women diagnosed with breast cancer between 1980-1992, and 210 age and race-matched controls, and estimated the historical environmental exposure to pesticides based on land use and contamination of drinking water.

4.3 ORGANOCHLORINE INSECTICIDES

Organochlorine insecticides persist in the environment, in food, in wildlife, and in our bodies. They were the first generation of insecticides, used in huge quantities all round the world, and as a result they contaminate the environment worldwide. They also contaminate humans worldwide, but most particularly people in agricultural areas—studies show these populations have body burdens of chlorinated pesticides second only to people in the pesticide industry (Brophy et al 2002). These pesticides are no longer used in developed countries, having been replaced by less persistent chemicals. Some are, however, still produced and used in developing countries; and leaking, unsealed stockpiles of obsolete organochlorines also occur throughout Asia and the Pacific Islands, posing a risk of ongoing unnecessary exposure, contamination, and breast cancer (UNEP 2002a,b,d).

Because of their persistence and widespread dispersal in the environment and the food chain, the organochlorine pesticides affect women in all corners of the globe. They have been found in female blood, urine, breast milk, adipose tissue, amniotic fluid, ovarian follicular fluid, placental tissue, umbilical cord blood, and infant meconium (first faeces).

In the Asia Pacific region aldrin, chlordane and its metabolites, DDT and its metabolites, dieldrin, endrin, endosulfan and it metabolites, HCB, heptachlor and its metabolite, and lindane have been found variously in breast milk in Australia, Cambodia, China, Hong Kong, India, Indonesia, Iran, Israel, Japan, Jordan, Kazakhstan, Kuwait, Kyrgyzstan, Malaysia, New Zealand, Pakistan, Papua New Guinea, Samoa, Saudi Arabia, Sri Lanka, Taiwan, Tajikistan, Thailand, Turkey, Turkmenistan, and Viet Nam.[3]

Organochlorine insecticides have been found in female adipose tissue in China (Nakata et al 2005), Hong Kong (Poon et al 2005), and Singapore (Li et al 2006). They have been found in blood samples in many countries in the region, including Australia, India, Japan, Kazakhstan, Kyrgyzstan, New Zealand, Pakistan, Singapore, Thailand, Viet Nam, and Uzbekistan.[4] They have also been found in umbilical cord blood in India, Japan, Thailand, Kazakhstan and Kyrgyzstan,[5] and meconium in the Philippines (Ostrea et al 2002), indicating maternal burden of, and foetal exposure to, organochlorine pesticides. UNEP (2002b) reported an almost complete lack of body burden studies in the Pacific Islands, except for those breast milk results cited here.

More epidemiological studies have been carried out on the potential links between breast cancer and organochlorine insecticides than with any other pesticides. This is no doubt because residues of these chemicals are easily measured in adipose tissue, serum and breast milk due to their persistence; and because many of the organochlorines have been shown in the laboratory to be endocrine disruptors influencing oestrogen levels, and

3 Australia (Stevens et al 1993), Cambodia (Kunisue et al 2004a), China (Kunisue et al 2004b; Sun et al 2005), Hong Kong (Wong et al 2002), India (Nair et al 1992, 1996; Kalra et al 1994; Banerjee et al 1997; Sanghi et al 2003), Indonesia (Burke et al 2003; Sudaryanto et al 2006), Israel (Westin 1993), Iran (UNEP 2002a), Japan (Konishi et al 2001; Kunisue et al 2005), Jordan (Nasir et al 1998), Kazakhstan (UNEP 2002d), Kuwait (Saeed et al 2000), Kyrgyzstan (UNEP 2002c), Malaysia (Sudaryanto et al 2005), New Zealand (Bates et al 1990, 1994, 2001), Pakistan (UNEP 2002a), Papua New Guinea (UNEP 2002b), Samoa (UNEP 2002b), Saudi Arabia (Al-Saleh et al 1998; UNEP 2002a), Sri Lanka (UNEP 2002a), Taiwan (Chao et al 2006), Tajikistan (Lederman 1996), Thailand (Zimmerman et al 2005), Turkey (Basri et al 1994; Erdogrul et al 2004), Turkmenistan (Lederman 1996), and Viet Nam (Minh et al 2004).

4 Australia (UNEP 2002d), India (UNEP 2002a; Mathur et al 2005), Japan (Tsukino et al 2006), Kazakhstan and Kyrgyzstan (UNEP 2002c), New Zealand (UNEP 2002d), Pakistan (UNEP 2002a), Singapore (UNEP 2002d), Thailand (Asawasinsopon et al 2006), Viet Nam (Scheter et al 1997), Uzbekistan (UNEP 2002c).

5 India (Nair et al 1996), Japan (Fukata et al 2005), Thailand (Asawasinsopon et al 2006), Kazakhstan and Kyrgyzstan (UNEP 2002d).

carcinogens. Some epidemiological studies have shown a link and some have not shown a link. A selection of these studies are summarised here. DDT and its metabolite DDE have been the main focus of studies, with dieldrin, HCB, and HCH less well studied; and endosulfan and heptachlor hardly at all, despite the laboratory evidence indicating a strong potential role in breast cancer.

One of the earliest studies—that by Wasserman et al (1997) on 9 women with breast cancer and five controls—found elevated levels of DDT in cancerous breast tissue as opposed to non-cancerous breast tissue. However, perhaps one of the most famous studies was that referred to as the "Israeli breast cancer anomaly" (Westin & Richter 1990; Westin 1993). Three pesticides—*alpha*-BHC, *gamma*-BHC (lindane), and DDT—were present in Israeli milk and diary products, for ten years or more, at mean concentrations up to 100 times those found in USA dairy products, resulting in concentrations in breast milk up to 800 times greater than those in the United States. After considerable public pressure and court action, the pesticides were banned. This resulted in a "precipitous drop" in the concentrations of the pesticides in milk. This was then followed by a "dramatic drop in breast cancer mortality rates", which is attributed to the removal of the pesticides (Westin 1993).

4.3.1 DDT

[endocrine, epidemiology, carcinogen, immune]

DDT is a persistent organochlorine insecticide that has been used around the world for many years. It was first synthesized in Strasbourg in 1874. A young chemistry student Paul Müller at the J.R. Geigy laboratories in Basel (Switzerland) discovered its insecticidal properties against the Colorado potato beetle in 1939 (Whorton 1974). Following successful trials in the USA in 1942, large-scale industrial production began in 1943 (Turusov et al 2002) and all available stocks of the insecticide were immediately appropriated by the US Army, for combating lice in Europe and mosquitoes in the Pacific. Its use on civilian populations to quell insect-borne epidemics was widespread, with the insecticide "being used so freely as even to replace rice at weddings" (Whorton 1974). It became available for widespread commercial use in US agriculture in 1945 (Biskind 1953). The first environmental problems—toxicity to fish and frogs—were noted as early as 1944. By 1945 scientists knew that DDT accumulated in the body fat and milk of laboratory animals. Warnings of adverse human health impacts soon began appearing. New York physician Dr Morton Biskind reported,

in 1953, that by 1950 the United States government had begun to recognize the human health implications of DDT (Watts 2000). In 1951 the United States Public Health Service acknowledged that:

> ***Due to the fact that DDT accumulates in the body tissues, especially in females, the repeated inhalation or ingestion of DDT constitutes a distinct health hazard. The deleterious effects are manifested principally in the liver, spleen, kidneys and spinal cord.***
>
> (English 1951)

In 1962 scientist Rachel Carson published her book *Silent Spring*, providing compelling evidence of the environmental effects of DDT, especially on the survival of bird species. In January 1968 the state of Arizona imposed an experimental one-year ban (Wildavsky 1995), but the first country to totally ban DDT was Hungary, in 1969. The USA followed suit in 1972.

Yet use of DDT remains widespread in many developing countries, principally for malaria control, even as evidence of its endocrine disrupting properties gathers. UNEP reports, dated 2002, state that DDT was still being used in India, Pakistan, Bangladesh, Myanmar, Nepal, Iran, Papua New Guinea, Philippines, and Solomon Islands for malaria control; and in rural Kazakhstan, Mongolia, Tajikistan and Turkmenistan (UNEP 2002a,b,c,d). Use has also been reported in Cambodia even though DDT was officially banned there (CEDAC 2004). China still has production facilities, as does India (UNEP 2002d). It is registered for use in India. DDT is on the list of chemicals for global elimination under the Stockholm Convention on Persistent Organic Pollutants, but China has an exemption to produce DDT as an intermediate in the production of dicofol until May 2009; and the Marshall Islands and Myanmar have exemptions to use DDT for mosquito control (UNEP 2006). In 2005 China produced 3,236 metric tonnes of DDT; of this 450 metric tonnes was exported (IHPA 2006). The Tajikistan customs services seized 7.5 tons of illegally imported DDT in 2005 (IHPA 2006).

In some developing Asian countries, children's estimated intake of DDT is reported to be 100 times greater than the admissible daily intake (ADI) established by the World Health Organisation (WHO), in 1985, at 0.02 mg/kg (Turusov et al 2002). Stuetz et al (2001) also reported that in 1998, the estimated daily intakes of DDT, heptachlor and heptachlor-epoxide by the infants in the Hmong hill tribe in Northern Thailand were found to exceed up to 20 times the acceptable daily intakes as recommended by the WHO.

DDT is actually a complex mixture of several congeners (related chemicals),

principally *p,p'*-DDT (about 77 percent) and *o,p'*-DDT (15-23 percent). In the environment it degrades to several metabolites, the most persistent and prevalent of which is DDE.

DDT is carcinogenic and an endocrine disruptor, and disrupts the immune system, all factors leading to an increased risk of breast cancer.

Carcinogenicity

The International Agency for Research on Cancer (IARC) classified *p,p'*-DDT as a 'possible human carcinogen' (Group 2B), on the basis of sufficient evidence of carcinogenicity in animals, but inadequate evidence in humans (IARC 1991).

The main metabolites, *p,p´*-DDE and *p,p´*-DDD, are also regarded as being carcinogenic, causing liver tumours, lung tumours, lymphomas, and adrenal adenomas in laboratory studies (Turusov et al 2002).

Results from laboratory studies on the genotoxicity of DDT are inconsistent and inconclusive (refer TOXNET: http://toxnet.nlm.nih.gov). However, recent studies on women and children in Mexico demonstrated significant associations between exposure to *p,p'*-DDT and *p,p'*-DDE, and damage to their DNA (Yanez et al 2004; Perez-Maldonado et al 2006).

DDT inhibits gap junction intercellular communication (GJIC) at non-cytotoxic concentrations (Tateno et al 1994), undermining its essential role in the regulation of cell proliferation and growth of tumours.

Immune effects

DDT affects the immune system, reducing the ability of Natural Killer T-cells to destroy tumour cells (Reed et al 2004).

Endocrine disruption

Many laboratory studies have identified some congeners of DDT as environmental estrogens (Snedeker 2001), and have found that they enhance the growth of oestrogen-positive breast tumours (Robison et al 1985). The congeners differ in their oestrogenic potential: the strongest is *o,p'*-DDT which has consistently shown an oestrogenic response in lab tests; *p,p'*-DDT has shown a weaker response, and *p,p'*-DDE an even weaker or no response. There is evidence that *o,p'*-DDT binds to the oestrogen receptor to exert its oestrogenic effect (Leaños-Castañeda et al 2007); and

there is evidence that DDE can bind to the androgen receptor, induce androgen receptor transcriptional activity, and act as an anti-androgen (Snedeker 2001). Kojima et al (2004) found DDE and DDT to be both oestrogenic and anti-androgenic. Technical DDT and *o,p´*-DDT can support the growth of oestrogen-dependent breast tumours in rats, whereas *p,p´*-DDD is unable to support breast tumour growth (Snedeker 2001). Additionally DDE, at very low concentrations, raises cellular calcium levels, which then cause rapid secretion of prolactin (Wozniak et al 2005).

Other evidence from recent studies:

(a) *Bradlow et al (1995)* – DDT and *o,p´*-DDE increased the ratio of 16-hydroxyestrone (the tumour promoting oestrogen) to 2-hydroxyestrone (the non-genotoxic oestrogen)—thus increasing the risk of breast cancer. The higher the ratio, the greater the effect on breast cancer cell proliferation, development, and promotion.

(b) *Brown & Lamatiniere (1995)* – in pubertal rats *o,p´*-DDT enhanced mammary gland differentiation and increased cell proliferation, which promotes maturation of the undifferentiated terminal end buds. Terminal end buds are the least mature ductal structures in the mammary gland, containing multipotent stem cells, and are the most susceptible to carcinogens.

(c) *Dees et al (1997)* – DDT increased the growth of MCF-7 human breast cancer cells and the effect was much stronger in the presence of insulin. Oestrogen-positive cells treated with DDT were found to have increased phosphorylation of cyclin-dependent kinase (an enzyme), and increased synthesis of cyclin D1 protein (a protein involved in the progression of cells through the cell cycle). This suggests that DDT can stimulate breast cancer cells by directly affecting key regulatory elements.

(d) *Burow et al (1999)* – DDT suppressed apoptosis in oestrogen-responsive cells. Apoptosis is a process of cell death in which specific cells undergo a programmed series of biochemical events ending in the elimination of the cells. The MCF-7 breast cancer cell line undergoes apoptosis, leading to tumour regression, if oestrogen is removed. DDT hence acts to prevent tumour regression.

(e) *Payne et al (2001)* – a mixture of *o,p'*-DDT, *p,p'*-DDT, *p,p'*-DDE, and *beta*-BHC acted together to produce proliferative effects in MCF-7 human breast cancer cells and the combined effect was additive.

(f) *Holloway et al (2005)* – DDE increased activity of the enzyme complex aromatase which catalyses the conversion of androgens to oestrogens, hence increasing circulating oestrogens.

(g) *Lemaire et al (2006)* – DDT activated oestrogen receptors.

Epidemiology

Summarised below are the studies showing a positive link between exposure to DDT/DDE and breast cancer. Those studies that did not find a link are summarised in Appendix 2.

(a) *California Child Health and Development Study (USA)* – Cohn et al (2007) found a statistically-significant five-fold increase in the risk of breast cancer associated with *p,p'*-DDT among young American women who were under the age of 14 in 1945 when widespread use of DDT began in the USA, and mostly under the age of 20 when that use peaked. With a prospective, nested case-control design involving 129 cases and 129 age-matched controls, they used blood samples obtained from young women from 1959 to 1967. This was the period of peak DDT use in America and these women were exposed during the vulnerable periods of childhood and adolescence. The median time to diagnosis was 17 years, and the mean age at diagnosis was 44 years. The authors noted that many US women heavily exposed to DDT during childhood have not yet reached the age of 50, and hence the period of elevated breast cancer incidence. So the full effects of DDT on breast cancer may not yet have been felt in the USA and other countries that banned its use long ago, let alone in those countries in which it is still being used, such as India and a number of African countries. Neither *o,p'*-DDT nor *p,p'*-DDE were associated with increased risk of breast cancer.

(b) *New York Women's Health Study (USA)* – Wolf et al (1993) found a nearly four-fold higher risk of developing breast cancer in women with the highest levels of serum DDE. They obtained blood from 14,290 women enrolled in the New York Women's Health Study between 1985 and 1991, and used 58 cases and 171 matched controls.

(c) *Denmark* – Hoyer et al (2000a) conducted a cohort nested case-control study of 155 cases and 274 matched breast cancer-free controls that had participated in the Copenhagen City Heart Study. They had donated blood twice, in 1976-1978 and 1981-1983. A high serum concentration of *p,p'*-DDT over the course of the two examinations

was associated with a more than three-fold increased risk of breast cancer, and a dose-response relationship was apparent.

(d) *Belgium* – Charlier et al (2003) compared the serum levels of total DDT (and HCB) in 159 women with breast cancer and 250 "presumably healthy" women. They found that mean levels of total DDT and HCB were significantly higher for breast cancer patients than for controls.

(e) *Belgium* – Charlier et al (2004) compared the serum levels of DDE and HCB in 231 women at the time of breast cancer discovery and in 290 age-matched healthy controls. DDE was found in 76.2 percent of cases and in 71.1 percent of controls but HCB was present only in 12.6 percent of cases (29 from 231) and in 8.9 percent of controls (26 from 290). They found that the presence of both residues was significantly associated with an increased risk of breast cancer development.

(f) *China* – After adjusting for confounding factors, Li et al (2006b) found that high serum *p,p'*-DDT and *p,p'*-DDD were positively correlated with breast cancer levels in premenopausal women. Their findings resulted from a case-control study involving 90 new breast cancer patients and 136 women from the same district in China.

(g) *Mexico* – Romieu et al (2000) analysed the relation between lactation history, serum levels of DDT and DDE, and the risk of breast cancer amongst 120 cases and 126 controls living in Mexico City between 1990 and 1995, who had given birth to at least one child. They found an increased risk of breast cancer associated with higher serum levels of DDE, more apparent among postmenopausal women. A longer period of lactation was associated with a slightly decreased risk of breast cancer independently of serum DDE levels. Serum DDT level was not related to the risk of breast cancer.

(h) *Germany* – Guttes et al (1998) found significantly higher levels of *p,p'*-DDE in breast tumour tissue of 45 women with breast cancer compared to tissue from 20 women with benign breast disease. On average, there was a 62 percent higher concentration of *p,p'*-DDE in cancer tissue. They also found a weakly significant increase in *p,p'*-DDT and HCB in cancer tissue.

(i) *Canada* – Aronson et al (2000) found higher levels of *p,p'*-DDT and *p,p'*-DDE in the biopsy tissue of 217 breast cancer cases in Ontario than in 213 benign controls, in a hospital-based case-control study (together with higher levels of HCB, *beta*-HCH, and mirex).

(j) *Colombia* – Olaya-Contreras et al (1998), in an epidemiological study of 153 breast cancer cases and 153 age-matched controls, found a positive association between serum DDE and risk of breast cancer.

(k) *Eastern Slovakia* – A small case-control study, in 1998-99, of 24 breast cancer patients and 88 population controls, found higher serum levels of DDE were positively associated with risk of breast cancer. There was no association for DDT, and a 'not statistically significant' inverse association for HCB (Pavuk et al 2003).

(l) *Canada* – Dewailly et al (1994) compared the concentrations of DDE in breast adipose tissue of nine women with oestrogen receptor positive breast tumours (ER +ve), nine women with oestrogen receptor negative tumours (ER –ve) and 17 controls with benign breast disease. They found that women with ER +ve breast tumours had a higher body burden of DDE than women with ER –ve tumours or benign breast disease.

(m) *Jaipur, India* – Mathur et al (2002) found that higher serum levels of organochlorine pesticides were associated with breast cancer among women originating from Jaipur, irrespective of age, diet, and geographic distribution. They sampled for DDT and its metabolites DDD and DDE, dieldrin, heptachlor, and HCH and its isomers (*alpha*, *beta*, and *gamma*).

(n) *USA* – Falck et al (1992) found elevated levels of DDE and DDT in fat samples from women with breast cancer, compared with those who had benign breast disease.

(o) *Egypt* – Ahmed et al (2002), using 43 breast cancer cases, 21 women with benign breast disease, and 11 controls, found higher levels of DDE in serum of women with breast cancer or benign breast disease than in controls. However the study was not well controlled for confounding factors, including age.

(p) *Spain* – Ibarluzea et al (2004) found higher levels of DDE, aldrin, endosulfan and lindane in adipose tissue of women with breast cancer cases (198) than in controls (260), and an increased risk of breast cancer associated with these findings, especially in leaner postmenopausal women—in a hospital-based case-control study involving 198 cases and 260 controls.

(q) *Mexico* – Waliszewski et al (2005) found consistently higher levels of

all organochlorine pesticides tested (DDT, HCB, *beta*-HCH) in breast adipose tissue of women with benign breast tumours than in women with malignant breast tumours; and similarly higher levels in women with malignant breast tumours than in the abdominal adipose tissue of women who had died in car accidents. The study carried out in the City of Veracruz involved 127 women with benign tumours, 127 with malignant tumours and 127 controls. Mexico was spraying DDT for malarial vector control up to 1999, so exposure is considered to be relatively recent.

(r) *Argentina* – Munoz-de-Toro et al (2006) concluded that organochlorine residues in adipose tissue adjacent to a malignant breast tumour generate an oestrogenic environment that may contribute to the severity of breast cancer by influencing the biological behaviour of the tumour, through activation of the alpha positive oestrogen receptor (ER alpha +ve) and subsequent ER alpha-dependent cell proliferation. There was a positive correlation with the expression of progesterone receptors (which are oestrogen induced) in the cancer cells. All the ER alpha +ve breast tumours in postmenopausal women exhibited high proliferation when organochlorine levels were higher than 2600ppb. The study involved 55 women with invasive breast cancer in Argentina. All had high levels of organochlorine pesticides in the breast adipose, most frequently DDE, HCB, and *beta*-HCH.

(s) *Canada* – Demers et al (2000) found that higher levels of *p,p'*-DDE, *beta*-HCB, and the metabolites of chlordane (oxychlordane and trans-nonachlor), were associated with increased invasiveness of the cancer into the lymph nodes, even though there was no association between levels of the chlorinated pesticides in blood and breast cancer. Their study included 315 women with primary breast cancer and 219 controls recruited from hospitals in Quebec, Canada.

(t) *Belgium* – Charlier & Dejardin (2007) found that higher levels of organochlorine pesticides, primarily *p,p'*-DDE, in serum were associated with relapse of breast cancer. This retrospective study involved 125 breast cancer patients who had undergone curative surgery followed by chemotherapy or hormonal therapy.

(u) *Canada* – Woolcott et al (2001) found that higher levels of DDE in breast adipose tissue were significantly associated with oestrogen receptor negative breast cancer, in a case-control study involving 217 cases and 213 biopsy controls matched for age.

Additionally Den Hond & Schoters (2006), in their review of epidemiological research studying the effect of endocrine disrupters on the onset of puberty, found that earlier age of menarche in girls was reported after exposure to DDT, effectively extending the window of life-time exposure to oestrogens.

The UNEP (2002c) report on persistent toxic substances in the South-East Asia and South Pacific region states that DDT residues may be implicated in breast cancer, based on findings reported in Australia and Singapore. It noted that plausible mechanisms exist for such an effect and, in Australia, the breast cancer incidence has significantly increased "consistent with the usual delay or latency period between exposure and effect for carcinogens".

Ritter et al (undated), in their assessment report on persistent organic pollutants for the International Programme on Chemical Safety (IPCS) stated that there is "limited data that suggest a possible association between organochlorines, such as DDT and its metabolite DDE, and risk of breast cancer".

4.3.2 Dieldrin

[endocrine, epidemiology]

Dieldrin is another organochlorine insecticide that has been used in many countries since production began in 1948, mainly for soil insects but also for cotton pests and in timber processing. Its use has resulted in environmental contamination worldwide. Dieldrin was reported to be still in use in India for locust control in 2002, and in Bangladesh, Myanmar, and Nepal (UNEP 2002a).

Dieldrin is widely found in breast milk, human adipose tissue and blood serum. It can cross the placenta and accumulate in the foetus (Jorgenson 2001).

Carcinogenicity

IARC has not been able to classify dieldrin as to its carcinogenicity because of inadequate evidence. In mice, it produced benign and malignant liver tumours and in trout it enhanced the incidence of liver tumours induced by dietary administration of aflatoxin B (IARC 1987). Barton et al (2005) reported that foetal or postnatal exposure to dieldrin has resulted in carcinogenic effects in animals. It has been suggested that the dieldrin-induced liver tumours result from oxidative stress causing DNA S-phase synthesis, rather than from mutagenic mechanisms (Bachowski et al 1997).

Endocrine disruption

A number of studies have shown that dieldrin has both oestrogenic and anti-androgenic properties (Soto et al 1994,1995; Danzo 1997; Petit et al 1997; Kojima et al 2004). Jorgenson (2001) reported that in 10 yeast-based assays for oestrogen receptors, performed by four laboratories, dieldrin in a mixture with toxaphene was found to have an additive effect.

Dieldrin causes changes to intracellular oestrogenic signalling by mimicking the effects of oestrogen—raising cellular Ca_2^+ (calcium) which then causes rapid secretion of prolactin which in turn causes cell proliferation—at very low (picomolar to nanomolar) concentrations such as 10^{-12} M (Wozniak et al 2005). The anti-androgenic effect occurs as a result of binding to the androgen receptor (Danzo 1997).

Epidemiology

Epidemiological studies have shown a more consistent association between dieldrin and increased risk and severity of breast cancer than they have for other organochlorine pesticides, in particular a series of studies that took place as a subset of the Copenhagen City Heart Study (Denmark). In 1976, researchers obtained blood serum samples from 7,712 women who participated in the study. Over the following two decades, 240 women in the study developed breast cancer. Subsequently a number of investigations were carried out, by Hoyer and colleagues, on possible links between this breast cancer and levels of organochlorine pesticides (lindane, chlordane, DDT, DDE, *beta*-HCH, and dieldrin) in the serum samples. Associations were found only with dieldrin and HCH.

(a) *Hoyer et al (1998) – positive link, greater aggressiveness of cancer*
This study reported a statistically significant dose-response relationship between dieldrin and breast cancer. The risk of breast cancer was more than twice as high in women with the highest serum concentrations of dieldrin compared with those with the lowest concentrations. Additionally the cancers in the women with higher dieldrin levels were more aggressive.

(b) *Hoyer et al (2000b) – decreased survival*
A total of 195 breast cancer cases, each of which provided two blood samples, in 1976-78 and 1981-83, were included in the survival analysis. Dieldrin had a significant adverse effect on overall survival and breast cancer specific survival. These findings suggest that past exposure to

oestrogenic organochlorines such as dieldrin may not only affect the risk of developing breast cancer but also survival.

(c) *Hoyer et al (2001) – oestrogen receptor negative*
Using a cohort nested case-control design including 161 cases and twice as many breast cancer-free controls, this study found that the observed increased breast cancer risk associated with exposure to dieldrin came from women with an oestrogen receptor negative tumour. In these women, the highest dieldrin serum levels were associated with larger tumours, and tumours that had more frequently spread at the time of diagnosis.

(d) *Cape Cod, USA* – Jorgenson (2001) reported that, although a study in Cape Cod in which workers exposed to dieldrin through their occupations showed no increases in breast cancer, the maps delineating areas with breast cancer mortalities and those showing areas with high dieldrin exposure have a high degree of correlation.

(e) *Long Island, USA* – A population-based case control study of 646 women with breast cancer and 429 controls on Long Island, New York, found an elevated odds ratio for dieldrin and breast cancer, of 1.37. However this was reported by the authors as being non-significant and showing no s*ubstantial* elevation in risk (Gammon et al 2002).

(f) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk associated with husbands' use of dieldrin in Iowa. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (16) amongst those whose husbands had used it precluded firm conclusions.

4.3.3 Chlordane

[endocrine, immune, epidemiology]

Chlordane has been used as a broad-spectrum insecticide since the 1950s (IARC 1991), commonly against cockroaches, ants, termites, and other household pests (UNEP 2002a). Technical grade chlordane is a mixture of at least 26 chemicals, some reports putting this at up to 140 chemicals, including heptachlor. The main components are cis- and trans-chlordane. These two isomers can be converted to the metabolites oxychlordane and heptachlor. All of these chemicals are very persistent and lipophilic, and

found in human tissue, blood and breast milk, as is another component of chlordane, nonachlor. They are mainly stored in adipose tissue (Wandji et al 1998a).

Chlordane is on the list of chemicals for global elimination under the Stockholm Convention on Persistent Organic Pollutants. Exemptions under this Convention allow for ongoing production and use in China, and use in Japan, as a termiticide (UNEP 2006). In 2002 agricultural use was still reported for Tajikistan (UNEP 2002a). Use was also reported in Cambodia even though chlordane is officially banned there (CEDAC 2004). It was still being exported by the USA to Malaysia, Singapore and India in 1995 (Sherman 2000). There were obsolete stocks in other countries such as Uzbekistan, Nepal, and Niue (UNEP 2002a,c,d).

Carcinogenicity

Chlordane is classified by IARC (1991) as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals (liver tumours, thyroid follicular-cell neoplasms). Mammary gland fibroadenomas have been reported in rats (Khasawinah & Grutsch 1989).

It is genotoxic in yeast (Chambers & Dutta 1976; Gentile et al 1982) and human cells (Ahmed et al 1977); and it is a tumour promoter (Williams & Numoto 1984).

Chlordane inhibits gap junction intercellular communication (Ruch et al 1990), and appears to be capable of generating oxidative tissue damage (Hassoun et al 1993).

There is limited evidence of cancer in humans following exposure to chlordane including neuroblastoma, leukaemia, non-Hodgkin's lymphoma, stomach cancer, and lung cancer (Wandji et al 1998a).

Immune effects

Chlordane interferes with the immune system, reducing the ability of Natural Killer T-cells to destroy tumour cells (Reed et al 2004). The developing foetal immune system appears to be particularly vulnerable to chlordane, with altered immune function being reported consistently for prenatal exposures (Wandji et al 1998a).

Endocrine disruption

Chlordane is oestrogenic (Soto et al 1995; Cossette et al 2002; Kojima et al 2004).

It also induces expression of prolactin (Rousseau et al 2002). It affects the metabolism of 17*beta*-estradiol and progesterone, both of which are important in stimulating breast cell proliferation in the mature breast (Wandji et al 1998). Trans-nonachlor and chlordane activate oestrogen receptors (Lemaire et al 2006). Chlordane has also been found recently to activate the oestrogen-forming enzyme aromatase in cancer cells in the human placenta (choriocarcinoma) (Laville et al 2006).

Epidemiology

Two studies have found an association between tissue levels of chlordane and breast cancer, and one between exposure to chlordane and breast cancer.

(a) *Canada* – Demers et al (2000) found higher levels of the metabolites of chlordane, oxychlordane and trans-nonachlor, (along with DDE, HCB) associated with increased invasiveness of breast cancer into the lymph nodes, even though there was no association between levels of the chlorinated pesticides in blood and breast cancer. Their study included 315 women with primary breast cancer and 219 controls recruited from hospitals in Quebec, Canada.

(b) *USA – Hispanic agricultural workers* – In a case-control study of breast cancer in farm labour union members in California, involving 128 breast cancer cases newly diagnosed in 1988-2001 and 640 cancer-free controls, Mills & Yang (2005) found increased risk of breast cancer associated with exposure to chlordane (and malathion and 2,4-D). Risk associated with chemical use was stronger in younger women, those with early-onset breast cancer, and those diagnosed earlier (1988-1994).

(c) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk associated with husbands' use, but not with own use, of chlordane in Iowa. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. There were 52 cases in which exposure through husband's use was identified.

4.3.4 Methoxychlor

[mammary tumours, endocrine, epidemiology]

Methoxychlor is an organochlorine insecticide still used on a wide range of crops, and in houses, as an alternative to DDT. It converts to 2,2-bis(p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE), which is thought to be the active agent. It is persistent in the environment and found in human blood (IARC 1979).

Methoxychlor is a mammary carcinogenic and an endocrine disruptor.

Carcinogenicity

In laboratory animals it has been found to cause liver, testes, bone, and ovarian cancers, as well as sarcomas of the spleen and abdomen, and tumours of the pituitary, adrenal glands, and mammary gland, and hyperplasia of the mammary gland and uterus (Reuber et al 1980).

Endocrine disruption

Methoxychlor is both oestrogenic and anti-androgenic (Kojima et al 2004; Murono & Derk 2005). It binds to oestrogen receptors and androgen receptors in MCF-7 human breast cancer cells (Okubo et al 2004), activates oestrogen receptors (Lemaire et al 2006), and affects prolactin release increasing serum levels (Lafuente et al 2000, 2003). Soto et al (1995) found that methoxychlor causes proliferation of MCF-7 cells. Methoxychlor has also induced mammary gland development in male rats (Wang et al 2006).

Methoxychlor has been found recently to activate aromatase in cancer cells in the human placenta (Laville et al 2006).

Prenatal exposure to methoxychlor produced an inverted U dose-response relationship in terms of the response of adult mice to 17*beta*-oestradiol, with a low dose of methoxychlor increasing uterus weight and a high dose decreasing it (Alworth et al 2002), indicating that the insecticide is hormonally active at low doses in ways that are not recognised by the normal toxicological assessment processes based on high dose exposure. Hence exposure to this chemical through normal agricultural use is of considerable concern with respect to breast cancer.

The metabolite, HPTE, is oestrogenic in MCF-7 breast cancer cells (Li et al 2006c).

Epidemiology

Mills & Yang (2006) evaluated the relationship between pesticide use data and breast cancer incidence rates in Hispanic women in California (USA), using 1988-2000 data from the California Cancer Registry and pesticide use data from 1970-1988. A total of 23,513 Latinas were diagnosed with breast cancer in California during the years 1988-1999. Risk of breast cancer was positively associated with pounds of methoxychlor and toxaphene used.

4.3.5 Heptachlor

[endocrine, epidemiology, carcinogen, immune]

Heptachlor is an insecticide used primarily against soil insects and termites, but also cotton insects, grasshoppers and malaria mosquitoes (UNEP 2002a). Heptachlor epoxide is its more persistent breakdown product.

Heptachlor has been banned or is not used in most countries in the region. It was still being used on pineapple fields in Hawaii in 1993 (Allen et al 1997). However it was reported to be still in use in Japan (wooden structures), Korea, Papua New Guinea, and Uzbekistan in 2002 (UNEP 2002d). It is widespread in the environment and food chain (UNEP 2002a), so it is likely that exposure is still occurring. Heptachlor is also on the list of chemicals for global elimination under the Stockholm Convention on Persistent Organic Pollutants; exemptions allow for ongoing use in Japan as a termiticide (UNEP 2006).

Both heptachlor and its epoxide accumulate in fat, and are commonly found in the breast milk of women, e.g. in Australia (UNEP 2002c), Turkey (Basri et al 1994), Iran (UNEP 2002a), Kuwait (Saeed et al 2000), Taiwan (Chao et al 2006), Hong Kong (Poon et al 2005), Saudi Arabia (Al-Saleh et al 1998). They are both also found commonly in umbilical cord blood—for example the epoxide was found in 100 percent of umbilical cord tissue and 95 percent of umbilical cord blood in a study in Japan (Fukata 2005) and in 8 out of 10 samples of umbilical cord blood from newborn infants in the USA (EWG 2005). This indicates transfer of the chemicals from mother to the foetus *in utero* at a time of heightened vulnerability of the developing breast tissue to influences that lead to breast cancer later in life.

On the island of Oahu, Hawaii, heptachlor was sprayed onto pineapple plants and the leaves subsequently chopped and fed to dairy cows. This led to the contamination of the commercial milk supply for 15 months between 1981 and 1982. Subsequently lactating women who had consumed

dairy and meat products were found to have an average of 200 ppm heptachlor in their breast milk, in some cases as much a 400 ppm. More than 10 years later the levels of heptachlor epoxide in breast milk were still higher on Oahu than on neighbouring islands (Allen et al 1997).

Carcinogenicity

Heptachlor is classified by IARC as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals for carcinogenicity, but inadequate evidence in humans (IARC 1991). It is classified as a 'probable human carcinogen' by the US EPA (IRIS 1997), and has been determined to be carcinogenic to the liver (National Toxicology Program 1997).

Endocrine disruption

Heptachlor epoxide is oestrogenic, reacting with oestrogen receptor ER-*beta* (Kojima et al 2004).

Breast cancer mechanisms

There are a number of mechanisms by which heptachlor may contribute to the initiation, promotion, and progression of breast cancer. At concentrations similar to those found in breast tissue from women with breast cancer it has been found to increase the levels of oxidants that potentially cause oxidative stress, and to cause damage to DNA and lymphocytes (Cassidy et al 2005). It has also been found to affect the liver's metabolism of oestrogen in a way that increases the circulating levels of oestrogen, to disrupt cell growth regulation in human breast cells in tissue culture (Dich et al 1997), to inhibit the immune system's Natural Killer T-cells which are important in tumour suppression (Reed et al 2004), as well as to modify the activity of the cytochrome P450 enzyme system involved in detoxifying chemicals in a manner that could "potentiate the ... carcinogenicity of environmental carcinogens" (Shewita et al 2004). Heptachlor epoxide also inhibits gap junction intercellular communication in normal human breast epithelial tissue at non-cytotoxic concentrations (Nomata et al 1996).

Epidemiology

(a) *Australia* – A recent study in a rural part of Australia, using breast cancer incident data from 1983 to 2002, found a positive dose-response

relationship between breast cancer and contamination of breast milk with heptachlor epoxide (Khanjani et al 2006, 2007).

(b) *USA* – Cassidy et al (2005) found an association between levels of heptachlor epoxide in biopsy tissue and incidence of breast cancer in 34 women evaluated for breast abnormality.

(c) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk associated with husbands' use, but not with own use, of heptachlor in Iowa. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (35) amongst those whose husbands had used it precluded firm conclusions.

4.3.6 Endosulfan

[endocrine, immune, carcinogenicity]

Endosulfan is another broad-spectrum insecticide, first made available for use in many countries in the 1950s. Unlike many of the other organochlorines that have become more or less obsolete or confined to public heath uses, endosulfan use in agriculture is still widespread, even though the pesticide is persistent and contaminates every aspect of the environment from soil to snow, including the bark of trees (see PAN Int 2007 for a summary of this). Although it has been banned in many countries in the region such as Cambodia, Kuwait, Sri Lanka, Philippines and Malaysia, other countries still use it, including India, New Zealand, Australia, Nepal, Bangladesh, Fiji, Pakistan, and Vanuatu (PAN Int 2007; UNEP 2002a,b).

Endosulfan is also a common human contaminant, and has been found in breast milk, adipose tissue, placental tissue, and umbilical cord blood (Cerrillo 2005). In 2003 infants in Bhopal, India were found to be consuming, through breast milk, 8.6 times more endosulfan than the average daily intake levels recommended by the World Health Organization (Sanghi et al 2003).

Carcinogenicity

Endosulfan is not classified by IARC as a carcinogen. However a number of independent studies have found it to be carcinogenic (Reuber 1981), genotoxic to bacteria (e.g. Chaudhuri et al 1999), to human cells (Jamil et al

2004; Lu et al 2000) and to mouse cells (Pandey et al 1990), a tumour promoter (Fransson-Steen 1992), and mutagenic (Yadav et al 1982).

Endosulfan is increasingly being described as a potential carcinogen in humans (Antherieu et al 2007). The authors of this recent study found that it generates reactive oxygen species causing oxidative stress, and that this results in endosulfan having mutagenic effects and causing increased DNA strand breaks. It was found to inhibit apoptosis which "could contribute to mutant cell survival and therefore have possible carcinogenic effects".

Endocrine disruption

Endosulfan is an endocrine disruptor: it is oestrogenic, causing proliferation of MCF-7 human oestrogen sensitive breast cancer cells (Soto et al 1994; Bonefeld-Jorgensen et al 2005). It is also anti-androgenic (Andersen et al 2002; Kojima et al 2004).

Endosulfan at very low concentrations may cause breast cancer by interfering with a number of hormonal mechanisms.

It is described as a weak inhibitor of aromatase, an enzyme that catalyses the conversion of androgens to oestrogens (Andersen et al 2002). It has also recently been found to activate aromatase in cancer cells in the human placenta (Laville et al 2006). It significantly increases the ratio of 16-hydroxyestrone (the tumour promoting oestrogen) to 2-hydroxyestrone (the non-genotoxic oestrogen)—thus increasing breast cancer cell proliferation, development, and promotion (Bradlow et al 1995). It potentiates 17*beta*-estradiol (Rousseau et al 2002). It has been found to cause changes to intracellular oestrogenic signalling that increase the risk of breast cancer at very low picomolar to nanomolar concentrations (e.g. 10^{-10} M)—by mimicking the effects of oestrogen and raising cellular Ca_2^+ (calcium) levels, which then causes rapid secretion of prolactin which in turn causes cell proliferation (Rousseau et al 2002; Wozniak et al 2005).

Endosulfan also interferes with mammary gland development by affecting mRNA transcriptional activity (Je et al 2005).

Immune function

Endosulfan induces the death of human Natural Killer T-cells, which are part of the immune system involved in tumour suppression (Kannan et al 2000).

Epidemiology

There appear to be surprisingly few epidemiological studies on endosulfan and breast cancer, considering its clear oestrogenic action and the continuing widespread use of this organochlorine insecticide. Ibarluzea et al (2004) found increased risk of breast cancer amongst women with elevated adipose tissue levels of DDE, aldrin, endosulfan and lindane in combination, in a hospital-based case-control study involving 198 cases and 260 controls.

4.3.7 Lindane (HCH, BHC)

[endocrine, epidemiology, carcinogen]

Lindane is one of eight stereoisomers of hexachlorocyclohexane (HCH), and is the most commonly used of these HCH isomers, although some insecticidal products contain mixtures of them (Kalanzi et al 2004). Lindane is also known as *gamma*-hexachlorocyclohexane (*gamma*-HCH) and *gamma*-benzene hexachloride (*gamma*-BHC). Its metabolites include the isomers *alpha*-BHC and *beta*-BHC, *alpha*-HCH and *beta*-HCH. These chemicals will all be addressed together here as lindane, although the name used in the original research will be adhered to, and some isomers of HCH are registered separately to lindane.

HCH was first manufactured in 1825 by adding chlorine to benzene in sunlight (Gandhi et al 1998). Since the 1950s it has been used on a wide variety of plants and animals, including humans for head lice and scabies control, seed treatments and textile and wood preservation, becoming one of the most widely used insecticides in the world (UNEP 2002a).

Use continues in many countries including India, Bangladesh, Nepal, Sri Lanka, as does environmental and food chain contamination (UNEP 2002a). Lindane is still produced in India, China and Romania (Vijgen 2006). Many countries report bans of lindane, however this may only apply to agricultural use: for example in New Zealand lindane is still used as a human 'health' treatment for head lice although banned in agriculture, and so is registered as a medicine not as a pesticide. It is still used on agricultural crops and for public 'health' in India (CAPE 2005), and is registered there for control of flies, fleas, cockroaches, mosquitoes, bed bugs, and beetles (Dutta & Schafer 2006). The extent of its human 'health' use, i.e. for head lice and scabies, in the Asia Pacific Region is unknown.

HCH, especially the *beta* isomer, is lipophilic and persistent and accumulates in breast tissue (Zou & Matsumura 2003). It has been found in breast milk in

many countries in the region including China, Hong Kong, India, Indonesia, Japan, Jordan, Kuwait, Taiwan, and Turkey; in umbilical cord blood in India; and in female adipose tissue in Hong Kong.[6]

Lindane is carcinogenic and an endocrine disruptor.

Carcinogenicity

In 1987 IARC classified lindane/HCH as 'possibly carcinogenic to humans' (Group 2B) on the basis of sufficient evidence of carcinogenicity in animals (liver tumours) and inadequate evidence in humans (leukaemia).

However lindane has since been shown to have genotoxic effects on human lymphocytes (chromosomal aberrations, sister chromatid exchanges—Rupa et al 1989), human nasal mucosal cells (Tisch et al 2005), and on poultry bone marrow (chromosomal aberrations, increased micronucleus formation—Bhunya et al 1992). Kalanzi et al (2004) have also suggested that 'environmental' concentrations of lindane can induce a number of subtle alterations in breast cells in the absence of cytotoxicity, including clastogenic effects.

Lindane interferes with gap junction intercellular communication (Ke et al 2005).

Endocrine disruption

Lindane has exhibited a number of endocrine disrupting effects in animals (Walsh & Stocco 2000b). It

- reduces female serum oestrogen and progesterone levels;
- reduces male serum testosterone levels;
- decreases luteinizing hormone secretion;
- disrupts ovarian cyclicity; and
- blocks the response of oestrogen-dependent tissues to oestradiol by competing with oestradiol for binding to the oestradiol receptor.

Concentrations of oestradiol were also significantly increased in ewes given lindane (Rawlings et al 1998), and oestrogenic activity has been demonstrated in trout cells (Petit et al 1997).

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6 (Basri et al 1994; Kalra et al 1994; Nair et al 1996; Konishi et al 2001; Nasir et al 1998; Saeed et al 2000; Burke et al 2003; Sanghi et al 2003; Chao et al 2006; Poon et al 2005; Wong et al 2002).

Lindane is regarded as being a "probable follicle-stimulating hormone or luteinizing hormone disruptor" (Farr et al 2004).

The breakdown product *beta*-HCH has an oestrogenic action, activating oestrogen receptors (Steinmetz et al 1996), which can contribute to breast cancer. It also induced biochemical changes in MCF-7 human breast cancer cells that assist "the progression of breast cancer cells to an advanced state of malignancy", including increased cell transformation and invasiveness (Zou & Matsumura 2003).

Lindane has demonstrated oestrogenic activity in MCF-7 human breast cancer cells, causing proliferation of the cells (Okuba et al 2004). It significantly increases the ratio of 16-hydroxyestrone (the tumour promoting oestrogen) to 2-hydroxyestrone (the non-genotoxic oestrogen)—increasing the risk of breast cancer. The higher the ratio, the greater the effect on the proliferation, development, and promotion of breast cancer cells (Bradlow et al 1995).

Lindane induces cytochrome P450 metabolic enzymes (Oropeza-Hernandez et al 2001), in particular enhancing aromatase activity (Nativelle-Serpentini et al 2003), which can play a significant role in the promotion of tumours (Kalanzi et al 2004).

During periods of lipolysis, which occurs during fasting, *beta*-HCH can be released from fat deposits in quantities sufficient to stimulate oestrogen target tissues (Bigsby et al 1997). This has implications for women suffering malnutrition and in periods of food shortages.

Epidemiology

Four studies have found an association between levels of lindane/HCH in women (three in adipose tissue and one in blood) and breast cancer. A further two studies have found an association between exposure to lindane and breast cancer.

(a) *India* – blood levels of gamma-HCH were significantly higher in 135 breast cancer patients, 41-50 years of age, compared to a control group without the disease, as was DDT and DDE (Mathur 2002).

(b) *Spain* – Ibarluzea et al (2004) found increased risk of breast cancer amongst women with elevated adipose tissue levels of lindane in combination with DDE, aldrin, and endosulfan; and a significantly increased risk of breast cancer with lindane individually in

postmenopausal women—in a hospital-based case-control study involving 198 cases and 260 controls.

(c) *Canada* – Aronson et al (2000) found higher levels of *beta*-HCH in the biopsy tissue of 217 breast cancer cases in Ontario than in 213 benign controls in a hospital-based case-control study (together with higher levels of *p,p'*-DDT, *p,p'*-DDE, HCB, *alpha*-chlordane, and *gamma*-chlordane).

(d) *Finland* – Mussalo-Rauhamaa et al (1990) analysed the breast adipose tissue of 44 breast cancer patients and 33 women free of cancer in Finland. Residues of *beta*-HCH were found more frequently in breast cancer patients. After adjusting for age and child-bearing, *beta*-HCH remained a significant risk factor for breast cancer.

(e) *Denmark* – Hoyer et al (1998) found an association between *beta*-HCH and breast cancer risk in women involved in the Copenhagen City Heart Study, using the stored serum of 240 women who developed breast cancer, collected between 1976 and 1996, and that of 477 controls.

(f) *UK* – Muir et al (2004) examined the spatial distribution of breast cancer incidence in urban and rural Lincolnshire and Leicestershire, and its association with the application of particular pesticides. They found a spatial association between the breast cancer incidence rates and the application of lindane in rural Leicestershire.

(g) *Canada* – Demers et al (2000) found that higher levels of *beta*-HCB were associated with increased invasiveness of the cancer into the lymph nodes, even though there was no association between levels of *beta*-HCB in blood and breast cancer. The study involved 315 women with primary breast cancer and 219 controls recruited from hospitals in Quebec.

(h) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk associated with husbands' use of lindane. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (29) amongst those whose husbands had used it precluded firm conclusions.

(i) *USA* – An epidemiological study of women living on farms, although

it did not look at breast cancer, did demonstrate the endocrine disrupting effects of lindane that can increase the risk of breast cancer. Farr et al (2004) found that use of lindane was associated with long menstrual cycles, missed periods, and intermenstrual bleeding.

4.3.8 Toxaphene

[mammary tumours, endocrine, epidemiology]

Toxaphene (also known as camphechlor) is a complex mixture of over 300 chlorinated hydrocarbons produced by the chlorination of camphene, and containing 67-69 percent chlorine by weight. Toxaphene was widely used from the late 1940s as an insecticide on crops, especially cotton, cereal grains, fruits, nuts and vegetables, and to control parasites on livestock. The use of toxaphene is now banned or restricted in many countries, but it persists in the environment and food (UNEP 2002a; IARC 2001). De Geus et al (1999) reported that Korea and Mexico were using toxaphene into the 1980s. Use was reported in Hawaii in the 1990s (Allen et al 1997). Obsolete stocks exist within the region e.g. in Kazakhstan (UNEP 2002d).

Carcinogenicity

Toxaphene is classified by IARC (2001) as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals (liver tumours, thyroid follicular-cell adenomas and carcinomas, and pituitary adenomas), but inadequate evidence in humans.

It has been found to be highly carcinogenic in rats and mice, causing malignant liver tumours, reticulum cell sarcomas, sarcomas in the uterus, tumours in the reproductive system, and in the mammary, pituitary, adrenal, and thyroid glands (De Geus et al 1999; Buranatrevedh 2004).

An increased frequency of chromosomal aberrations has been observed in the lymphocytes of workers exposed to toxaphene (IARC 2001). Toxaphene has been found to be genotoxic in mammalian cell systems and mutagenic in the Ames Salmonella test (De Geus et al 1999). It also induced sister chromatid exchange.

It inhibited gap junction intercellular communication in cultured mammalian cells (IARC 2001).

Endocrine disruption

Some studies have found toxaphene to be oestrogenic but others have

not. De Geus et al (1999) reported technical grade toxaphene and some individual congeners to be weakly estrogenic. Soto et al (1994, 1995) found toxaphene to be oestrogenic, causing proliferation of MCF-7 human oestrogen-sensitive breast cancer cells. Kojima et al (2004) also found it to have oestrogenic activity. Lemaire et al (2006) found that toxaphene activated oestrogen receptors.

Immune effects

It is immunotoxic (IARC 2001).

Epidemiology

(a) *California, USA* – Mills & Yang (2006) evaluated the relationship between pesticide use data and breast cancer incidence rates in Californian Hispanic females, using 1988-2000 data from the California Cancer Registry and pesticide use data from 1970-1988. A total of 23,513 Latinas were diagnosed with breast cancer in California during the years 1988-1999. Risk of breast cancer was positively associated with pounds of toxaphene used.

(b) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk associated with husbands' use of toxaphene in Iowa. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (29) amongst those whose husbands had used it precluded firm conclusions.

4.3.9 Hexachlorobenzene (HCB)

[carcinogenic, epidemiology]

Hexachlorobenzene is a chlorinated hydrocarbon which has been used as an insecticide, a fungicide and a seed dressing in agriculture. It may contain dioxins as impurities. The production and use of hexachlorobenzene have decreased since the 1970s owing to bans and restrictions on its use in many countries (IARC 2001). Now environmental releases of HCB occur mainly as a by-product in the production of a large number of chlorinated compounds, particularly chlorinated benzenes, solvents and several pesticides, and from incineration (UNEP 2002a). Some stockpiles were reported to exist in the Asia Pacific region, e.g. in Nepal and Bhutan (UNEP 2002a).

Carcinogenicity

IARC have classified it as 'possibly carcinogenic to humans' (Group 2B), on the basis of sufficient evidence of carcinogenicity in animals and inadequate evidence in humans (leukaemia). They reported findings of liver tumours, renal tubular tumours, parathyroid adenomas, adrenal tumours, and thyroid and follicular-cell adenomas in animal studies (IARC 2001).

IARC have identified concern that HCB may be a factor in human breast cancer but report no consistent findings.

HCB is a co-carcinogen, stimulating tumour development induced by a known carcinogen (N-nitroso N-methylurea). The mechanism of action is thought to be through the disruption of the signalling pathway for the insulin growth factor family, which is known to be involved in the regulation of breast cancer cell growth (Randi et al 2006). It is also genotoxic (Salmon et al 2002).

Endocrine disruption

IARC report effects on steroid hormones in exposed female mice (IARC 2001).

Immune effects

HCB is known to have auto-immune effects in humans and rats (Ezendam et al 2004), including inflammatory skin and lung lesions and spleen effects (Michielsen et al 1999). The presence of HCB in breast milk has been associated with altered immune function in Inuits (IARC 2001).

Epidemiology

HCB is a co-contaminant in a number of breast cancer studies that have found an association between contaminant levels and breast cancer.

(a) Sweden – Liljigren et al (1998) found an increased risk of oestrogen receptor positive tumours with higher levels of HCB for postmenopausal women, in a case-control study of 43 patients with invasive breast cancer and 35 patients with benign breast disease.

(b) USA – Dorgan et al (1999) studied serum organochlorine levels of 105 blood donors who subsequently were diagnosed with breast cancer, and 210 controls matched on age and date of blood collection. Women with higher levels of HCB were at twice the risk of breast cancer, but

the authors appear to have discounted the finding because there was no evidence for a dose-response relationship, and the association was limited to women whose blood was collected close to the time of diagnosis. As explained earlier in this chapter, a dose-response relationship should not be expected for chemicals that are endocrine disruptors or genotoxic.

(c) *Canada* – Aronson et al (2000) found higher levels of HCB in the biopsy tissue of 217 breast cancer cases in Ontario than in 213 benign controls in a hospital-based case-control study (together with higher levels of DDT, DDE, *beta*-HCH and mirex).

(d) *Belgium* – Charlier et al (2003) compared the serum levels of HCB (and DDT) in 159 women with breast cancer and 250 "presumably healthy" women. They found that mean levels of HCB and total DDT were significantly higher for breast cancer patients than for controls.

(e) *Canada* – Demers et al (2000) found that higher levels of *beta*-HCB, (along with DDE and chlordane metabolites), were associated with increased invasiveness of the cancer into the lymph nodes, even though there was no association between levels of the chlorinated pesticides in blood and breast cancer. Their study included 315 women with primary breast cancer and 219 controls recruited from hospitals in Quebec, Canada.

(f) *Belgium* – Charlier et al (2004) compared the serum levels of DDE and HCB in 231 women at the time of breast cancer discovery and in 290 age-matched healthy controls. DDE was found in 76.2 percent of cases and in 71.1 percent of controls, but HCB was present only in 12.6 percent of cases (29 from 231) and in 8.9 percent of controls (26 from 290). They found that the presence of both residues was significantly associated with an increased risk of breast cancer development.

(g) *Germany* – Guttes et al (1998), in a case–control study, found a weakly significant increase in DDT and HCB in breast tumour tissue.

4.3.10 Chlordecone (Kepone)

[endocrine, carcinogenic]

Chlordecone is also commonly known by its trade name Kepone. It is a pesticide in its own right, and also a breakdown product of mirex (IARC 1979). Its uses included control of the Colorado potato beetle, rust mite on citrus, and potato and tobacco wireworm, rootborer in bananas, as a bait

for ants and other indoor pests, and as a fungicide against apple scab and powdery mildew (UNEP 2002c). It was still being used in Hawaii in the 1990s (Allen et al 1997). It is persistent in the environment and there are many reports of it contaminating human fluids (IARC 1979).

Chlordecone is reported to have both carcinogenic and endocrine disrupting properties that may increase the risk of breast cancer. It also disrupts the 'architecture' of human breast epithelial cells in ways that might increase risk of breast cancer (Starcevic et al 2001).

Carcinogenicity

It is classified by IARC (1979) as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals (liver tumours) but inadequate evidence in humans.

Endocrine disruption

Chlordecone is oestrogenic (Kocarek et al 1994; Petit et al 1997), and indeed more oestrogenic than DDT analogs (Johnson et al 1992). It binds particularly to oestrogen receptors and to a lesser extent to androgen receptors in MCF-7 human breast cancer cells (Okubo et al 2004); and activates human oestrogen receptor cells (Lemaire et al 2006). Additionally, it increases serum levels of prolactin (Rosencrans et al 1985).

It also significantly increases the ratio of 16-hydroxyestrone (the tumour promoting oestrogen) to 2-hydroxyestrone metabolites, thus increasing the risk of breast cancer, as the higher the ratio, the greater the effect on breast cancer cell proliferation, development, and promotion (Bradlow et al 1995).

4.3.11 Dicofol

[endocrine, carcinogen]

Dicofol is an organochlorine insecticide, introduced in 1955 (IARC 1983), and still widely used on cotton and many other crops.

Carcinogenicity

Dicofol is classified as a 'possible human carcinogen' (Group C) by the US EPA (2004), due to liver adenomas and carcinomas in male mice (US EPA 1998a). Epidemiological studies have linked exposure to dicofol with childhood leukaemia (Reynolds et al 2005a), and prostate cancer (Settimi et al 2003).

It is a potent inhibitor of gap junction intercellular communication (Flodstrom et al 1990).

Endocrine disruption

Dicofol showed oestrogenic activity in an oestrogen receptor dependent MCF-7 human breast cancer cell proliferation assay (Okubo et al 2004), and in yeast cells transfected with the alpha oestrogen receptor (Vinggaard et al 1999).

4.3.12 Mirex

[carcinogen, epidemiology]

Mirex is an insecticide mainly used in bait for ants, but largely discontinued (IPCS 1990a). It is still used in Australia for ants (UNEP 2002c; CCC 2005), and China for termites (UNEP 2002d). It has caused widespread environmental contamination and is found in human breast milk, and brain, liver, and adipose tissue (Porter et al 2002); and in follicular fluid (Younglai et al 2002).

Carcinogenicity

Mirex is classified by IARC (1979) as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals (liver tumours) but inadequate evidence in humans. It is a potent skin tumour promoter, three times more so in female than male mice, indicating interplay with ovarian hormones (Porter et al 2002).

Endocrine disruption

Mirex is classified by the European Union as an endocrine disruptor. It even appears on a list of endocrine disrupting substances offered for sale by Cambridge Isotope Laboratories (CIL 2006), although Soto et al (1995) state it is non-oestrogenic. However very little information seems to be available about the exact nature of its endocrine effects.

Epidemiology

(a) *USA* – In a case control study in the US involving 154 postmenopausal breast cancer cases and 192 postmenopausal community controls, Moysich et al (1998) found increased risk from mirex amongst parous women who had never lactated.

(b) *Canada* – Aronson et al (2000) found an increased risk of breast cancer associated with higher levels of mirex in the biopsy tissue of 217 breast cancer cases in Ontario than in 213 benign controls in a hospital-based case-control study. This risk was greater for women who had never lactated.

4.3.13 Endrin

[mammary carcinogen]

Endrin is a foliar insecticide that was used mainly on field crops such as cotton, rice, sugar cane, maize and grains, and it has also been used as a rodenticide to control mice and voles and for killing birds (UNEP 2002c,d; Ritter et al undated).

It is banned or not registered in all countries in the region, but still contaminates it. Endrin has been found in breast milk in Kuwait and Saudi Arabia. Recent food residue findings include vegetable oils and mustard seed in India, milk and butter in Pakistan, and tea leaves, chillies and onions in Sri Lanka. In the environment, it has been found in the air in China; marine sediment in Korea and India; shellfish in Korea, and fish in Kuwait and Malaysia; in seawater and rivers in Indonesia, Philippines and Thailand; and in rivers in Malaysia (UNEP 2002a,c,d). Few analyses have been carried out in the Pacific Islands, although it has been found in soil and sediment in Fiji, and in Guam it has been detected in public water supply wells at levels that exceed regulatory drinking water standard (UNEP 2002b). A stockpile has been reported in Nepal (UNEP 2002a).

Endrin has been reported to cause a number of carcinomas in rats, including carcinomas of the mammary gland in female rats (Reuber 1979), although other studies have not reported this finding. It is also structurally related to aldrin, dieldrin, chlordane, and heptachlor, which are known to be carcinogenic in animals, and which are implicated in breast cancer.

Endrin is oestrogenic (Kojima et al 2004).

4.3.14 Aldrin

[carcinogen, epidemiology]

Aldrin is another organochlorine insecticide, once used widely to kill soil insects, but now banned globally. Although it is no longer used in the region it still contaminates the environment and human breast milk.

It is classified by the US EPA as a probable human carcinogen (B2), based on liver tumours in rats and mice and evidence of mutagenicity (US EPA 1987). There is little information indicating that aldrin may cause breast cancer; however as it is metabolised in the liver of mammals to form dieldrin, the findings reported previously for dieldrin are also relevant for aldrin.

Oestrogenic activity has been identified for aldrin (Kojima et al 2004).

Epidemiology

(a) *USA – farmers' wives* – Engel et al (2005) examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina. The women had no history of breast cancer prior to enrolment in the study from 1993 to 1997. By 2000, 309 breast cancer cases were identified. Risk of breast cancer was modestly elevated among women whose homes were closest to areas of pesticide application. There was also significantly increased risk associated with husbands' use of the aldrin, but only in North Carolina and not in Iowa and with no dose-response relationship.

(b) *Spain* – Ibarluzea et al (2004) found higher levels of aldrin, along with DDE, endosulfan and lindane in adipose tissue of women with breast cancer cases (198) than in controls (260), and an increased risk of breast cancer associated with these findings, especially in leaner postmenopausal women—in a hospital-based case-control study involving 198 cases and 260 controls.

4.4 TRIAZINE HERBICIDES

The triazine herbicides are the second mostly commonly suspected group of pesticides with respect to breast cancer. Unlike the organochlorines, these pesticides are still in widespread use across the globe. Although they are not as environmentally persistent as the organochlorines, some are known to contaminate ground and drinking waters.

There is evidence that all the triazines may increase the risk of breast cancer, primarily from laboratory studies revealing mammary tumours in one strain of rats, although there is some limited epidemiological evidence that supports these studies. The strongest link is with atrazine, but controversy surrounds results of the US EPA's downgrading of its cancer risk following

industry pressure occasioned by regulatory action against atrazine, particularly in Europe (see p98). Most of the toxicological studies carried out on the triazine herbicides focus on atrazine, but the effects of the triazines appear to be similar.

Epidemiology

(a) *USA – atrazine, simazine, cyanazine in corn production*
A "statistically significant increase in breast cancer risk with medium and high levels of triazine exposure" was found in an ecological study in Kentucky, USA. Kettles et al (1997) examined data on use of atrazine, simazine and cyanazine, corn production, and water contamination, to estimate exposure to the herbicide. However, assumptions made in determining exposure limit the validity of the results according to Snedeker & Clark (1999).

(b) *UK – atrazine*
Muir et al (2004) examined the spatial distribution of breast cancer incidence in Lincolnshire and Leicestershire, and its association with the application of particular pesticides. It found no overall association between breast cancer and application of pesticides in the urban areas, but it did reveal a spatial association between the breast cancer incidence rates and the application of atrazine, in rural Leicestershire.

(c) *USA – women on farms – atrazine*
A US epidemiological study of women living on farms, although it did not look at breast cancer, did demonstrate the endocrine disrupting effects of pesticides that can increase the risk of breast cancer. Farr et al (2004) found that mixing or applying pesticides and using hormonally active pesticides showed trends toward increased menstrual cycle length, increased odds of missed periods, and intermenstrual bleeding. Use of atrazine was associated with long cycles, missed periods, and intermenstrual bleeding.

(d) *USA – contaminated drinking water – atrazine*
An analysis of Iowa's drinking water supplies and rates of low birth weight, prematurity, and intrauterine growth retardation revealed an association between atrazine and the latter effect (Munger et al 1996). Intrauterine growth retardation has been shown to increase susceptibility to breast cancer in later life (Sanborn et al 2004).

4.4.1 Atrazine

[mammary tumours, endocrine, epidemiological, immune]

Atrazine, first introduced in 1957, is a herbicide used for broadleaf and grassy weeds in a wide variety of agricultural crops and non-agricultural situations. It is reputed to be the most widely used pesticide in the world; it can travel up to 1,000 kilometres from where it is used, and persist for decades after its use ceases (Hayes et al 2006b). It contaminates groundwater, surface waters, rainfall and drinking water supplies (IARC 1991; Snedeker & Clark 1999). Hayes et al (2006a) described it as being ubiquitous in the environment. Therefore human exposure to this herbicide is likely to be considerable.

Atrazine is a mammary carcinogen and an endocrine disruptor (Greiner et al 2000).

Carcinogenicity

Atrazine is classified by IARC (1991) as 'possibly carcinogenic to humans' (Group 2B) on the basis of adequate evidence in animals but inadequate evidence in humans. In the late 1980s, the US EPA classified atrazine as a class C 'possible carcinogen', then in the 1990s changed this to 'likely human carcinogen' in accordance with their new terminology, but then in 2000, controversially, reclassified it as 'not likely to be carcinogenic to humans' (US EPA 2002a).

IARC (1991) reported one study showing increased mammary tumours (mainly benign) in males, and a variety of mutagenic effects in other studies.

Since then, Fukamachi et al (2004) found that atrazine at high doses enhanced the incidences of mammary adenomas and adenocarcinomas in rats that had been exposed to a known carcinogen (DMBA), but that it did not cause proliferation of MCF-7 human breast cancer cells *in vitro*.

Gammon et al (2005), from the California Environmental Protection Agency, found the following, in their recent risk assessment of atrazine:

- malignant mammary tumours in female rats, which increased in a dose-dependent manner;
- evidence for a genotoxic basis for these tumours was either equivocal or negative;

- triazines have been shown to be clastogenic in Chinese hamster ovary cells, but without showing a convincing dose-response relationship;
- atrazine can be converted into genotoxic N-nitrosoatrazine in the environment or the digestive system, suggesting that N-nitrosamines derived from triazines could be oncogenic.

However, they concluded that N-nitrosotriazines are unlikely to play a significant role in the rat mammary gland tumours, and instead proposed an endocrine basis for them, that is not based on the standard oestrogen mimicry:

> "a suppression of the luteinizing hormone surge during the estrus cycle by atrazine leads to the maintenance of elevated blood levels of 17*beta*-oestradiol and prolactin. The mechanism for tumor development may include one or more of the following: the induction of aromatase and/or other cytochrome P450 oxygenases, an antagonist action at the estrogen feedback receptor in the hypothalamus, an agonist action at the mammary gland estrogen receptor or an effect on adrenergic neurons in the hypothalamic-pituitary pathway."

Although most studies have found atrazine not to be genotoxic (Snedeker & Clark 1999), there are some that have. For example, in one study atrazine has been shown to be genotoxic but only at very high doses: it induced a small dose-related increase in DNA damage (Tennant et al 2001). However another study found that atrazine—at concentrations found in drinking water in the USA—caused genetic damage to Chinese hamster ovary cells (Taets et al 1998). Other studies have found atrazine genotoxic to human lymphocyte cells, frog erythrocytes, and mouse bone marrow (Snedeker & Clark 1999).

The 'conversion' product, N-nitrosoatrazine which is formed in the presence of nitrites—frequently found in food and formed from nitrates used as fertilizers and contaminating ground and drinking water—has been found to be mutagenic, causing chromosome breakage and increased mitotic index, in human lymphocytes (Meisner et al 1993).

Endocrine disruption

There have been many findings of endocrine disrupting effects of atrazine that add weight to the conclusions of Gammon et al (2005), that the mammary tumours induced by atrazine may be of endocrine origin:

- Wetzel et al (1994), working for Ciba-Giegy, acknowledged that atrazine caused the following endocrine effects on laboratory rats:

  (i) lengthening of the oestrous cycle;

  (ii) increased number of days in oestrus or under the influence of exposure to oestrogen;

  (iii) earlier onset of galactocele formation (a milk-containing mammary cyst);

  (iv) earlier onset of mammary and pituitary tumour formation but not an increased incidence of mammary and pituitary tumours.

- Atrazine caused a statistically significant inhibition of specific binding to the androgen receptor (Danzo 1997).

- It significantly increased the ratio of 16-hydroxyestrone (the tumour promoting oestrogen) to 2-hydroxyestrone (the non-genotoxic oestrogen)—thus increasing the risk of breast cancer (the higher the ratio, the greater the effect on breast cancer cell proliferation, development, and promotion—Bradlow et al 1995).

- Atrazine and two of its metabolites—atrazine-desethyl and atrazine-desisopropyl—induced aromatase, the enzyme that converts androgens to estrogens, in adrenocortical carcinoma cells, but not in MCF-7 human breast cancer cells (Sanderson et al 2001).

- Farr et al (2004) described atrazine as being a "probable follicle-stimulating hormone or luteinizing hormone disruptor": atrazine alters the levels of luteinizing hormone and prolactin in serum in rats by altering the control of these hormones by the hypothalamus (Cooper et al 2000).

- Ueda et al (2005) found that atrazine tended to increase the proportion of oestrogen receptor *alpha*-positive tumours in rats and stimulated cell proliferation, but with no clear effects on serum hormone levels. Hayes et al (2006b) point out that in breast cancer local induction of aromatase has permanent effects on cell and tissue differentiation but does not result in changes in plasma hormone levels. Ueda et al concluded that "atrazine has a potential for enhancing the growth of mammary tumours, partly through increasing cell proliferation in the promotion/progression stage in female rats under ovarian hormone-free conditions."

- Fan et al (2007) found that atrazine increases aromatase activity but only in tissues that use a particular aromatase promoter (known as the steroidogenic factor 1 dependent aromatase promoter II; or SF-1 dependent ArPII promoter). Normal breast tissue does not use this, but breast cancer cells are dependent on ArPII to increase the production of oestrogen in breast adipose tissue, which in turn stimulates the growth of the cancer. This finding further supports the role of atrazine in promoting the growth of breast cancer.

Additionally, atrazine is known to be a potent endocrine disruptor to amphibians at very low doses, causing feminization, hermaphrodism, and gonadal abnormalities. Hayes et al (2006b) have found that atrazine-induced gonadal malformations result from the depletion of androgens and production of oestrogens, "perhaps subsequent to the induction of aromatase by atrazine, a mechanism established in fish, amphibians, reptiles, and mammals (rodents, and humans)".

Immune effects

A number of studies have resulted in adverse effects on the immune system, including decreased production of tumour necrosis factor, a protein that kills tumour cells (Hooghe et al 2000).

Other relevant effects

Several studies on prenatal exposure to atrazine have revealed effects on mammary gland development that include increased presence of terminal buds—structures sensitive to carcinogens—and delayed mammary gland development, extending the window of sensitivity to potential carcinogens (Brown et al 1998; Birnbaum & Fenton 2003; Rayner et al 2005). Low dose exposure to atrazine and to a mixture of its 4 metabolites during late pregnancy caused persistent alterations in mammary gland development, in particular significant delays in development (Enoch et al 2006).

Epidemiology

A number of epidemiological studies have linked exposure to atrazine with cancers—ovarian, colon, leukaemia, non-Hodgkin's lymphoma (IARC 1991), and breast cancer (see above).

In summary: there is general agreement that atrazine can cause mammary tumours in rats—even the pesticide industry agrees (e.g. Stevens et al 1999).

The debate however is about how relevant these tumours are to humans. There appears to be general agreement that the tumours result from endocrine rather than genotoxic or mutagenic processes, with the pesticide industry and the US EPA arguing that these endocrine processes are irrelevant to humans (e.g. O'Connor et al 2000; US EPA 2002b). Others disagree. Snedeker & Clark (1999) classified atrazine as a 2B 'possible breast carcinogen'. They concluded that "although atrazine is not an estrogen mimic, there is evidence that it can affect hormones along the hypothalamic

The effect of industry pressure

Atrazine was classified by the US EPA as a carcinogen "but industry pressure forced a lengthy and controversial risk assessment process, resulting in the reregistration of atrazine as a permissible chemical" (Evans 2006). The industry acknowledges that atrazine has caused mammary tumour in rats in the laboratory but repeatedly argues that this finding is not relevant to humans. For example, Stevens et al (1999), working for Novartis, acknowledged that atrazine has caused mammary tumours in rats after the chemical increased levels of oestrogen and prolactin, claiming the increase in hormones occurred as a result of "an acceleration of the normal reproductive aging process". They then claim that the particular rats on which these effects were noticed—Sprague-Dawley rats—differ from other rats and mice and humans "in the endocrine control mechanisms affecting reproductive senescence and the development of the mammary tumors during aging" so that the carcinogenic effect observed "does not have biological relevance to humans". Snedeker & Clark (1999) did not support this view.

O'Connor et al (2000) from DuPont asserted that atrazine-induced mammary tumours in rats are mediated via a prolactin mechanism which they concluded "is thought to be of low relevance to humans".

Yet there is gathering evidence to confirm the role of increased levels of prolactin in the development and growth of breast tumours and a critical role in the mammary gland development (Welch & Nagasawa 1977; Tomblyn et al 2005; Hankinson 2005-2006; Eliassen et al 2007; Greendale et al 2007). Prolactin increases the motility of human breast cancer cells (Miller et al 2007), and several studies show a link between elevated prolactin levels and elevated breast cancer risk in humans (e.g. Eliassen et al 2007; Hankinson 2005-2006). High levels of prolactin have been claimed to confer a two-fold increase in the risk of breast cancer, and prolactin is said to act "directly on the mammary epithelial cells to increase cell proliferation in pre-invasive lesions, resulting in more neoplasia and acceleration of the transition to invasive carcinoma" (Oakes et al 2007).

pituitary gonadal axis. Changes in the levels of hormones in this pathway may affect levels of estradiol or estradiol metabolites such as 16-hydroxyestrone, which may affect breast cancer risk". Dankwardt (2000), in her review of the triazine herbicides, also expressed a view that it is unclear what effect the triazines' interference with the pituitary and hypothalamus hormones has in humans. Hayes et al (2006b) stated that "atrazine exposure elevates estrogens in every species (and class of vertebrate)". There is also the issue of delaying sexual maturity of the mammary gland and the consequent increased sensitivity to other carcinogens. Regardless of whether or not the mechanism by which atrazine generates mammary tumours in rats, the evidence above indicates a number of other mechanisms by which exposure to atrazine may increase the risk of breast cancer.

4.4.2 Simazine

[mammary tumours, endocrine]

Simazine was introduced in 1957 as a systemic herbicide for use on grasses and weeds in food crops, especially maize, and for general weed control (IARC 1991).

Carcinogenicity

Simazine increased the incidence of benign and malignant mammary gland tumours in female rats (IARC 1999). It is classified by the US EPA (2004) as a 'possible human carcinogen' (Group C).

There is evidence of genotoxicity, although some studies have not found it (e.g. Kligerman et al 2000). One study found that simazine—at concentrations found in drinking water in the USA—induce whole-cell clastogenicity in Chinese hamster ovary cells (Taets et al 1998).

Simazine has been linked to prostate cancer in California (USA) farm workers (Mills & Yang 2003).

Endocrine

The mechanism by which simazine induces mammary tumours is thought to be the same as for atrazine, involving the induction of prolactin (US EPA 2002b).

Simazine induced aromatase, the enzyme that converts androgens to estrogens, in adrenocortical carcinoma cells, but not in MCF-7 human breast cancer cells (Sanderson et al 2001).

4.4.3 Cyanazine

[mammary tumours]

Cyanazine is classified by the US EPA (2004) as a 'possible human carcinogen' (Group C). It has also caused mammary tumours in rats (Bogdanffy et al 2000), and the mechanism is thought to be the same as for atrazine (US EPA 2002b). However, again, there is also some evidence of genotoxicity: Tennant et al (2001) found it induced a marginal increase in DNA damage with dose, but no individual dose was significantly increased compared to the control. Another study found it to be mutagenic in *Salmonella* and plant-based assays (Roloff et al 1992).

4.4.4 Propazine

[mammary tumours]

Propazine is classified by the US EPA (2004) as a 'possible human carcinogen' (Group C), and it too has been found to cause mammary tumours in rats (US EPA 1990b).

As with simazine, propazine induced aromatase, the enzyme that converts androgens to estrogens, in adrenocortical carcinoma cells, but not in MCF-7 human breast cancer cells (Sanderson et al 2001).

4.4.5 The Other Triazines

[mammary tumours]

Terbuthylazine, terbumeton, and terbutryn were all found to induce mammary gland tumours in female rats (US EPA 2002b). Terbutryn is classified by the US EPA (2004) as a 'possible human carcinogen' (Group C).

4.5 SYNTHETIC PYRETHROID INSECTICIDES

Synthetic pyrethroids are modified versions of a natural chemical, pyrethrin, which is found in chrysanthemums. The main modification is the addition of chlorine molecules, which make the compounds lipophilic (i.e. drawn to fat) and persistent, and that increases the likelihood of accumulation in human tissue. Synthetic pyrethroids, introduced in the 1970s as replacements for the organochlorines, are used widely as insecticides against flies, fleas, ticks, mites, mosquitoes (including in bednets as a control against malaria), and as a treatment for human head lice and scabies. Human exposure from indoor use of these insecticides can be substantial.

A number of synthetic pyrethroids are endocrine disruptors, mimicking oestrogen and promoting the growth of human breast cancer cells. One study (Chen et al 2002) rated the oestrogenic potency (based on ability to induce MCF-7 human breast cancer cell proliferation) of some pyrethroids as follows:

permethrin > fenvalerate > cypermethrin > deltamethrin.

Permethrin, cyfluthrin, cypermethrin, deltamethrin, and *sigma*-pyrethroid have been found recently in breast milk in South Africa (Bouwman et al 2006).

4.5.1 Permethrin

[endocrine, carcinogenicity]

Permethrin shows significant carcinogenic and endocrine disrupting potential that increases the risk of breast cancer.

Carcinogenicity

The California EPA reported lung and liver tumours in mice (Cal EPA 1987a), and the US EPA described permethrin as having 'suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential' (US EPA 2004). It has been reported to be genotoxic in human nasal mucosal cells (Tisch et al 2002), and mutagenic in human lymphocytes (chromosomal aberrations, DNA lesions) (Barrueco et al 1994; Undeger & Basaran 2005). There is also a case report of congenital leukaemia following significant household exposure to permethrin during pregnancy (Borkhardt et al 2003).

Permethrin increased the expression of the proto-oncogene WNT10B, which has been implicated in the development of human breast cancer through its effect on mammary gland development. This effect occurred at a lower concentration of permethrin, but not at the higher concentration (Kasat et al 2002).

It also inhibited gap junction intercellular communication at non-cytotoxic concentrations (Tateno et al 1993).

Endocrine disruption

It is oestrogenic in human oestrogen receptor assays (Kojima et al 2004), anti-progestagenic in T47D human breast cancer cells (Kim et al 2005a), and significantly increases the proliferation of MCF-7 human breast cancer

cells (Go et al 1999; Chen et al 2002). When MCF-7 cells were exposed to a combination of permethrin and oestradiol, there was a significant increase in breast cancer cell proliferation when compared to exposure to oestradiol alone (Kakko et al 2004).

Additionally 3-(4-hydroxy-3-phenoxy)benzyl alcohol, a metabolite of permethrin, showed oestrogenic potential—in particular the ability to interact with human oestrogen receptors (McCarthy et al 2006).

4.5.2 Deltamethrin

[mammary tumours, endocrine]

Deltamethrin also appears to have both carcinogenic and endocrine disrupting properties that may increase the risk of breast cancer.

Carcinogenicity

Deltamethrin has not been classified as carcinogenic, although there are a number of indications that it may be. It produced thyroid adenomas in rats (Cabral et al 1990). IARC (1991) reported that it induced micronuclei and chromosomal aberrations in bone marrow and abnormal sperm morphology in mice treated in vivo (also Bhunya & Pati 1990), and chromosomal aberrations in plants. It has been found to be mutagenic in human lymphocytes (Dolara et al 1992) and in mouse bone marrow cells (Chauhan et al 1997), causing sister chromatid exchange; and clastogenic in rat bone marrow causing increased frequency of chromosome aberrations and micronucleated erythrocytes (Agarwal et al 1994).

The IPCS (1990b) reported a study that showed increased mammary tumours in rats, but appeared to discount the result because "there was no clear dose–response relationship".

It also inhibits gap junction intercellular communication at non-cytotoxic concentrations (Tateno et al 1993).

Endocrine disruption

It is oestrogenic, anti-androgenic, and significantly induces MCF-7 human breast cancer cell proliferation (Andersen et al 2002; Birkhoj et al 2004; Kojima et al 2004),

4.5.3 Cypermethrin

[endocrine, carcinogenicity]

Cypermethrin has endocrine disrupting and carcinogenic properties that may increase the risk of breast cancer.

Carcinogenicity

The US EPA (2004) classified cypermethrin as a 'possible human carcinogen' (Group C). It was described by Shukla et al (2002) as having "complete carcinogenic as well as tumour initiating and promoting potential" in experiments on mice. It caused sister chromatid exchange in mouse bone marrow cells (Chauhan et al 1997), significantly increased DNA damage in human lymphocytes (Undeger & Basaran 2005).

Cypermethrin inhibited gap junction intercellular communication at non-cytotoxic concentrations (Tateno et al 1993).

Endocrine disruption

Cypermethrin also has endocrine disrupting properties that increase the risk of breast cancer:

- It is oestrogenic (Kojima et al 2004), and it induced MCF-7 human breast cancer cell proliferation significantly in three different assays (Chen et al 2002).
- With MCF-7 breast cancer cells exposed to a combination of cypermethrin and oestradiol, there was a significant increase in cell proliferation compared to exposure to oestradiol alone, i.e. cypermethrin potentiates oestradiol (Kakko et al 2004).
- Exposure to low-dose mixtures of cypermethrin and methyl parathion affected serum levels of oestradiol and immune function in rats (Liu et al 2006).
- The metabolite of cypermethrin, 3-(4-hydroxy-3-phenoxy)benzyl alcohol, showed oestrogenic potential, in particular the ability to interact with human oestrogen receptors (McCarthy et al 2006).

Cypermethrin has also been found recently to activate the oestrogen-forming enzyme aromatase in cancer cells in the human placenta (Laville et al 2006).

4.5.4 Fenvalerate

[mammary tumours, endocrine]

Carcinogenicity

Mammary tumours in rats have also been reported for fenvalerate (IARC 1991), although they were benign and not apparent at higher doses in a second study.

Mutations in mice and human cells are reported (IARC 1991; Giri et al 2002b; Xia et al 2004).

Fenvalerate, at all concentrations, increased the expression of the proto-oncogene WNT10B, which has been implicated in the development of human breast cancer through its effect on mammary gland development (Kasat et al 2002).

It inhibited gap junction intercellular communication at non-cytotoxic concentrations (Tateno et al 1993).

Endocrine disruption

Fenvalerate appears to have significant endocrine effects that increase the risk of breast cancer:

- It is both oestrogenic and anti-androgenic (Kojima et al 2004): it demonstrated significant oestrogenicity and significantly antagonized the action of progesterone in T47D human breast cancer cells and the authors concluded that exposure may contribute to hormone-sensitive cancer (Garey & Wolff 1998). Kim et al (2005a) also found it to be anti-progestagenic in T47D cells.
- It provoked mRNA induction in MCF-7 breast cancer cells at very low (nanomolar) levels, but higher exposures were required to cause cell proliferation (Go et al 1999).
- It stimulated MCF-7 human breast cancer cell proliferation (Chen et al 2002, 2005).
- It activated oestrogen receptors in oestradiol-sensitive cell lines (Lemaire et al 2006).

4.5.5 d-trans allethrin

[endocrine, carcinogenicity]

Carcinogenicity

d-trans allethrin increased the expression of a proto-oncogene related to mammary gland development, WNT10B, at a lower concentration, but not at the higher concentration. Human breast cancer MCF-7 cells under normal growth conditions do not express WNT10B (Kasat et al 2002).

Endocrine disruption

It also appears to increase the risk of breast cancer by several other mechanisms, including antagonising progesterone and stimulating cell proliferation, and these effects do not follow the normal positive dose–response pathway:

- It significantly antagonized the action of progesterone in T47D human breast cancer cells and Garey & Wolff (1998) concluded that exposure may contribute to hormone-sensitive cancer.
- At very low levels (1 µM) it was a moderate oestrogen blocker in MCF-7 human breast cancer cells, but at higher levels it provoked breast cancer cell proliferation. At even higher levels it was toxic to the cells. The dose-response curve had the classic inverted U form of a non-monotonic relationship (Go et al 1999).

4.5.6 Sumithrin (d-phenothrin)

[endocrine, carcinogenicity]

Sumithrin, or d-phenothrin as it is also known, is widely used as a household insecticide and as a 'disinsection' agent on international aircraft (i.e. spraying the aircraft cabin to prevent the importation of insects such as fruit fly and mosquitoes).

Carcinogenicity

Although sumithrin is not classified as a carcinogen, Cal EPA (1987b) reported increased incidence of liver tumours in rats. It has tested positive for mutagenicity in a salmonella test (Nishi et al 1985).

Sumithrin, at all concentrations, increased the expression of the proto-oncogene WNT10B, which has been implicated in the development of

human breast cancer through its effect on mammary gland development (Kasat et al 2002).

Endocrine disruption

Sumithrin is oestrogenic in T47D, MCF-7, and MCF-7 BUS human breast cancer cells, provoking mRNA induction and cell proliferation in a dose-response manner (Garey & Wolff 1998; Go et al 1999; Kim et al 2004).

4.5.7 Cyhalothrin

[mammary tumours]

Carcinogenicity

The US EPA reported an "equivocal finding" for mammary tumours in mice (FR 1995a). The International Programme on Chemical Safety (IPCS 1990c) also reported a statistically significant increase in the incidence of mammary adenocarcinoma in female mice, but then qualified it: "However, the frequency of these tumours was not unduly at variance with that normally seen in the strain of mouse used, and no dose relationship was apparent". Mutagenicity (chromosomal aberration) has been reported in rat bone marrow cells (Celik et al 2003), as has oxidative stress in rabbit red blood cells (El-Demerdash 2007). Further work is obviously required on this insecticide.

4.5.8 Flucythrinate

[mammary tumours, endocrine]

Evidence linking flucythrinate to breast cancer appears to be limited, however it is sufficient to warrant fuller investigation of mechanisms.

Carcinogenicity

An increased incidence of mammary adenomas in rats, but not in a dose-related manner, was reported by INCHEM (1985). The lack of a positive-dose response may indicate possible endocrine involvement.

Endocrine disruption

Kojima et al (2004) found that flucythrinate displayed both oestrogenic and anti-androgenic activity.

4.5.9 Pyrethrins

[endocrine, carcinogenicity]

The US EPA (2004) described pyrethrins as having 'suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential'.

When MCF-7 human breast cancer cells were exposed to a combination of pyrethrin and oestradiol, there was significant increase in cell proliferation when compared to exposure to oestradiol alone (Kakko et al 2004).

4.5.10 Cyfluthrin

[endocrine, carcinogenicity]

There appears to be little available information linking cyfluthrin to breast cancer. However Tisch et al (2005) found that cyfluthrin has a genotoxic effect on the epithelial cells of human nasal mucosa, and Kojima et al (2004) reported that it displays both oestrogenic and anti-androgenic effects.

4.6 ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

The potential involvement of organophosphate and carbamate insecticides in breast cancer is less well known and less well researched than that of organochlorines, and seldom mentioned in reviews on pesticides and breast cancer (e.g. Cocco 2002). Nevertheless there is evidence, and the link is arguably of much greater importance because organophosphates are still so widely used in agriculture, and in the case of malathion in head lice shampoos and in public health campaigns that directly expose millions of people. These pesticides do not generally persist in the environment but do frequently contaminate food as residues.

Although some authors report no oestrogenic activity of organophosphates (e.g. Chen et al 2002), others do report positive oestrogenic activity (e.g. Andersen et al 2002). In fact Japanese researchers Kojima et al (2004) found that organophosphates, together with organochlorines, were predominant among the 51 pesticides or pesticide metabolites to have oestrogenic effects. In all, 16 organophosphates and one carbamate were found to have oestrogenic effects, 11 of these also exhibiting anti-androgenic activity. A number of organophosphates have also been shown to cause human breast cancer cell proliferation. Furthermore it appears that some organophosphates may also contribute to breast cancer risk by being carcinogenic.

There appear to be very few epidemiological studies on breast cancer and organophosphates or carbamates.

(a) *Crete – greenhouse insecticides:* Dolapsakis et al (2001) undertook a study to test if occupational exposure to pesticides in greenhouses (mainly organophosphates and carbamates) might increase the risk of malignant or premalignant findings in mammographic examination. A total of 1,062 women (aged 40-75 years) were recruited between 1988 and 1993 and followed-up until 1998: 522 worked for at least 10 years in greenhouses for more than four hours daily (exposed), and 540 never worked in agriculture (non-exposed). 'Exposed' women had a significantly higher risk than 'non-exposed' for fibroadenoma, ductal hyperplasia, sclerotic adenosis, fibrohyperplastic disease, cystic disease and inflammatory mastitis. There were no overall significant differences in the detection rates of fibrocystic changes, lipoma and malignant changes or malignant tumours. The results indicate that exposed women may have higher risks for a number of lesions that are risk markers for subsequent invasive breast cancers. Furthermore, younger women (aged 40-49 years), particularly in the exposed group, had a higher detection rate of malignant tumours than older women (aged 50-75 years).

(b) *USA – Agricultural Health Study* – Engel et al (2005) found significantly increased risk of breast cancer associated with husbands' use of organophosphate insecticides, and in some cases women's own use, especially chlorpyrifos, diazinon, dichlorvos, malathion, and parathion, although the results were inconsistent. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. There were 122 breast cancer cases whose husbands had used organophosphates.

4.6.1 Malathion

[mammary tumours, epidemiology]

The insecticide malathion was introduced in 1950 (IARC 1983), and since then there has been on-going widespread use in agriculture, vector control, household applications and personal health treatment (head lice).

Malathion has been found in breast milk in Bhopal, India, at levels that result in infants consuming 4.1 times more malathion than the average

daily intake levels recommended by the World Health Organization (Sanghi et al 2003). It has also been found in infant meconium in the Philippines, indicating foetal exposure (Ostrea et al 2002).

Carcinogenicity

IARC (1983) did not find malathion to be carcinogenic. However subsequent studies and evaluations have found both malathion (e.g. Giri et al 2002) and its major metabolite malaoxon (Blasiak et al 1999) to be genotoxic in human cells, as well as causing chromosomal aberrations in mouse bone marrow cells (Amer & Fahmy 2004). The USA's National Institute for Occupational Safety and Health concluded that malathion is mutagenic (NIOSH 2005). It also has been found to cause liver tumours (US EPA 2000). The US EPA described malathion as having 'suggestive evidence for carcinogenicity' (US EPA 2004). Exposure to malathion has also been linked to non-Hodgkin's lymphoma in Canada (McDuffie et al 2001).

Of most importance here, malathion has been found to cause mammary tumours in rats (Cabello et al 2001). Malathion increased cell proliferation of terminal end buds of the mammary gland of rats, followed by formation of mammary tumours in 24 percent of cases. These effects were associated with a reduction in acetylcholinesterase activity, and the authors concluded that malathion induces changes in the epithelium of the mammary gland stimulating the process of carcinogenesis, and this effect occurs as a result of increasing cholinergic stimulation (Cabello et al 2001). Malathion increases PCNA and induces mutant p53 protein expression of MCF-7 breast cancer cells, thus inducing the progression of breast cancer cells (Cabello et al 2003).

Endocrine disruption

There appears to be little evidence of endocrine disruption.

Epidemiology

(a) *California, USA* – Mills & Yang (2005) found increased risk of breast cancer associated with exposure to malathion in a case-control study of breast cancer in Hispanic agricultural workers in California, involving 128 breast cancer cases newly diagnosed in 1988–2001 and 640 cancer-free controls.

(b) *USA – Agricultural Health Study* – Engel et al (2005) found increased

risk associated with husbands' use of malathion, but not with women's own use. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. There were 101 breast cancer cases whose husbands had used malathion.

4.6.2 Parathion

[mammary tumours]

Parathion is a highly toxic insecticide, introduced in 1947, and subsequently used in many countries (IARC 1983), although now more restricted. It has been found in infant meconium in the Philippines, indicating foetal exposure (Ostrea et al 2002).

Carcinogenicity

IARC (1983) was unable to classify it as to carcinogenicity because of insufficient information; however the US EPA (2004) classified it as a 'possible human carcinogen' (Group C). It has been found to be mutagenic in salmonella (Kawai et al 1987).

Parathion is a mammary carcinogen in rats: it increased cell proliferation of terminal end buds of the 44-day-old mammary gland of rats, followed by formation of mammary tumours in 14 percent of cases after about 28 months. These effects were, as with malathion, associated with a reduction in acetylcholinesterase activity, and the authors concluded that parathion induces changes in the epithelium of the mammary gland stimulating the process of carcinogenesis, and this effect occurs as a result of increasing cholinergic stimulation. The dosage of parathion used was low and the authors concluded that prolonged exposure to low doses may lead to "serious health effects" (Cabello et al 2001).

Parathion appears to also be a mammary carcinogen in humans: as with malathion, the parathion increases PCNA and induces mutant p53 protein expression of MCF-7 cells, thus inducing the progression of breast cancer cells (Cabello et al 2003b). Further, it was found to induce malignant transformation of MCF-10F human breast cancer cells as indicated by increased cell proliferation, anchorage independency and invasive capabilities (Calaf & Roy 2007). The authors concluded that parathion "is an initiator factor in the transformation process in breast cancer".

Epidemiology

In the Agricultural Health Study, USA, Engel et al (2005) found slightly increased risk associated with husbands' use of parathion in Iowa but not in North Carolina. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (18) amongst those whose husbands had used it precluded firm conclusions.

4.6.3 Dichlorvos

[mammary tumours]

Dichlorvos has been used widely as an insecticide since 1961 to control internal and external parasites in livestock and domestic animals, to control insects in houses, and in crop protection (IARC 1991). It has been found in breast milk in Taiwan (Gandhi & Snedeker 1999).

Carcinogenicity

Dichlorvos is classified by IARC (1991) as 'possibly carcinogenic to humans' (Group 2B), based on sufficient evidence in experimental animals but inadequate evidence in humans.

It has also been found to be mutagenic in a number of studies, including in human cells (e.g. Aquilina et al 1984), and Chinese hamster ovarian cells (e.g. Oshiro et al 1991). Epidemiological studies have indicated a slightly increased risk of leukaemia, non-Hodgkin's lymphoma, multiple myeloma and childhood brain cancer from exposure to dichlorvos.

A number of laboratory studies have shown elevated rates of mammary tumours in rodents (Gandhi & Snedeker 1999).

Gandhi & Snedeker concluded in 1999 that there was limited evidence of carcinogenicity in humans and of mammary gland carcinogenicity in animals.

Endocrine disruption

There seems to be little evidence of endocrine activity that might increase breast cancer risk, although Andersen et al (2002) found that it reacted as a very weak antagonist of androgen receptors.

Epidemiology

In the Agricultural Health Study, USA, Engel et al (2005) found slightly increased risk of breast cancer associated with husbands' and women's own use of dichlorvos in Iowa. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (18) amongst those whose husbands had used it precluded firm conclusions.

4.6.4 Methyl parathion

[endocrine, carcinogenicity]

Methyl parathion, a closely related insecticide, was introduced in 1949 and has been widely used since, especially on cotton crops.

It has been found in breast milk samples from Bhopal, India (Sanghi et al 2003), and in Turkmenistan, Tajikistan, and Kazakhstan (Lederman 1996).

Carcinogenicity

Methyl parathion has the potential to cause cancer, based on evidence of mutagenicity, although IARC in 1983 was unable to provide a classification on cancer. In 1987 IARC acknowledged findings of mutagenicity in non-human cells. Results of most *in vitro* genotoxicity studies on both mammalian and bacterial cells were positive. Some more recent studies have provided further evidence of mutagenicity (e.g. Das & John 1999). Undeger & Basaran (2005) found that methyl parathion at 100 and 200 microgm/ml significantly increased DNA damage in human lymphocytes.

Endocrine disruption

There is evidence that methyl parathion is an endocrine disruptor. The US EPA (2003a) reported possible endocrine disruption in mammals. The ATSDR (2001) also reported indications of weak oestrogenic activity. It showed oestrogenic potency similar to 17*beta*-estradiol in trout cells (Petit et al 1997). It has also been found recently to activate the oestrogen-forming enzyme aromatase in cancer cells in the human placenta (choriocarcinoma) (Laville et al 2006).

4.6.5 Chlorpyrifos

[endocrine, carcinogenicity]

Chlorpyrifos has been found in breast milk (Dogheim et al 1996; Sanghi et al 2003) and in infant meconium (Whyatt & Barr 2001; Ostrea et al 2002) indicating transfer to the foetus *in utero* from the mother.

Carcinogenicity

Although not classified as carcinogenic, some studies have found chlorpyrifos to induce mutagenicity, sister-chromatid exchanges, chromosomal loss and the development of oxidative stress. An association between exposure to chlorpyrifos and non-Hodgkin's lymphoma was found in a case–control study of male farmers and a prospective cohort study of licensed pesticide applicators, both in the USA (Lee et al 2004; Jamil et al 2004).

Endocrine disruption

Chlorpyrifos is weakly oestrogenic and causes proliferation of MCF-7 human breast cancer cells (Andersen et al 2002; Kojima et al 2004).

Gandhi et al concluded in 1999 that gaps in research do not allow a conclusion as to whether chlorpyrifos increases breast cancer risk.

Epidemiology

In the Agricultural Health Study, USA, Engel et al (2005) found slightly increased risk associated with women's own use, and their husband's use, of chlorpyrifos. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. There were 16 cases of women who had used chlorpyrifos themselves and an additional 61 cases whose husbands had used it.

4.6.6 Diazinon

[endocrine, carcinogenicity]

Diazinon has been found in infant meconium in the Philippines, indicating foetal exposure (Ostrea et al 2002).

Carcinogenicity

There appears to be no evidence of mammary carcinogenicity, and it has not been classified as a carcinogen, although it has been found to be mutagenic in mouse lymphocyte cells (McGregor et al 1988), and genotoxic in human cells (Tisch et al 2002).

A recent epidemiological study in the USA did find a possible link between exposure to diazinon and cancer: in a prospective cohort of 4,961 licensed pesticide applicators who reported using diazinon, 301 incident cancer cases were diagnosed during the follow-up period compared with 968 cases among 18,145 participants who reported no use. Increased risks for lung cancer and leukaemia were observed (Freeman et al 2005). Use of diazinon was also associated with increased non-Hodgkin's lymphoma incidence in two other studies (Waddell et al 2001; De Roos et al 2003).

Endocrine disruption

A recent study has shown that diazinon alters oestrogen-regulated gene expression in MCF-7 human breast cancer cells, disrupting their ability to repair DNA damage (Mankame et al 2006), and it may contribute to breast cancer risk by this mechanism.

Epidemiology

In the Agricultural Health Study, USA, Engel et al (2005) found slightly increased risk of breast cancer associated with husband's use of diazinon. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the risk of breast cancer related to women's use of diazinon was significantly elevated for women with a family history of breast cancer. But the small number of cases (39) amongst those whose husbands had used it precluded firm conclusions.

4.6.7 Other Organophosphates

There is weak evidence suggesting that a number of other organophosphate insecticides may contribute to elevated breast cancer risk, and more study is required of these chemicals in order to determine how significant the risk might be.

***Phosmet** [mammary tumours]*

There is limited evidence of mammary gland tumours in rats and mice, of mutagenicity, and of carcinogenicity; and epidemiological studies have observed an increased risk for leukaemia and non-Hodgkin's lymphoma (Hasegawa et al 1993). The US EPA (2004) described phosmet as having 'suggestive evidence of carcinogenicity'.

***Isofenphos** [endocrine, carcinogenicity]*

Isofenphos appears to have both carcinogenic and endocrine disrupting potential. Boros & Williams (1998) reported a case of acute myeloid leukaemia following chronic isofenphos poisoning. Subsequently they demonstrated a leukemogenic process involving promotion of DNA proliferation simultaneous with poor differentiation (Boros & Williams (2001); and that isofenphos at "remarkably low concentrations" caused mutations in human lymphocyte DNA (Williams et al 2004). Its degradation product, isofenphos oxon, has been shown to be mutagenic (Onodera et al 1995). Additionally Kojima et al (2004) report both oestrogenic and androgenic activity.

***Ethion** [endocrine, carcinogenicity]*

Ethion was genotoxic in a chromosome aberration assay in chicks (Bhunya & Jena 1994), and oestrogenic and anti-androgenic in human receptor assays (Kojima et al 2004).

***EPN** [endocrine, carcinogenicity]*

EPN (ethyl nitrophenyl phenylphosphonothionate) showed oestrogenic activity in an oestrogen receptor-dependent MCF-7 breast cancer cell proliferation assay (Okubo et al 2004), and both oestrogenic and anti-androgenic activity in another assay (Kojima et al 2004). Its degradation product, EPN oxon, has been shown to be mutagenic (Onodera et al 1995).

***Monocrotophos** [endocrine, carcinogenicity]*

Monocrotophos has been found to be genotoxic (clastogenic) in one test (de Kergommeaux et al 1983), and mutagenic in human fibroblasts (Mitchell et al 1983). It increased proliferation of MCF-7 human breast cancer cells at relatively low concentrations (Isoda et al 2005).

Omethoate *[endocrine, carcinogenicity]*

Little information appears to be available on the potential carcinogenicity of omethoate, although Dolara et al (1992) found it to be mutagenic, causing increases in sister chromatid exchanges in human lymphocytes. But it increased proliferation of MCF-7 human breast cancer cells at relatively low concentrations (Isoda et al 2005).

Phenthoate *[endocrine, carcinogenicity]*

Phenthoate has been found to be mutagenic in mice maternal bone marrow and embryonic liver cells, causing chromosomal aberrations in both mothers and foetuses, indicating risk to transplacentally-exposed babies (El Nahas et al 1997). It is also oestrogenic (Kojima et al 2004).

Tolchlofos-methyl *[endocrine]*

Tolchlofos-methyl is oestrogenic in MCF-7 human breast cancer cells, causing cell proliferation (Andersen et al 2002; Bonefeld-Jorgensen et al 2005). It was also anti-androgenic in a human androgen receptor assay (Kojima et al 2004).

Other organophosphate insecticides in which oestrogenic activity has been reported include ***bromophos-methyl, cyanofenphos, isoxathion, and pirimiphos-methyl*** (Kojima et al 2004). ***Bromophos-ethyl, butamiphos, dichlofenthion, leptophos,*** and ***prothiofos*** have both oestrogenic and anti-androgenic properties (Kojima et al 2004); and ***quinalphos*** increases prolactin secretion at least in male rats (Sarkar et al 2000).

4.6.8 Carbamate insecticides

Aldicarb *[epidemiology, carcinogenicity]*

Although the carbamate insecticide aldicarb has not been classified as a carcinogen, there is some evidence that it may cause cancer. It has been found to cause pituitary tumours in female rats and fibrosarcomas in male mice, and to be weakly mutagenic in *Salmonella* tests (IRIS 1993). It also induced chromosomal aberrations in rat bone-marrow cells, gene mutation in rodent cells, and various kinds of chromosomal damage and gene mutation in cultured human cells (IARC 1991).

Epidemiology

Muir et al (2004) examined the spatial distribution of breast cancer incidence in Lincolnshire and Leicestershire, UK, and its association with the application of particular pesticides. It found no overall association between breast cancer and application of pesticides in the urban areas, but it did reveal a spatial association between the breast cancer incidence rates and the application of aldicarb, in rural Leicestershire.

***Other Carbamates** [endocrine]*

Propamocarb – oestrogenic effects in MCF-7 breast cancer cells, potentiates the effects of 17*beta*-oestradiol, and weakly stimulates aromatase activity (Andersen et al 2002; Bonefeld-Jorgensen et al 2005).

Pirimicarb – potentiates the effects of 17*beta*-oestradiol and weakly stimulates aromatase activity (Andersen et al 2002; Bonefeld-Jorgensen et al 2005).

Methiocarb – oestrogen agonist and androgen antagonist (Andersen et al 2002; Kojima et al 2004).

4.7 OTHER HERBICIDES

A number of herbicides, other than the triazines described in section 4.3, are associated with mammary tumours in laboratory studies and/or with endocrine disruption that may increase the risk of breast cancer, although the evidence is less.

4.7.1 2,4-D

[mammary tumours, endocrine, epidemiological]

The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) may increase breast cancer risk through both carcinogenic and endocrine mechanisms.

Carcinogenicity

IARC (1987) classified 2,4-D as 'possibly carcinogenic to humans' (Group 2B). It has been found to be "carcinogenic in male and female rats and probably also in mice"—including tumours of the mammary gland in female rats, carcinomas of the endocrine organs in male rats, lymphosarcoma in rats of both sexes, cancer of the lymphoreticular system in female mice

(2,4-D isooctyl ester), and tumours of the lung in male mice (2,4-D isopropyl ester). It has been found to be mutagenic (e.g. Reuber et al 1983; Pavlica et al 1991).

Epidemiological studies have linked chlorophenoxy herbicides generally (which includes 2,4-D) with soft tissue sarcoma, lung cancer, bronchial carcinoma, Hodgkin's and non-Hodgkin's lymphoma (IARC 1987). Other studies have linked 2,4-D specifically with non-Hodgkin's lymphoma (Hoar et al 1986; Zahm et al 1990; Hoffmann 1996), lung cancer (Kogevinas et al 1997)—and with breast cancer (see below).

Two commercial formulations of 2,4-D (LV4 and 2,4-D Amine) have induced cell proliferation in MCF-7 breast cancer cells. The active ingredient 2,4-D by itself did not induce the cell proliferation, so it seems the other components in the formulations—the so-called inerts—may have been responsible (Lin & Garry 2000).

Additionally 2, 4-D disrupts mitochondria membrane potential (Tusch & Schwab 2003) and there is growing evidence that this increases oxidative stress leading to cancer (Mukherjee et al 2006).

Endocrine disruption

2,4-D showed oestrogenic activity in an *in vivo* rainbow trout vitellogenin assay. Additionally, when combined with an alkylphenol ethoxylate-containing surfactant, it showed a greater than additive estrogenic response at the lowest concentrations tested, but a less than additive response at the highest combined concentrations (Xie et al 2005).

It also affects luteinizing hormones in vertebrates (Kashian & Dodson 2002), and inhibits androgen binding in human prostate cancer cells (Kim et al 2005b).

2,4-D increased the formation of cytochrome P450 enzymes, which in turn was accompanied by increases in the formation of 2-hydroxyestrone and 4-hydroxyestrone in the mammary gland, the latter of which in particular is associated with increased risk of human breast cancer (Badawi et al 2000).

Additionally a commercial formulation containing 2,4-D (plus mecoprop, dicamba, and 'inerts') displayed the classic inverted U-shaped dose-response of endocrine disrupting substances: pregnant mice exposed to the formulation showed an inverted U-shaped dose-response pattern for reduced litter size, with the low end of the dose range producing the

greatest decrease in the number of live pups born. The decrease in litter size was associated with a decrease in the number of implantation sites, but only at very low doses that are environmentally relevant (Caviares et al 2002).

Epidemiology

In a recent case-control study of breast cancer in farm labour union members in California, USA, involving 128 breast cancer cases newly diagnosed in 1988-2001 and 640 cancer-free controls, Mills & Yang (2005) found increased risk of breast cancer associated with exposure to 2,4-D, especially in younger women, those with early-onset breast cancer, and those diagnosed earlier (1988-1994).

4.7.2 Paraquat

[mammary tumours]

Carcinogenicity

Paraquat has been found to cause mammary tumours—the US EPA (1997) reported mammary gland cysts, adenomas, fibromas, fibroadenomas and adenocarcinomas in a trial on rats.

Paraquat has also been shown to have some genotoxic effects (e.g. D'Souza et al 2005), including both mutagenic (el-Abidin et al 1993) and clastogenic effects such as increases in the frequency of sister-chromatid exchanges in human lymphocytes (Ribas et al 1997-98).

Paraquat disrupts mitochondria membrane potential (McCarthy et al 2004) and there is growing evidence that this increases oxidative stress leading to cancer (Mukherjee et al 2006).

Women with the inherited breast cancer susceptibility gene BRCA1 may be at greater risk for breast cancer from paraquat exposure, as the gene confers sensitivity to the oxidizing effect of paraquat (Bae et al 2004).

Epidemiology

(a) *Malaysia* – Among the symptoms reported by women sprayers using paraquat in Malaysian plantations are breast pain, swelling and/or the development of pus in their breasts (Joshi et al 2002). Although these symptoms themselves are not indicative of breast cancer,

evidence suggests that inflammation may be a key event in cancer development (Lu et al 2006).

(b) *USA – Agricultural Health Study* – Engel et al (2005) found a slightly increased risk of breast cancer associated with husband's use of paraquat. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (30) amongst those whose husbands had used it precluded firm conclusions.

4.7.3 Alachlor

[mammary tumours, endocrine]

There is limited evidence that alachlor is both carcinogenic, including causing mammary tumours, and oestrogenic.

Carcinogenicity

The US EPA (2004) has classified alachlor as 'likely to be carcinogenic to humans at high doses, but not at low doses'. Snedeker (2000) found some evidence of mammary tumours in animal tests (but reported them as not statistically significant). Alachlor has also been found to be mutagenic in human lymphocytes (Ribas et al 1996).

Endocrine disruption

Alachlor is oestrogenic: it mimics the primary endogenous oestrogen, 17*beta*-oestradiol, and suppresses apoptosis in oestrogen-responsive cells. Apoptosis is a process of cell death in which specific cells undergo a programmed series of biochemical events ending in the elimination of the cells. The MCF-7 breast cancer cell line undergoes apoptosis, leading to tumour regression, if oestrogen is removed. Alachlor hence acts to prevent tumour regression (Burow et al 1999).

4.7.4 Diuron

[mammary tumours]

Carcinogenicity

The US EPA (2003b) has classified diuron as a 'known/likely' human carcinogen, based on urinary bladder carcinomas in both sexes of the Wistar

rat, kidney carcinomas in the male rat (a rare tumour), and mammary gland carcinomas in female mice.

Endocrine

Bauer et al (1998) reported that diuron could bind to androgen receptors, and Thiabut & Porte (2004) describe diuron as anti-androgenic.

4.7.5 Triclopyr

[mammary tumours]

Mammary tumours (adenocarcinomas) have been found in both female mice and rats (US EPA 1998b).

A mixture of triclopyr with an alkylphenol ethoxylate-containing surfactant, Target Prospreader Activator (TPA) caused greater than additive oestrogenic responses in an *in vivo* rainbow trout vitellogenin assay—in two middle concentrations—when compared to TPA or triclopyr alone (Xie et al 2005).

4.7.6 Tribenuron methyl

[mammary tumours. endocrine]

A sulphonylurea herbicide with a triazine moiety, tribenuron methyl induces mammary gland tumours in female rats (US EPA 2002b) and is classified as a 'possible human carcinogen' (Group C) (US EPA 2004).

It is weakly oestrogenic (Andersen et al 2002).

4.7.7 Oryzalin

[mammary tumours]

Oryzalin is classified by the US EPA as a 'possible human carcinogen' (Group C), based on mammary gland tumours in female rats (US EPA 1995a). It produced mammary gland adenomas, fibroadenomas and adenocarcinomas (IRIS 1989a).

4.7.8 Ethalfluraline

[mammary tumours]

The US EPA (2004) classified the herbicide ethalfluraline as a 'possible human carcinogen' (Group C), based on mammary gland fibroadenomas in female rats (US EPA 1995b).

4.7.9 Sulfallate

[mammary tumours]

The herbicide sulfallate was introduced in 1954 (IARC 1983). It is classified by IARC as a 'possible human carcinogen' (Group 2B) based on sufficient evidence that sulfallate is carcinogenic to experimental animals. It causes mammary gland tumours in female mice and rats, lung tumours in male mice, and tumours of the forestomach in male rats. It is mutagenic in bacterial systems.

4.7.10 Prosulfuron

[mammary tumours]

The US Federal Register (FR 1995b) reported a "slight increase" in the incidence of mammary gland adenocarcinomas in female rats.

4.7.11 Silvex (2,4,5-TP; fenoprop)

[epidemiology]

Engel et al (2005) found a possible association between use of silvex and breast cancer in a large prospective cohort study of 30,454 farmers' wives in Iowa and North Carolina, USA. The women had no history of breast cancer prior to enrolment in the study from 1993 to 1997. By 2000, 309 breast cancer cases were identified. Small numbers of cases among those who had personally used the pesticide precluded firm conclusions.

4.7.12 Trifluralin

[endocrine, carcinogenicity]

Trifluralin is a selective pre-emergence herbicide used for the control of annual grasses and broadleaf weeds, first registered for use in 1963 (IARC 1999). It has both carcinogenic and endocrine disrupting properties.

Carcinogenicity

Trifluralin is classified by the US EPA (2004) as a 'possible human carcinogen' (Group C). It caused urinary tract tumours (renal pelvis carcinomas and urinary bladder papillomas), and thyroid tumours (adenomas and carcinomas) in rats (IRIS 1989b), and in mice it caused liver carcinomas and squamous-cell carcinomas of the forestomach (IARC 1991). It has been found to be genotoxic in fruit fly and mice (Kaya et al 2004: Gebel et al 1997), but not in human lymphocytes (Ribas et al 1996b). Use of trifluralin was

associated with an increased risk for non-Hodgkin's lymphoma in a study in the USA (IARC 1991).

Endocrine disruption

Concentrations of oestradiol were significantly increased in ewes given trifluralin (Rawlings et al 1998).

Other Herbicides

Other herbicides that have demonstrated oestrogenic activity include ***diclofop-methyl*** (Petit et al 1997) and ***fluazifop-butyl***; ***chlornitrofen, pendimethalin,*** and ***thenylchlor*** display both oestrogenic and anti-androgenic properties (Kojima et al 2004). ***Chlornitrofen*** has also been found to be mutagenic in a number of tests (Oguri et al 1995).

4.8 FUNGICIDES

Although most of the evidence linking pesticides to breast cancer relates to insecticides and to a lesser extent herbicides, there are a number of fungicides for which there is evidence—epidemiology, mammary tumours in laboratory studies, and/or endocrine disrupting effects—that exposure to some fungicides may also increase the risk of breast cancer.

4.8.1 Mancozeb

[mammary tumours]

Mancozeb was first registered in the USA in 1948 (US EPA 2005a) as a broad-spectrum fungicide and is used worldwide in agriculture, professional turf management, and horticulture. Mancozeb is a member of the ethylene bisdithiocarbamate group of pesticides, which includes the related fungicides ferbam, maneb, metiram, nabam, propineb, zineb, and ziram, the fumigant metam-sodium, and the herbicide sulfallate. All break down into the carcinogen ethylene thiourea.

Carcinogenicity

Mancozeb is classified as a 'probable human carcinogen' (Group B2), based on thyroid follicular cell adenomas and carcinomas in rats (US EPA 2005a). It is metabolized to ethylene thiourea, which causes similar thyroid tumours in rats and mice, and pituitary and liver tumours in mice (US EPA 2005a). It

has also caused malignant mammary tumours, Zymbal gland and ear duct carcinomas, liver carcinomas, malignant tumours of the pancreas, osteosarcomas of the bones of the head, and haemolymphoreticular neoplasias in rats, according to Belpoggi et al (2002), who described mancozeb as "a multipotent carcinogenic agent". It has oxidative and genotoxic effects on cells (Calviello et al 2006).

Mancozeb or its metabolite are capable of crossing the placental barrier and can cause DNA damage and tumour initiation in the foetal cells in mice (Shukla & Arora 2001).

Epidemiology

A USA epidemiological study of women living on farms, although it did not look at breast cancer, did demonstrate endocrine disrupting effects that indicate a potential to increase the risk of breast cancer. Farr et al (2004) found that women who had used mancozeb or maneb had four times the odds of experiencing long menstrual cycles and twice the odds of experiencing missed periods as women who had never used pesticides.

Other epidemiological findings include an increased risk of leukaemia in Californian farm workers where mancozeb and toxaphene have been used, compared to farm workers employed elsewhere (Mills et al 2005).

4.8.2 Captafol

[mammary tumours]

The fungicide captafol has been widely used since 1961 for the control of fungal diseases in a variety of plants (IARC 1991). It is classified by the US EPA (2004) as a 'probable human carcinogen' (Group 2b). It causes mammary tumours in rats (Quest et al 1993). It also causes adenocarcinomas of the small intestine and tumours of the heart and spleen in mice; and in rats it causes renal carcinomas and liver tumours (IARC 1991). It causes gene mutation and chromosomal aberrations in human and other mammalian cells, and DNA damage and gene mutation in fungi and bacteria (IARC 1991).

4.8.3 Folpet

[mammary tumours]

The fungicide folpet is classified by the US EPA (2004) as a 'probable human carcinogen' (Group 2b). It causes mammary tumours in rats (Quest et al

1993), carcinomas of the stomach and duodenum in mice (Nyska et al 1990). It shows mutagenic activity including chromosomal aberrations (Quest et al 1993).

4.8.4 Fenarimol

[endocrine, co-carcinogen]

Carcinogenicity

The fungicide fenarimol is not classified as a carcinogen, however there is evidence that it is genotoxic (de Castro et al 2005). Additionally, fenarimol had a greater than additive genotoxic effect when combined with a known genotoxic substance, which supports other findings suggesting that fenarimol may have co-toxic, co-mutagenic, cancer-promoting and co-carcinogenic potential (Poli et al 2003).

Endocrine disruption

Fenarimol displays oestrogenic activity that induces an increase in proliferation of MCF-7 human breast cancer cells (Vinggaard et al 1999; Okubo et al 2004). It can interfere with the steady state levels of the mRNA of *alpha* and *beta* oestrogen receptors: it significantly decreased the *alpha* and increased the *beta* mRNA levels in MCF-7BUS breast cancer fibroblast cells. Co-exposure with 17*beta*-oestradiol elicited a significantly increased *beta* oestrogen receptor mRNA (Grunfeld et al 2004).

It has also has the ability to act as an androgen antagonist in MCF-7 human breast cancer cells (Anderson et al 2002).

Fenarimol exhibits a dual effect, being an aromatase inhibitor at low concentrations and oestrogenic at higher concentrations in *in vitro* tests (Andersen et al 2006). The authors also confirmed that fenarimol is oestrogenic in *in vivo* tests, causing significantly increased uterine weight in ovariectomized female rats. They commented that they knew of only two other pesticides for which this ability has been demonstrated: the organochlorine insecticides *o,p´*-DDT and methoxychlor (see section 4.2).

4.8.5 Triphenyltin

[endocrine, carcinogenic]

Triphenyltin is another fungicide with carcinogenic and endocrine disrupting properties.

Carcinogenicity

Lin & Garry (2000) found that triphenyltin induced aneuploidy (chromosomal disorder common in cancerous cells) in MCF-7 human breast cancer cells.

It is classified by the US EPA (2004) as a 'probable human carcinogen' (Group B2).

Endocrine

Triphenyltin was found to be a potent stimulator of aromatase activity in human placental choriocarcinoma cells. Alterations of aromatase function *in utero* have been shown to permanently affect human embryos and increase the risk of both breast and endometrial cancers (Nakanashi et al 2002).

4.8.6 Captan

[epidemiology, carcinogenicity]

The non-systemic fungicide captan was introduced commercially in 1951 (IARC 1983). It is used to control diseases in many crops, seeds, turf, and ornamentals, and applied as a post-harvest dip to fruit. It is also incorporated into paint and adhesives as a preservative (US EPA 1999).

Carcinogenicity

Captan is classified by the US EPA (2004) as a 'probable human carcinogen' (Group B2), based on increased incidence of intestinal tumours in mice. It has also caused an increased incidence of renal tumours in male rats and an increased incidence of sarcomas in the uterus of female rats (US EPA 1999). It is mutagenic to bacteria and yeast, and induced chromosomal aberrations, sister chromatid exchange and mutations in cultured mammalian cells (IARC 1983). It is also mutagenic in Chinese hamster ovarian cells (Oberly et al 1990).

Epidemiology

In the USA Agricultural Health Study, Engel et al (2005) found significantly increased risk of breast cancer associated with husband's use of captan. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases (23) amongst those whose husbands had used it precluded firm conclusions.

4.8.7 Maneb

[epidemiology, carcinogenicity]

Maneb is a broad-spectrum fungicide, first registered in the USA in 1962, and used globally on a wide variety of fruit, nut, vegetable, field and forage crops, grapes, seeds, ornamental plants in nurseries and greenhouses, and home gardens. Maneb is a member of the ethylene bisdithiocarbamate group of fungicides, which includes the related active ingredients mancozeb and metiram, and breaks down into ethylene thiourea (US EPA 2005b).

Maneb is included here because of its possible effects on the endocrine system (see below), its carcinogenic metabolite ETU, and its similarity to mancozeb.

Carcinogenicity

Maneb is classified as a 'probable human carcinogen' (Group B2) by the US EPA, based on female mouse liver tumours caused by the ethylene thiourea (US EPA 2005b). It has been found to be mutagenic in human fibroblasts (cells of connective tissue) (Mitchell et al 1983).

Epidemiology

Farr et al (2004) found women who had used maneb had four times the odds of experiencing long menstrual cycles and twice the odds of experiencing missed periods as women who had never used pesticides (refer mancozeb).

4.8.9 Vinclozolin

[mammary tumours, endocrine]

Vinclozolin is a potent anti-androgen that binds to androgen receptors (Gray et al 1999), and there is increasing evidence that it too increases the risk of breast cancer.

In 1997 Kelce & Wilson asserted that strong anti-androgens such as the fungicide vinclozolin, are implicated in the increasing incidence of breast cancer. Two years later in 1999, Gray et al found that vinclozolin, already well known for its feminising effects on male reproductive development, also caused the permanent development of nipple tissue in male mice, at doses an order of magnitude lower than those required to cause malformations.

Anway et al (2006) found that embryonic exposure to the fungicide vinclozolin at critical times resulted in breast tumour development in subsequent generations of adult rats. They found a consistently high incidence of breast tumours across all four generations that they tested, and described it as a "transgenerational disease state", concluding that it appeared to be "due in part to epigenetic alterations in the male germ line".

Other fungicides:

Oestrogenic activity has also been reported in the fungicides ***biphenyl, dodemorph, triademefon,*** and ***triademenol*** (Vinggaard et al 1999; Petit et al 1997; Okubo et al 2004).

4.9 OTHER PESTICIDES

There is strong evidence supporting an association between some other pesticides and breast cancer, in particular fumigants.

4.9.1 DBCP (1,2-dibromo-3-chloropropane)

[mammary tumours, epidemiology]

DBCP is a nematicide and soil fumigant. Production is believed to have ceased (IARC 1999), however it remains persistent in soil and continues to be detected as a groundwater contaminant in areas of past high use (Clark & Snedeker 2005).

Carcinogenicity

It is classified as a 'probable human carcinogen' (Group 2b) by the US EPA (2004), and by IARC. It produced adenocarcinomas of the mammary gland in female rats, squamous-cell carcinomas of the forestomach in rats and mice, as well as tumours of the nasal cavity, lung, tongue, pharynx, and liver (IARC 1999). It is described as a mutagen and clastogen (Clark & Snedeker 2005). It causes DNA damage and genotoxicity in animal cells *in vitro* and *in vivo* (IARC 1999).

In humans, lung, liver, biliary tract and cervical cancer, and a non-significant excess of melanoma and leukaemia have been observed (IARC 1999).

Endocrine disruption

It disturbs spermatogenesis and has caused male infertility in humans (IARC 1999).

Epidemiology

In Hawaii, a significantly higher rate of breast cancer was reported for the small village of Kunia, on the island of Oahu, than for the town of Poamoho 5 miles away. Kunai is located on a pineapple plantation and was home to 65 percent of Del Monte's full time employees. The drinking water had become contaminated with the DBCP used on the pineapples, with average levels two orders of magnitude greater than the US EPA's drinking water standard. The drinking water in Poamoho did not contain DBCP (Allen et al 1997).

4.9.2 Ethylene dibromide (1,2-dibromoethane)

[mammary tumours, epidemiology – male breast cancer]

Ethylene dibromide is a nematicide and fumigant, and also a petroleum additive.

Carcinogenicity

It is classified as 'probably carcinogenic to humans' (Group 2B)(US EPA 2004). It causes mammary tumours in rats and mice, and cancer of the nasal cavity, respiratory system, and circulatory system (National Toxicology Program 1982). It is genotoxic in human lymphocytes (Channarayappa et al 1992).

Epidemiology

Men occupationally exposed to this product, as part of petroleum vapours and combustion products, have been found to have an increased incidence of breast cancer (Hansen 2000).

4.9.3 Ethylene dichloride (1,2-dichloroethane)

[mammary tumours, epidemiology – male breast cancer]

Ethylene dichloride is a fumigant, and also a constituent of petrol.

Carcinogenicity

It causes mammary tumours in rats and mice, and a number of other cancers including endometrial tumours in mice (National Toxicology Program 1978a).

Epidemiology

Men occupationally exposed to this product, as part of petroleum vapours and combustion products, have been found to have an increased incidence of breast cancer (Hansen 2000).

4.9.4 Ethylene oxide

[mammary tumours]

Ethylene oxide is a fumigant, used primarily for the fumigation of spices.

Carcinogenicity

It is classified as 'carcinogenic to humans' (Group 1). It is a powerful mutagen and clastogen of all species. It has induced a persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers, and has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals. Mammary tumours have been reported from studies on rats, but not epidemiological studies of humans (IARC 1994).

4.9.5 Propylene dichloride (1,2-dichloropropane)

[mammary tumours]

Propylene dichloride is a fumigant for soil and grain, and also used against fruit tree borer. Its industrial uses include the production of tetrachloroethylene and carbon tetrachloride, and as a solvent in some furniture finishes, dry cleaning fluids, and paint removers.

Carcinogenicity

It has caused mammary tumours in rats and liver tumours in mice (National Toxicology Program 1986). It is classified as 'probably carcinogenic to humans' (Group 2B) (US EPA 2004).

4.9.6 PFOS (perfluorooctane sulfonic acid potassium salt)

[mammary tumours]

PFOS is an insecticide, and can also be an inert ingredient in other pesticide formulations.

Carcinogenicity

It is hepatotoxic and carcinogenic in rats, inducing tumours of the liver, thyroid and mammary glands (OECD 2002).

4.9.7 Clonitralid

[mammary tumours]

Clonitralid is a molluscicide, used for controlling water snails.

Carcinogenicity

The USA's National Toxicology Program (1978b) reported mammary adenocarcinomas in female rats exposed to clonitralid.

4.9.8 Chlorobenzilate

[endocrine, carcinogenic]

The insecticide chlorobenzilate was introduced in 1952 and has been used for controlling mites on citrus and other crops.

Carcinogenicity

It has induced liver tumours in mice (IARC 1983).

Endocrine

It has also been observed to have oestrogenic and anti-androgenic activity (Kojima et al 2004).

Others:

Oestrogenic and anti-androgenic activity has also been reported in the insecticides ***bromopropylate*** and ***chloropropylate*** (Kojima et al 2004).

4.10 ADJUVANTS, INERT INGREDIENTS AND CONTAMINANTS

The active ingredients that have been reviewed in this chapter are only part of the problem with pesticides and breast cancer. Pesticide formulations contain a number of other chemicals, so-called inert ingredients and/or contaminants. Additionally when a pesticide formulation is applied, an adjuvant may be added to help it adhere, prevent breakdown in sunlight, or prevent it being washed off by rain. Any of these chemicals may also contribute to breast cancer risk.

For example, the dioxin 2,3,7,8-TCDD is a contaminant of some chlorinated pesticides, such as 2,4-D (US EPA 1994). Dioxin is a known human carcinogen and an endocrine disruptor. Recent laboratory evidence has implicated it in the development of mammary tumours in mice (Brown et al 1998; Fenton et al 2002), and epidemiological evidence has revealed that women exposed to a tenfold increase in dioxin after the chemical plant explosion in Serveso, Italy, in 1976 suffered a twofold increase in breast cancer (Warner et al 2002).

As reported earlier, commercial formulations of 2,4-D were found to induce proliferation of MCF-7 breast cancer cells when the 2,4-D active ingredient alone did not, so it seems the inerts may have been responsible (Lin & Garry 2000).

The adjuvants X-77 and Activate Plus were also found to induce significant cell proliferation of MCF-7 breast cancer cells (Lin & Garry 2000).

Because the number of possible inert ingredients, adjuvants and contaminants is so large, they will not be addressed here – with the exception of nonylphenol and 1,4-dioxane.

4.10.1 Nonylphenol

[mammary tumours, endocrine]

Nonylphenol and the related nonylphenol ethoxylates are used as inert ingredients in some pesticide formulations, and as an adjuvant.

Nonylphenol is the term used to refer to a family of compounds all of which have a central aromatic (or benzene) ring and a nine-carbon side chain. 4-nonylphenol is the most common form. Nonylphenol and its ethoxylate are part of a wider family of alkylphenol and alkylphenol ethoxylates. These chemicals are used in laundry detergents, general

purpose cleaners, floor care products, non-chlorine sanitizers, degreasers and deodorizers, contraceptives, hair colourings, shampoos, and hair conditioners and styling aids. All are of concern because of their environmental persistence, bioaccumulation and endocrine disrupting effects.

Carcinogenicity

Nonylphenol stimulates the formation of mammary tumours in rats and mice, but this is thought to be via endocrine rather than traditional carcinogenic mechanisms (see below).

Endocrine disruption

Nonylphenol is oestrogenic. As described in Chapter 3.2, nonylphenol was found to be leaching out of plastic laboratory test plates and causing the proliferation of human breast cancer cells in culture in 1998 (Colborn et al 1996; Soto et al 1991). Although it was already known that nonylphenol was oestrogenic and affected gene expression in human breast cancer cells (e.g. Mueller & Kim 1978; Ren et al 1997), the discovery that this chemical could exert these effects after leaching out of plastic containers was of considerable concern. Subsequently, Vivacqua et al (2003) found that nonylphenol contaminants in food also stimulated the proliferation of human breast cancer cells and warned about the potential influence on hormone-dependent breast cancer, because of the widespread human exposure to nonylphenol.

Additionally nonylphenol, at very low concentrations, raises cellular calcium levels, which then cause rapid secretion of prolactin (Wozniak et al 2005).

4-nonylphenol is known to increase the proliferation of MCF-7 human breast cancer cells in a dose-dependent manner. The lowest concentration that significantly increased the proliferation of MCF-7 cells was 1 microM (Blom et al 1998).

It has also been found to cause mammary tumours in mice in a dose-dependent manner (Acevedo et al 2005), and rats in a non dose-dependent manner (Fukamachi et al 2004).

4-nonylphenol can increase the liver formation of cytochrome P450 enzymes responsible for the production of the oestrogenically active 16-hydroxyoestriol in a dose-dependent manner (Acevedo et al 2005). It also reduces 17*beta*-oestradiol binding to the oestrogen receptors (Danzo et al 1997).

4.10.2 1,4-dioxane

[mammary tumours]

1,4-dioxane (not to be confused with dioxin) is a contaminant of pesticide formulations containing the surfactant POEA—such as Roundup, the common herbicide containing the active ingredient glyphosate. It is formed as a by-product of the production of POEA (polyethoxethyleneamine). Exactly which pesticide formulations contain the surfactant POEA, and hence the carcinogen 1,4-dioxane, is unknown but those that do can be considered to contribute to an increased risk of breast cancer.

It is not even known which of the many formulations of the herbicide ingredient glyphosate contain POEA. However, registration data from New Zealand showed that Roundup contained 18% POEA (Watts 1994), and according to the US EPA (1991), Roundup contained 300ppm 1,4-dioxane at final dilution.

The USA'S Consumer Product Safety Commission considers the presence of 1,4-dioxane, even as a trace contaminant, a cause for concern, including as residues on food crops treated with pesticides containing 1,4-dioxane (National Toxicology Program 2005).

Carcinogenicity

1,4-Dioxane has formed tumours in laboratory animals in the liver, gall bladder, nasal cavity, lung, peritoneum, skin, and mammary gland. It has been classified by IARC as a Group 2B carcinogen, based on sufficient evidence that it is carcinogenic in animals (IARC 1999b).

Table 3: Summary of evidence of potential to increase breast cancer risk

Pesticide	Epidemiology (breast cancer)	Mammary tumours	Oestrogenic activity	Other hormonal effects	Evidence of carcinogenicity	Relevant immune	GJIC inhibition	Mammary gland development
Organochlorines								
aldrin	+		+		+			
chlordane	+		+	+	+	+	+	
chlordecone			+	+	+			
DDT/DDE	+		+	+	+	+	+	+
dicofol			+		+		+	
dieldrin	+		+	+	+			
endosulfan	+		+	+	+	+		+
endrin		+	+					
HCB	+			+	+	+		
heptachlor	+		+		+	+	+	
lindane	+		+	+	+		+	
methoxychlor	+	+	+	+	+			+
mirex	+			+	+			
toxaphene	+	+	+		+	+	+	
Triazine herbicides								
atrazine	+	+	+	+	+	+		+
cyanazine		+		+	+			
propazine		+		+	+			
simazine		+		+	+			
terbumeton		+						
terbuthylazine		+						
terbutryn		+			+			
Synthetic pyrethroids								
allethrin			+	+				+
cyfluthrin			+	+	+			
cyhalothrin		+			+			
cypermethrin			+		+		+	
deltamethrin		+	+	+	+		+	
fenvalerate		+	+	+	+		+	+
flucythrinate		+	+	+				
permethrin			+	+	+		+	+
pyrethrins			+		+			
sumithrin			+		+			+

Table 3: Summary of evidence of potential to increase breast cancer risk

Pesticide	Epidemiology (breast cancer)	Mammary tumours	Oestrogenic activity	Other hormonal effects	Evidence of carcinogenicity	Relevant immune	GJIC inhibition	Mammary gland development
Organophosphates								
bromophos-ethyl			+	+				
bromophos-methyl			+					
butamifos			+	+				
chlorpyrifos	+		+		+			
cyanofenphos			+					
dichlofenthion			+	+				
diazinon	+		+		+			
dichlorvos	+	+		+	+			
EPN			+	+	+			
ethion			+	+	+			
isofenphos			+	+	+			
isoxathion			+					
leptophos			+	+				
malathion	+	+			+			
methyl parathion			+		+			
monocrotophos			+		+			
omethoate			+		+			
parathion	+	+			+			
phenthoate			+		+			
phosmet		+			+			
pirimiphos-methyl			+					
prothiophos			+	+				
quinalphos				+				
tolclofos-methyl			+	+				
Carbamates								
aldicarb	+				+			
methiocarb			+	+				
pirimicarb			+					
propamocarb			+					
Other herbicides								
alachlor		+	+		+			
chlornitrofen			+	+	+			
2,4-D	+	+	+	+	+			

Table 3: Summary of evidence of potential to increase breast cancer risk

Pesticide	Epidemiology (breast cancer)	Mammary tumours	Oestrogenic activity	Other hormonal effects	Evidence of carcinogenicity	Relevant immune	GJIC inhibition	Mammary gland development
Other herbicides								
diclofop-methyl			+					
diuron		+		+	+			
ethalfluraline		+						
fluazifop-butyl			+					
oryzalin		+						
paraquat	+	+			+			
pendimethalin			+	+				
prosulfuron		+						
silvex	+							
sulfallate		+			+			
thenylchlor			+	+				
tribenuron methyl		+	+		+			
triclopyr		+	+					
trifluralin			+		+			
Fungicides								
biphenyl			+					
captan	+				+			
captafol		+			+			
dodemorph			+					
fenarimol			+	+	+			
folpet		+			+			
mancozeb		+		+	+			
maneb				+	+			
triademefon			+					
triademenol			+					
triphenyltin			+		+			
vinclozolin		+		+				
Other pesticides								
bromopropylate			+	+				
chlorobenzilate			+	+	+			
chloropropylate			+	+				
clonitralid		+						
DBCP	+	+		+	+			

Table 3: Summary of evidence of potential to increase breast cancer risk

Pesticide	Epidemiology (breast cancer)	Mammary tumours	Oestrogenic activity	Other hormonal effects	Evidence of carcinogenicity	Relevant immune	GJIC inhibition	Mammary gland development
Other pesticides								
ethylene dibromide	+ (male)	+			+			
ethylene dichloride	+ (male)	+			+			
ethylene oxide		+			+			
PFOS		+			+			
propylene dichloride		+			+			
Inerts								
nonylphenol		+	+	+				
Contaminants								
1,4-dioxane		+			+			

5

CONCLUSION AND RECOMMENDATIONS

A total of 98 different pesticides, plus one adjuvant and two contaminants, have been identified here as having the potential to increase the risk of breast cancer, that is the risk of developing breast cancer in the first place or of stimulating the growth of breast cancer cells or tumours. Breast cancer initiation and development is a complex process not yet completely understood, so the ways in which pesticides might affect that process are also complex, varied and not yet completely understood. Therefore this list should not be regarded as definitive. It may be that, as more is learned about the exact cellular mechanisms of breast cancer and the opportunities for pesticides to interrupt these processes, more pesticides will become implicated. Additionally, studies have not been carried out for many pesticides, including those listed here, to fully identify their ability to effect even those mechanisms identified here—such as effects on cytochrome P450 enzymes, gap junction intercellular communication, Natural Killer T-cells and other tumour regression factors, as well as the effects on progesterone, prolactin, prostaglandins, and melatonin and the subsequent implications for breast cancer.

The evidence presented here linking these pesticides with breast cancer is very variable in quality. For some pesticides, such as DDT and dieldrin, there is sufficient evidence of sufficient quality for a number of reviews (e.g. Brody & Rudel 2003; Evans 2006) to assert a positive link with breast cancer. Some remain a subject of controversy e.g. the triazine herbicides because of dispute about the relevance of studies on rodents to humans, or DDT because of the conflicting results of epidemiological studies. For the others, the evidence is slimmer, largely because of lack of studies, and

the pesticides do not appear in other review lists. However they are included here, on the basis of the precautionary principle, as an early warning that these pesticides possess the ability to interfere with mechanisms involved in the genesis and development of breast cancer.

Exposure to these pesticides at any time of a woman's life may increase the risk of breast cancer. However there are clearly periods of greater vulnerability: *in utero*, early childhood, menarche, at first childbirth and perimenopause. One of the most important routes of exposure for these pesticides that have been identified as potentially increasing the risk of breast cancer is maternal transfer to the foetus *in utero*—at a time when the unborn child is exquisitely sensitive to minute amounts of carcinogens and endocrine disrupting chemicals. There is no doubt that such transfer occurs—in Chapter 2 some information was provided on a small number of chemicals measured in umbilical cord blood or infant meconium. But that appears to be just the tip of the iceberg.

There is also concern about the transference of pesticide residues contaminating breast milk to the newborn infant through breastfeeding. The concern is valid, however this ***does not*** mean that breastfeeding should be replaced with bottle-feeding. Breastfeeding should be maintained because, despite the residues, breastfeeding confers health benefits on both the infant and the mother—maternal protection from uterine and breast cancer, infant protection from infections, allergies, obesity, hypertension, insulin-dependent diabetes mellitus, Sudden Infant Death Syndrome, and enhanced cognitive development. Breastfeeding is key to the well-being of the baby, providing the best available sustenance and defence against disease. This is especially important in households that do not have enough to eat and where women and children are often nutritionally deprived. Therefore, in spite of concerns about chemical contamination, the advice from scientists and health professionals is to continue breastfeeding.

The solution to the problem of transferring residues to the infant is not to stop the breastfeeding but to stop the contamination of the breast milk in the first place. As Sandra Steingraber said in 2005:

> ***"It should be the right of every child to toxic-free food. Right now no child in the world has that right because breast milk universally is contaminated, and the number one contaminant around the world is still the pesticide DDT, which was first identified in human milk in 1951."***

In order to achieve this, the following recommendation of the UK Royal Commission on Environmental Pollution (Blundell 2003) should be put into effect worldwide:

> ***"We recommend that where synthetic chemicals are found in elevated concentrations in biological fluids such as breast milk and tissues of humans, marine mammals or top predators, regulatory steps be taken to remove them from the market immediately."***

There is no longer any doubt that exposure to toxic synthetic chemicals contributes significantly to cancers worldwide, including breast cancer. The Standing Committee of European Doctors (CPME 2005) concluded that:

> ***"Doctors believe that the chronic diseases registered by the WHO, in particular cancer, have risen alarmingly; that cancer rates have increased steadily among the populations of the industrialised countries since 1950; that cancer affects all age ranges; and that chemical pollution could contribute to the onset of cancer" and "Doctors have stated that the current proliferation of a number of diseases is a consequence of environmental degradation and that chemical pollution poses a serious threat to children and to the human race."***

PESTICIDE ACTION NETWORK ASIA AND THE PACIFIC, THEREFORE, RECOMMENDS:

1. No woman or girl should be exposed to pesticides that have the potential to increase the risk of breast cancer, and especially not pregnant woman because of the exquisite vulnerability of the unborn child to carcinogens and endocrine disruption.

2. The rights of women to health, including reproductive health, must be given primacy in national and international policies and processes. Each country should develop breast cancer prevention plans that include the rapid removal of pesticides for which there is evidence of a potential to increase breast cancer risk.

3. Women should be encouraged to breast feed their children despite the current contamination of breast milk, and every effort must be made to reduce as fast as possible, and eventually eliminate,

contamination of human breast milk, through reduction and eventual elimination of exposures to persistent pesticides and other synthetic chemicals.

4. The precautionary principle must be applied to the evidence indicating a potential increase in risk of breast cancer from pesticides.

5. The continued use of pesticides that are persistent and which contaminate human tissue and fluids should cease completely. Currently some of the persistent pesticides identified here as breast cancer risks are covered by the Stockholm Convention on Persistent Organic Pollutants (POPs). These include aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, HCB, lindane, mirex, and toxaphene. But for some of these pesticides there are exemptions permitting ongoing use that continues to expose women, children and the unborn foetus. For example, DDT is still widely used for malaria control in Africa, and its ongoing manufacture in India contaminates local communities. Others such as endosulfan are not even on the POPs list yet: endosulfan should be placed on the POPs list with urgency and all further uses eliminated speedily.

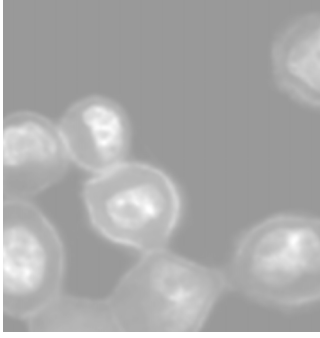
6. The burden of responsibility for the potential role of individual pesticides in increasing the risk of breast cancer must shift to the pesticide industry and the regulatory authorities. It must be lifted from the shoulders of women who breast-feed their children. The burden must shift to the pesticide industry to prove that individual pesticides will not cause or promote or increase the risk of breast cancer. It should not be left to public interest organisations and independent scientists to provide sufficient evidence of a link with breast cancer before regulatory authorities take action to remove the offending pesticide, because such proof, if it can be gathered to the extent that satisfies the regulatory process, is always too late for many women who will have already died from breast cancer.

7. Regulatory processes must be improved so that they incorporate all the mechanisms by which pesticides may contribute to breast cancer and hence can identify all pesticides that contribute to increasing the risk of breast cancer. Current regulatory processes for pesticides focus on identifying carcinogens that are genotoxic, and tend to ignore those chemicals that promote the growth of cancer cells or tumours, as many of the chemicals reviewed here do. The focus should be on hazard identification and elimination, rather than risk management.

8. The substitution principle must be applied and those pesticides that have the potential to increase the risk of breast cancer must be speedily replaced by safer substitutes, particularly by non-pesticide ecological methods of pest, weed and agri-ecosystem management.

9. Every effort should be made to support community monitoring of the effects of pesticides and to include the results of such monitoring in national and international pesticide regulatory and management processes. Community monitoring can act as an "alert system", identifying pesticides that are potentially causing health effects including chronic effects, as well as identifying other pesticide problems.

GLOSSARY



Adenoma – a benign tumour of glandular epithelium.

Adenocarcinoma – a cancerous tumour of glandular epithelium.

Aneuploidy – a change in the number of chromosomes that can lead to a chromosomal disorder.

Androgens – natural hormones, the primary and most well-known of which is testosterone; androgens are also the precursor of all oestrogens.

Apoptosis – one of the main types of programmed cell death; too little results in uncontrolled cell proliferation, i.e. cancerous tumours.

Aromatase – steroids are converted to estrogens in a number of human tissues by the aromatase enzyme complex, which consists of aromatase cytochrome P450 (product of the CYP19 gene) and NADPH-cytochrome P450 reductase; it catalyses the final rate-limiting step in the conversion of androgens to oestrogen and so increases the amount of circulating oestrogen.

Assay – a laboratory test.

Carcinogenicity – two types are generally recognised: genotoxicity, which causes irreversible self-replicating DNA damage, and non-genotoxic carcinogenicity, which involves mechanisms such as promotion, proliferation of peroxisomes (structures in cells), hormone imbalance, and cytotoxicity leading to compensatory cell division. Mutagenicity and clastogenicity are specific indicators of genotoxicity. All these are strong indicators of carcinogenicity. Chemicals which have been demonstrated to be mutagenic and clastogenic, and are therefore, genotoxic, are presumed to be the initiating events in carcinogenicity.

Carcinoma – any malignant cancer that arises from epithelial cells; carcinomas invade surrounding tissues and organs, and may spread to lymph nodes and distal sites (metastasis).

Clastogenic – causing damage to the chromosome in general (the clump of DNA strands where the genes reside). This damage could be loss, breaks or rearrangements of chromosomal segments. It could also be in the

form of "sister chromatid exchanges", interchanges and re-attachments of strands in the chromosome during DNA replication. Thus, "clastogenic" could involve several genes in the DNA strand.

Choriocarcinoma – a malignant and aggressive cancer of the placenta.

Congeners – related chemicals, derivatives of the same parent compound.

Covalent bonding – a form of chemical bonding characterized by the sharing of one or more electrons between two atoms; in general the bonds are defined by a mutual attraction that holds the resultant molecule together.

Cytochrome P450 – a generic term for a large number of related, but distinct, enzymes important in a number of processes, including the breakdown of pesticides and other toxic chemicals, and natural hormones.

Cytotoxic – substances that are toxic to cells.

Embryotoxic – any chemical that is harmful to an embryo.

Epidemiological studies – epidemiology is the scientific method used to track population health and to find causes of disease in groups of people; there are several different types of study:

- case study: describes the experience of a single patient or group of patients.
- case-control study: selects subjects on the basis of disease status; the study population consists of individuals with the disease, matched with a control group that comes from the same population but does not have the disease, and looks at potential exposures that both populations may have encountered.
- cohort study: selects subjects based on their experience and follows them through time to assess their later disease status.
- nested case-control study: a type of case-control study that draws its cases and controls from a cohort population that has been followed for a period of time.

Fetotoxic – toxic to the foetus.

Fibroadenoma of the breast – benign breast tumours characterized by proliferation of both glandular and stromal elements; usually it appears before age 30 as a result of oestrogenic hormonal excess.

Fibroma – benign breast tumours composed of fibrous or connective tissue.

Gap junctions – plasma membrane channels between cells that allow intercytoplasmic movement of small molecules such as nutrients, ions and secondary messengers between neighbouring cells.

Gap junction intercellular communication (GJIC) – the communication between cells via gap junctions; this plays an essential role in the regulation of cell proliferation and differentiation, and hence the growth of tumours.

Genotoxic – causing damage to a gene (usually through covalent binding), which could result in cell death or change in the structure or function of the gene. The damage can be mutagenic or non-mutagenic. One of the main health implications of toxicity to the gene is carcinogenesis, if the damage carries through to the offspring of the cell that is initially assaulted.

Glucuronidation – a biochemical pathway for the metabolism of the natural hormones oestradiol and oestrone, involving chemical binding of the hormone to glucuronic acid, and producing metabolites that are implicated in the growth of breast cancer cells.

Haematopoietic – of the blood cellular components.

Hyperplasia – increase in the number of the cells of an organ or tissue causing it to increase in size.

in vitro – studies conducted on cells in laboratory dishes rather than in a living organism.

in vivo – studies conducted in living organisms.

Isomers – molecules with the same chemical formula and often with the same kinds of chemical bonds between atoms, but in which the atoms are arranged differently.

Lipoma – benign tumour composed of fatty tissue.

Lymphoma – cancer that originates in lymphocytes.

Mastitis – inflammation of the breast.

Melatonin – hormone produced by the pineal gland.

Mitosis – cell division in which the nucleus divides into nuclei containing the same number of chromosomes; mitogenic means causing mitosis.

Multipotent stem cells – cells that can give rise to several other cell types.

Mutagenic – causing a change in the genetic structure usually through base-pair substitution (change in amino acid sequence), deletion, or addition of gene fragments, or some other mechanism.

MCF-7 human breast cancer cells – cells that are sensitive to oestrogen and used to screen chemicals for their estrogenic effects. The test—also called the E-SCREEN—is based on the dose-response relationship between the proliferation of MCF-7 cells and the amount of oestrogen to which the cells are exposed during 6 days of culture. Oestradiol is used as a standard.

Methylation – a biochemical pathway for the metabolism of the natural hormones oestradiol and oestrone, involving the chemical binding of a methyl group (CH_3) to the hormone; a metabolite of this pathway, 2-methoxyoestradiol, inhibits the growth of breast cancer cells.

Natural Killer T-cells – a form of lymphocyte that is a major component of the innate immune system. They target tumor cells and protect against a wide variety of infectious microbes, and do not need to recognize a specific antigen before swinging into action.

Neoplasm – scientific term for a tumour.

Oestrogen hormones – there are three major types—oestradiol, oestriol, oestrone—and they exist in a number of forms, including:

- 17*beta*-oestradiol = the primary active endogenous oestrogen.
- 16-hydroxyestrone = a metabolite of 17*beta*-oestradiol; it binds to oestrogen receptors.
- 2-hydroxyestrone = a metabolite of 17*beta*-oestradiol; stimulates cell repair, inhibits cancer.
- 4-hydroxyestrone = a metabolite of 17*beta*-oestradiol; highly carcinogenic.

Oestrogen receptor – receptors on the surface of breast tumours that respond to either oestrogen or progesterone – named ER *alpha*, ER *beta*.

Oncogene – a modified gene, or a set of nucleotides that codes for a protein, that increases the malignancy of a tumour.

Oncogenic – tumour-forming.

Oxidative stress – the level of oxidative damage in a cell, tissue, or organ, caused by the reactive oxygen species (such as free radicals). It is caused by an imbalance between the production of reactive oxygen and a

biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage. The cellular redox environment is preserved by enzymes that maintain the reduced state through a constant input of metabolic energy. Disturbances in this normal redox state can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. In humans, oxidative stress is involved in many diseases, including cancer.

Papilloma – a benign epithelial tumour.

Parous – producing offspring.

PCNA – Proliferating Cell Nuclear Antigen, a protein that acts as a cofactor for DNA polymerase delta which assists DNA replication.

Polymorphism – a particular genetic form, e.g. of the cytochrome P450 enzyme complex; polymorphism describes multiple possible forms of a single gene.

Prolactin – hormone primarily associated with lactation; during breastfeeding, the infant suckling the nipple stimulates the production of prolactin, which fills the breast with milk in preparation for the next feed.

Prostaglandins – a group of lipid compounds, technically hormones, that are derived enzymatically from fatty acids; produced in small amounts, they act at exceedingly low concentrations on local target organs. They are mediators and have a variety of strong physiological effects.

Sarcoma – cancer of the connective or supportive tissue (bone, cartilage, fat, muscle, blood vessels).

Sulfonation – a biochemical pathway for the metabolism of the natural hormones oestradiol and oestrone, involving chemical binding of the hormone to sulfonic acid, and producing metabolites that are implicated in the growth of breast cancer cells.

Terminal buds / terminal end buds – the least mature ductal structures in the mammary gland, containing multipotent stem cells, and the most susceptible to carcinogens. On maturating they either differentiate into alveolar buds, which further mature during pregnancy, or regress to terminal ducts. In rats, and perhaps also in humans, more differentiated lobular structures give rise only to benign breast tumours (Bouker & Hilikiva-Clarke 2000). These structures are sensitive to carcinogens.

Transcription – the transfer of genetic information from DNA into RNA.

Vitellogenin – a yolk protein produced normally in the liver of female fish under oestrogen control. Very little, if any, vitellogenin can be detected in male fish. However, exposure to oestrogens activates the vitellogenin gene, resulting in increased vitellogenin levels in the blood of male fish.

APPENDIX 1: EPIDEMIOLOGICAL STUDIES THAT FOUND NO LINK BETWEEN PESTICIDES AND BREAST CANCER

1.1 Pesticides in general

(a) Italy – women in farming - 1999

A hospital-based case-control study (Settimi et al 1999) was conducted in five Italian rural areas to examine the association between cancer and farming among women. It examined 945 newly diagnosed cases aged 20-75 years from March 1990 to September 1992. It found statistically significant increased risks in association with farming for skin melanoma and bladder cancer, and non-statistically significant increased risk of lung cancer. However it also found a lower risk of postmenopausal breast cancer. The study suggests that women in farming might experience increased risk of cancers, not usually found in excess among male farmers, as well as a protective effect for postmenopausal breast cancer.

(b) USA – women exposed to pesticides in Cape Cod - 2004

A population-based case-control study of 1,165 women in Cape Cod, USA, found no consistent pattern of association between pesticide use and breast cancer, but "weak" evidence of associations with certain types of pesticide use. But the results must be interpreted with caution. They used geographic information systems (GIS) technology to determine historical exposures because of the limitations of one-time tissue measurements of residues of long ago banned pesticides. However, uncertainties about exposures, especially home addresses and unrecorded spray events, limit the accuracy of the data, and the results were inconsistent and statistically unstable in some cases. There appeared to be some "suggestive associations" such as increased risk associated with women in homes with no tree buffer to protect them from drift of persistent insecticides applied aerially to Cranberry bogs and trees. (Brody et al 2004)

(c) USA – women pesticide applicators - 1999

Fleming et al (1999a, 1999b), in a retrospective cohort study, found decreased incidence of, and no increased mortality from, breast cancer

amongst approximately 3,600 female licensed pesticide applicators in Florida – over and above the general population in Florida.

(d) USA – living near pesticide applications - 2005

Reynolds et al (2005b) carried out a broad assessment of the relationship between agricultural pesticide use patterns in California and breast cancer incidence in women. They found no evidence that women living in areas of *recent*, high agricultural pesticide use experience higher breast cancer incidence rates.

1.2 Specific pesticides

(a) France – women exposed to chlorophenoxy herbicides - 1993

No increase in incidence of, or mortality from, breast cancer was found in women workers exposed to chlorophenoxy herbicides (Kogevinas et al 1993).

(e) USA – atrazine in corn production - 2002

Hopenhayn-Rich et al (2002), in an ecologic study, examined data on atrazine use, corn production, and water contamination, to estimate exposure to the herbicide. They found no association with incidence of breast cancer, but noted that limitations with the study precluded firm conclusions.

APPENDIX 2: STUDIES SHOWING NO LINK BETWEEN ORGANO-CHLORINE INSECTICIDES AND BREAST CANCER:

(a) DDT - Viet Nam

Schecter et al (1997) found no increase in relative risk of breast cancer with increased serum concentration of *p,p'*-DDT/*p,p'*-DDE in their study of 21 women newly diagnosed with invasive adenocarcinoma of the breast, who served as cases, and 21 women of similar age with fibrocystic breast disease, who served as controls. The study was conducted among patients admitted to a single hospital in Hanoi in 1994.

(b) DDE - Mexico

Lopez-Carrillo et al (1997) found an increased level of serum DDE in women with breast cancer over age-matched controls (562.48 ppb to 505.46 ppb serum) but this was not statistically significant. They concluded "these results do not lend support to the hypothesis that DDT is causally related to breast cancer at the body-burden levels found in our study population but do not exclude the possibility that higher levels of exposure could still play a role in the aetiology of this tumor".

(c) DDE, dieldrin, chlordane - USA

A population-based case-control study of 646 women with breast cancer and 429 controls on Long Island, New York, found no substantial elevation in breast cancer risk with higher serum levels of the organochlorine pesticides DDE, dieldrin and chlordane (Gammon et al 2002).

Stellman et al's (2000) study of 232 women with breast cancer and 323 hospital controls from Long Island also did not find an association between adipose tissue levels of DDE, DDT, DDD, *beta*-HCH, HCB, or chlordane metabolites and breast cancer, although most of the pesticide adipose concentrations analyses did not show significant differences between cases and control.

(d) DDT, HCB – USA

Dorgan et al (1999) studied serum organochlorine levels of 105 blood donors who subsequently were diagnosed with breast cancer, and 210

controls matched on age and date of blood collection. They measured five DDT analogs and 13 other organochlorine pesticides. Women with higher serum levels of organochlorine pesticides, except for HCB (see above), showed no increased risk of breast cancer overall.

(e) DDE – Brazil

Mendonca et al (1999) investigated 177 cases of breast cancer at the Instituto Nacional de Cancer in Rio de Janeiro, and 350 controls selected among female visitors to the hospital. No statistically significant association was found between breast cancer risk and serum levels of DDE or history of exposure to pesticides.

(f) DDE – USA

Hunter et al (1997) measured plasma levels of DDE in 236 women with breast cancer and 236 matched controls, drawn from the 'Harvard Nurses Health Study'. They found a non-significant lower level of DDE amongst women with breast cancer than controls.

(g) DDE – USA

Laden et al (2001) followed up on their 1997 case-control study nested in the Nurses' Health Study cohort, adding 143 postmenopausal cases and controls to the original 238 pairs. They measured plasma levels of DDE, the major metabolite of DDT, comparing women who were diagnosed with breast cancer between one month and four years after blood collection with control women in whom breast cancer did not develop. Median concentrations of lipid-adjusted DDE were similar among the cases and controls, and the authors concluded that the results do not support the hypothesis that exposure to DDT increases the risk of breast cancer.

(h) DDE – USA

Helzlsouer et al (1999) carried out a nested case-control study to examine the association between serum concentrations DDE and the development of breast cancer up to 20 years later. They selected 346 cases and 346 controls from cohorts of women who donated blood in 1974, 1989, or both. Analyses were stratified by cohort participation because median concentrations among the controls were 59 percent higher in 1974 than 1989, respectively. Median concentrations of DDE were lower among cases than controls in both time periods. The risk of developing breast cancer among women with the highest concentrations of DDE was roughly half that among women with the lowest concentrations. The strongest inverse association was observed

among women diagnosed 16-20 years after blood sampling. Even after 20 years of follow-up, exposure to relatively high concentrations of DDE or PCBs showed no evidence of contributing to an increased risk of breast cancer.

(i) DDE, DDT, HCB, BHC, chlordane – USA

Zheng et al (1999 a,b,c; 2000 a,b) conducted a case-control study in Connecticut from 1994 to 1997 to investigate the relation between DDE, DDT, HCB, trans-nonachlor (TNC) and oxychlordane (metabolites of chlordane) in breast adipose tissue, and DDE in serum, and breast cancer risk. The 304 breast cancer cases and 186 controls with benign breast disease who had biopsies were women aged 40-79 years. The authors concluded that the results do not support an association between adipose tissue levels of DDE, DDT, HCB, chlordane, or serum levels of DDE, and breast cancer risk.

(j) DDE, DDT, chlordane – USA

A hospital-based case-control study of breast cancer risk related to organochlorine pesticide exposure was conducted in a multiethnic setting in New York City. It involved 175 breast cancer patients and 355 control patients. The overall racial/ethnic distribution was 57 percent Caucasian, 21 percent Hispanic, and 22 percent African-American. DDE levels were highest among African-American and Hispanic women; DDT was highest among Hispanics, and trans-nonachlor was highest among African-Americans. However, organochlorine levels were not associated with risk for breast cancer. (Wolff et al 2000a)

(k) DDE – USA

A prospective investigation of breast cancer and organochlorine exposures was undertaken in the New York University Women's Health Study. 148 cases and 295 matched controls were identified among women whose blood had been obtained six months or more prior to breast cancer diagnosis. In addition, among 84 cases and 196 controls, two or more consecutive annual blood samples were available to estimate half-lives of DDE. Cases and controls had similar levels of DDE. The authors concluded that there was no evidence for an association of breast cancer risk with DDE levels in blood (Wolff et al 2000b).

(l) DDE – USA

Millikan et al (2000) examined plasma DDE levels in relation to breast cancer in a population-based case-control study of African-American

women (292 cases and 270 controls) and white women (456 cases and 389 controls) in North Carolina. They found no overall strong link between DDE and breast cancer, but did find that link was greater in African-American women than white women.

(m) DDE – USA

In a nested case-control study Krieger et al (1994) drew 150 cases and 150 matched controls from a cohort of 57,040 women who had donated blood from 1964-1971, a period when DDT was still in use in the USA. They found no statistically significant link between levels of DDE and risk of developing breast cancer. They found no significant differences between Asian, African American or white subgroups.

(n) HCH, HCB – Mexico

Lopez-Carillo et al (2002) analysed serum levels of beta-HCH and HCB in 95 women with breast cancer and 95 hospital controls, aged 20-79 years of age. They found no evidence of a relationship between beta-HCH, HCB and breast cancer risk.

(o) DDT, DDE – USA

Bagga et al (2000) studied organochlorine levels in the breast adipose tissue of 73 women with breast cancer and 73 women undergoing breast reduction surgery. They found no relationship between DDT or DDE levels and breast cancer.

(p) DDT, DDE, HCB, HCH, mirex, aldrin, chlordane – Canada

Demers et al (2000) found no association between levels of chlorinated pesticides in blood and breast cancer amongst 315 women with primary breast cancer and 219 controls recruited from hospitals in Quebec, Canada. The pesticides were aldrin, chlordane and its metabolites, DDT, DDE, HCB, HCH, and mirex. However they did find that higher levels of *p,p'*-DDE, *beta*-HCB, and the metabolites of chlordane oxychlordane and trans-nonachlor, were associated with increased invasiveness of the cancer into the lymph nodes.

(q) DDE – Germany, the Netherlands, Northern Ireland, Switzerland, and Spain

Van't Veer et al (1997) analysed buttock adipose tissue from 265 postmenopausal women with breast cancer and 341 controls matched for age and centre. They found that women with breast cancer had adipose DDE concentrations 9.2 percent lower than control women. No increased risk of breast cancer was found at higher concentrations.

(r) DDE, DDT, chlordane, HCH, heptachlor – Norway

Ward et al (2000) carried out a prospective analysis of blood serum from 25,431 women, collected from 1973 through 1991. 150 controls were matched to cases by birth dates and dates of sample collection. The serum was analysed for HCH, heptachlor epoxide, oxychlordane, trans-nonachlor, *p,p'*-DDE, and *p,p'*-DDT. There was no evidence of higher mean serum levels among cases for any of these compounds, nor any trend of increasing risk associated with higher quartiles of exposure. No positive association was found between dieldrin and breast cancer.

(s) DDE – USA

Cocco et al (2000) did not find an association between mortality from breast cancer and serum levels of DDE, when they examined the association of the 1968 adipose DDE levels of population samples from 22 U.S. states with age-adjusted mortality rates between 1975 and 1994. In fact they found an inverse correlation. However mortality from breast cancer is not a good surrogate for incidence of breast cancer, as data rates are influenced by treatment. Additionally this study failed to control for many of the variables known to affect incidence rate such as hormonal risk factors for like, early age at menarche, and late menopause.

(t) chlordane, HCH, HCB – Belgium

Raaschou-Nielsen et al (2005) found no indication of higher breast cancer risk in association with higher adipose tissue concentrations of any of the chlorinated pesticides; and found inverse associations between the risk of breast cancer and concentrations of *beta*-HCH, oxychlordane, trans-nonachlor, and HCB in women with oestrogen receptor negative tumours. The study was a nested case-control involving 409 cases and 409 controls.

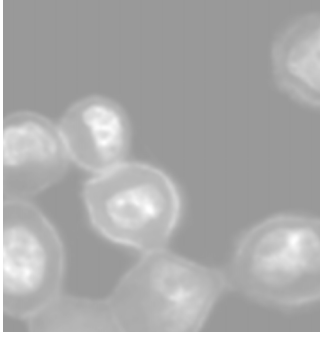
(u) DDT, HCH – India

Siddiqui et al (2005) found mixed results in their hospital-based case-control study among 50 women undergoing surgery for breast disease. Total HCH and total DDT levels were higher in the blood of the study group (25 cases) than in those of the controls (25 cases) with only *gamma*-HCH being significantly different. The level of total HCH (*alpha*-HCH was significantly different, $P<0.05$) was higher in the breast adipose tissue of the study group, whereas total DDT was higher in the breast adipose tissue of the control group. The study is too small

to have statistical significance and the authors' conclusion that it does not support an association between organochlorines and breast cancer should not be interpreted as a negative association.

(v) DDE – USA

Gatto et al (2007) found no association between serum levels of DDE and occurrence of breast cancer in a population-based case control study of African-American women, involving 355 cases and 327 controls.



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