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DDT and human health

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Abstract

1,1,1-Trichloro-2,2′bis(*p*-chlorophenyl) ethane (DDT) was the first widely used synthetic pesticide and is extremely persistent in both the environment and the human body. The introduction of DDT revolutionised agricultural production and has been credited with the elimination of malaria from the United States and Europe. However, DDT is also known to have had major environmental consequences and has been associated with dramatic declines in many animal populations.

Although DDT use has generally been restricted since the early 1970s, exposure to the pesticide remains widespread. In developed countries, slow elimination from the body means a large proportion of the population still have detectable levels of DDT, or its metabolite DDE, in their serum or adipose tissue. In developing countries, the pesticide continues to be used for vector control and a significant proportion of breast-fed babies has daily intakes above recommended levels.

This review considers the epidemiological evidence for possible adverse effects of human exposure to DDT. Much of this research is weakened by methodological flaws. However, recent methods in breast cancer research using nested studies in cohorts with stored biological samples have allowed a more rigorous assessment of a putative role for DDT in disease aetiology. While DDT does not appear to play a causative role in breast cancer development, there is suggestive evidence for a role in the aetiology of other conditions such as pancreatic cancer, neuropsychological dysfunction, and reproductive outcomes. Research into these and other conditions would benefit from the same rigorous approaches used in breast cancer research. Until further high quality evidence is available, it is still too early, even 60 years after the introduction of this once ubiquitous chemical, to pass judgement on the role of DDT in a number of common diseases.

Keywords: DDT; Pesticides; Endocrine disrupters; Pancreatic cancer; Neuropsychological disorders; Reproductive disorders

1. Introduction

1,1,1-Trichloro-2,2′bis(*p*-chlorophenyl)ethane (DDT) was the first widely used synthetic pesticide. Originally synthesised in 1874, its action as an

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insecticide was not discovered until 1939. It was used extensively by allied forces during the Second World War for the protection of military personnel from malaria and was released commercially in 1945. The availability of such an effective and cheap insecticide heralded an agricultural revolution (WHO, 1979). While the post war period also saw the introduction of most of the other major families of insecticides still in use today, DDT remained the most extensively used insecticide throughout the world until the mid 1960s. By this time, it had been credited with a number of significant public health successes, including the eradication of malaria from the United States and Europe (Attaran and Maharaj, 2000).

Part of the success of DDT can be attributed to its persistence in the environment, thus reducing the need for frequent application. However, chemical stability and an associated lipophilicity also result in DDT being only slowly eliminated by most living creatures (IARC/WHO, 1991). This tendency is also shared by the key DDT metabolite 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE). A large number of organisms, in particular marine filter feeders, can also act as bioconcentrators, creating levels of DDT in their own flesh above ambient environmental concentrations.

These traits result in accumulation of DDT through the food chain, in particular in predatory animals at the top of the ecological pyramid (Jensen et al., 1969). Humans are not excluded from this trend and biological sampling in the 1960s showed increasing DDT levels in most human communities, mainly due to exposure to residues in food (Walker et al., 1954).

Even today, DDT remains so widespread in the environment that it is likely that exposure to it is unavoidable. While exposure in the industrialised world has fallen dramatically, exposure remains high in some developing countries where DDT continues to be used in vector control. A recent Mexican study of DDT in breast milk estimated that 6.0% of breast-fed babies had daily intakes of DDT above recommended levels (Torres-Arreola et al., 1999). Ironically, it has also been suggested that increased levels of DDT are associated with a reduced period of lactation (Gladen and Rogan, 1995).

By the mid 1950s, animal studies began to suggest that exposure to DDT may have adverse impacts, in particular on reproductive success, and it quickly became apparent this could extend to the broader environment (Ramade, 1987). For example, the thickness of eggshells in peregrine falcons stored in British museums was found to have decreased dramatically following the pesticide's introduction (Ratcliffe, 1970). This relationship was later confirmed experimentally and is thought to be due to hormonal effects and changes in calcium metabolism (Peakall, 1969).

Fish-eating birds at the top of the food chain appeared to be at particular risk. Colonies of brown pelicans in southern California plummeted from 3000 breeding pairs in 1960 to only 300 pairs and 5 viable chicks in 1969. However, a large number of other animal communities were also affected including fish and invertebrates (Ramade, 1987).

As a result of these environmental concerns, the use of DDT was increasingly restricted or banned in most developed countries after 1970.

These dramatic ecological trends also raised questions about the possible impact of widespread pesticide exposure on human communities (Carson, 1962). Since DDT and its metabolites are so persistent in the environment and human tissues, these questions remain important today. Unfortunately, they are not easily answered since epidemiologic research in this field is plagued by methodological challenges (Blondell, 1990). Foremost among these is the difficulty in getting accurate information on subject exposure since many of the possible adverse effects of DDT (for example, cancer) may not become evident until many years after a causative exposure.

Early human studies of DDT were small and limited in scope. A review of animal studies in 1945 in the British Medical Journal concluded, "there is no reason to anticipate any danger in man" (Cameron and Burgess, 1945). In 1956, 51 volunteers from correctional institutions were administered large doses of DDT daily for up to 18 months (Hayes and Durham, 1956). Extensive information on absorption and storage was gained and "no volunteer complained of any symptom or showed, by the tests used, any sign of illness". A 1967 study of 59 highly exposed workers at a US chemical factory found high levels of DDT in fat and, although subjects were not compared to a control group, 8.6% of the study group were noted to have diabetes (Laws et al., 1967). Other early studies found associations between organochlorine levels and cancer at autopsy, however these were criticised on the grounds that the storage and mobilisation of DDT

may have been altered by the disease process (Unger and Olsen, 1980).

It is only in the last 25 years that more rigorous epidemiological research has focussed on the possible adverse effects of exposure to DDT in humans. This review considers the evidence generated by this research and examines current epidemiological approaches to this challenging issue.

2. Epidemiological studies

The crudest form of epidemiological research compares rates of disease in regions that differ with respect to the exposure of interest, in this case DDT. These "ecological" studies have often been unable to distinguish between exposure to specific pesticides, such as DDT, and pesticide exposure in general. Exposure categorization in such studies is often vague, for example, residents of "counties with high agricultural activity determined from agricultural census". Results from these studies are inconsistent and subject to a number of potential biases but can be useful as a source of hypotheses. Overall death rates are often reduced, a pattern that may relate to rural lifestyles. However, a number of positive associations with pesticide exposure in general have been suggested including leukaemia (Viel and Richardson, 1993), prostate cancer (Keller-Byrne et al., 1997), brain cancer (Viel et al., 1998), lymphopoietic cancers (Godon et al., 1991), non-Hodgkins lymphoma (Ritter et al., 1990) and multiple myeloma (Cantor and Blair, 1984).

Only two ecological studies appear to have specifically explored the impact of DDT. One failed to find an association with prostate or testicular cancer mortality (Cocco and Benichou, 1998), while another found an increase in mortality from liver cancer and a decreased mortality from breast and uterine cancer (Cocco et al., 2000).

A far stronger form of epidemiological research is the cohort study, where a group of individuals with known exposures are followed over a period of time to monitor the subsequent development of disease. A number of cohort studies in subjects with unspecified pesticide exposures have either not been able to demonstrate any convincing adverse outcomes or appear to identify a protective effect (Amoateng-Adjepong et al., 1995; Littorin et al., 1993; Faustini et al., 1993; Torchio et al., 1994). Even though some of these studies are large and include significant follow-up periods, one explanation for this absence of effect may be that most studies base their analysis on a comparison of outcomes in the study cohort (often drawn from occupational groups such as pesticide applicators or farmers) and those in the general community. Such comparisons can be biased by the "healthy worker effect" (McMichael et al., 1976) since subjects actively employed may be intrinsically healthier than the broader community, which includes people who cannot gain employment because of illness. This bias may also be compounded for substances as widely distributed as DDT, as even the comparison population is likely to have faced some exposure, thus reducing the distinction between the exposed and "unexposed" groups and making it harder for such studies to demonstrate a true causal association.

A number of other cohort studies have identified positive associations with pesticide exposure in general including leukaemia (Blair et al., 1992), brain cancer (Littorin et al., 1993), prostate cancer (Alavanja et al., 2003), liver cancer (Figa-Talamanca et al., 1993), diabetes (Beard et al., 2003; Wong et al., 1984) and pancreatic cancer (Alavanja et al., 1990).

Fewer studies have been undertaken among cohorts specifically exposed to DDT. Some of these studies have failed to identify increased mortality (Wong et al., 1984), however, others have found positive associations with pancreatic cancer (Beard et al., 2003; Garabrant et al., 1992), liver and biliary tract cancer (Brown, 1992), multiple myeloma (Cocco et al., 1997), cardiovascular disease and possibly diabetes (Morgan et al., 1980).

These findings also need to be interpreted with caution since cohort studies often examine a large range of outcomes leading to the statistical problem of multiple comparisons. Isolated positive findings in cohort studies need to be considered with this in mind. Cohort smoking patterns also need to be considered when assessing the significance of identified increases in smoking related disease.

Most other epidemiological research has used case-control approaches to examine the relationship of DDT and specific outcomes. In these studies, subjects with and without a particular disease (for example

breast cancer) are compared with respect to their exposure history. A major methodological challenge for these studies is estimating the past exposure of cases and controls. Since it is rare for past exposure to have been accurately recorded at the time, exposure estimation has often been based on the response by subjects to questioning. However, subjects may have been unaware of significant past exposures to DDT through the food chain and even occupationally exposed subjects are unlikely to accurately remember and quantify exposures faced 20–30 years in the past. It is also likely that cases differ significantly from controls in their ability to recall past exposures. This can lead to "recall" bias. For example, in searching for an explanation for their disease, subjects with breast cancer may be more likely to recall past exposure to DDT than subjects without cancer, even though they actually faced the same past exposures. This may lead to a study finding an association between DDT and breast cancer even when this did not exist.

The best way to overcome recall bias is to get an accurate measure of past exposure. In the absence of a recorded exposure history, biological sampling of subjects may give some measure of their past exposure, although most substances are rapidly metabolized and excreted from the body. However, unlike other pesticides, DDT and DDE are only very slowly eliminated, making biological monitoring a relatively accurate, easy and cheap means of assessing past exposure. Serum levels of DDT and DDE are closely correlated with levels in adipose tissue and thus provide a relatively non-invasive measure of total body burden (Mussalo-Rauhamaa, 1991) although, as DDE is carried in the lipid fraction of blood, it is generally recommended that serum levels are first adjusted for lipid content (Snedeker, 2001).

Unfortunately, biological monitoring of DDT presents its own potential for epidemiological bias since levels can also be influenced by factors that relate directly to the outcome of interest, in particular weight change. Thus, for example, subjects with advanced breast cancer may have lost considerable amounts of weight, mobilising DDE stores and increasing serum levels. Comparison of these subjects with healthy individuals would suggest an association between high levels of DDT and breast cancer even though this association was caused by the disease, rather than being a cause of the disease.

Recall bias and exposure misclassification often flaw otherwise well constructed studies and need to be constantly borne in mind when considering the results of case-control research into specific diseases.

2.1. Reproductive disorders

Reproductive disorders in birds were among the first adverse impacts linked to organochlorine exposure. More recently, in vitro studies have shown DDT and its metabolites to have human oestrogenic activity (Chen et al., 1997) and DDE has been shown to act as an androgen antagonist (Kelce et al., 1995). Some researchers have also suggested a trend for decreasing semen quality in the general human community following the introduction of DDT (Carlsen et al., 1992; Sharpe and Skakkebaek, 1993). These findings have prompted suggestions that environmental exposure to organochlorines may be causing endocrine disruption in human populations.

However, the dietary estrogenic contribution of all industrial chemicals has been estimated at only a fraction that of naturally occurring bioflavinoids, which are widespread in the human diet (Safe, 1995). In addition, not all studies of sperm quality confirm a general decline (Bromwich et al., 1994) and the observed patterns may simply reflect geographic variations and lifestyle factors (Hauser et al., 2002).

A number of reviews have examined the possible influence of pesticide exposure in general on pregnancy outcome. All have agreed that much of the epidemiologic research in this field suffers from significant methodological problems. However, there appears to be a building consensus that pesticide exposure may be related to reproductive and developmental effects (Sever et al., 1997) or fetal deaths (Arbuckle and Sever, 1998).

The largest and most rigorous study of DDT and adverse reproductive outcomes was conducted after these reviews were published. This study was nested in a US perinatal cohort of over 44,000 children born between 1959 and 1966 (Longnecker et al., 2001). DDE concentration was estimated in stored serum taken during pregnancy from mothers of 2380 children. The adjusted odds ratios (ORs) of preterm births showed a steady and statistically significant increase with increasing concentrations of serum DDE, while the adjusted odds of small-for-gesta-

tional-age also showed a similar and significant, although less consistent, trend.

These findings are supported by a recent small study of intra-uterine growth retardation (Siddiqui et al., 2003) and another recent study which also found an additional significant association with maternal diastolic blood pressure (Siddiqui et al., 2002). Other studies have failed to find any relationship between maternal DDT exposure and birth weight (Gladen et al., 2003).

Spontaneous abortion is the most common adverse pregnancy outcome and both animal models and early studies have suggested a link with exposure to the DDT. (Saxena et al., 1980) However, epidemiological research in this field is challenging due to difficulties accurately identifying cases, which may not require medical management. It is also possible that full term pregnancy may itself influence serum organochlorine levels. The results of recent research are inconsistent. One small case-control study nested in a longitudinal study of Chinese textile workers found significantly higher levels of DDE in women with spontaneous abortion than full term controls. (Korrick et al., 2001) Other studies have been unable to find an association (Gerhard et al., 1998).

Another study examined the impact of DDT on fertility using preserved maternal serum samples drawn immediately after delivery and compared with "time to pregnancy" in daughters 28–31 years later (Cohn et al., 2003). While daughters' probability of pregnancy fell with increasing levels of DDT in maternal serum, the probability of pregnancy increased with increasing levels of DDE. The significance of these findings is unclear.

2.2. Reproductive abnormalities

In animals, concentrations of DDE in fetal tissues similar to those measured in first-trimester human fetal tissues in the late 1960s are correlated with reproductive abnormalities in male offspring such as hypospadias and undescended testes. This is thought to relate to their interaction with the androgen receptor or fetal steroidogenesis. (Gray et al., 2001) These impacts have also been studied in humans, including a case-control study nested in a US birth cohort begun in 1959–1966 and using stored maternal serum (Longnecker et al., 2002). There were small increases in crypt-orchidism, hypospadias, and polythelia among boys with the highest maternal levels when compared with those with the lowest maternal levels, although none of these were statistically significant.

Several cross-sectional studies exploring the potential influence of DDT exposure on hormone levels in adult men have also been unable to demonstrate a significant association. (Hagmar et al., 2001; Martin et al., 2002) Another cross-sectional study failed to find a significant association between DDT levels and sperm concentration or mobility in male partners of sub-fertile couples (Hauser et al., 2003), while a small case-control study has suggested an association between undescended testes and two other organochlorines but not for DDT (Hosie et al., 2000).

2.3. Bone mineral density

Another possible outcome of endocrine disruption may be altered bone mineral density, which is regulated by the antagonistic effect of androgens and oestrogens. DDT has also been shown to modulate trophoblast calcium handling functions in vitro (Derfoul et al., 2003). Two small cross-sectional studies have suggested there may be a weak association between serum DDE levels and reduced bone mineral density (Beard et al., 2000; Glynn et al., 2000), however, a third study failed to demonstrate any correlation (Bohannon et al., 2000). A recent cohort study in fishermen and their wives in regions of high and low organochlorine contamination found a significantly increased rate of hospitalized vertebral but not hip or osteoporotic fractures in women from the exposed region (Alveblom et al., 2003). There was a similar but non-significant trend in men.

2.4. Other endocrine conditions

In vitro studies suggest that PCBs can influence thyroid metabolism. However, DDT and its metabolites do not appear to share this affinity and while they have been included in a number of epidemiological studies, no convincing evidence of an association has been identified (Langer et al., 2003; Rathore et al., 2002).

Other research has failed to find a significant association with endometriosis, a hormone dependant pelvic inflammatory disease (Lebel et al., 1998).

2.5. Hormonally sensitive cancers

Perhaps the most intensively investigated outcome in relation to DDT exposure is breast cancer. A number of case studies and small analytical studies undertaken in the early 1990s suggested an association between breast cancer and organochlorine pesticides, in particular DDT (Falck et al., 1992; Wolff and Toniolo, 1995). While other case-control studies relying on contemporaneous tissue sampling for exposure assessment did not support this observation (Lopez-Carrillo et al., 1997), it was hypothesised that DDT cogeners and metabolites might act as tumour promoters in hormonally sensitive cancers due to their oestrogenic and anti-androgenic properties. Cellular researchers have also suggested that free-radical mediated oxidative stress may be associated with some organochlorine residues in human breast tumors (Iscan et al., 2002).

More recently, larger and better designed studies have generally not supported this hypothesis. Two recent reviews concluded that available evidence does not support an association between DDT and breast cancer (Calle et al., 2002; Snedeker, 2001). These conclusions have generally been based on nested case-control studies accessing historical tissue samples.

This approach overcomes the potential for bias when the disease process itself may have influenced the levels of DDT in samples taken after diagnosis. An early example is a nested study that compared breast cancer cases with controls drawn from a San Francisco cohort from whom a sample of blood had been obtained, then stored, in the late 1960s (Krieger et al., 1994). The diagnosis in the nested subjects was defined in 1990, up to 20 years after the specimens had been taken. After adjusting for relevant confounders, analyses found no differences in serum levels of DDE between exposure groups.

These findings are supported by several similar nested studies using historical blood samples (Dorgan et al., 1999; Helzlsouer et al., 1999; Hunter et al., 1997; Laden et al., 2001). In all of these studies, breast cancer cases tended to have lower levels of DDT/DDE in serum than controls.

Another nested study did find a significant association with stored levels of *p*,*p*′-DDT (Hoyer et al., 2000). However, there was no significant association for the group with the greatest total DDT levels, nor for DDE, although for both substances odds ratios for these groups were greater than 1.0.

Other recent case-control studies of breast cancer using contemporaneous, rather than stored, blood or self-reported exposure have been inconsistent, with some finding a positive association (Charlier et al., 2003) and some finding no, or an inverse, association (Wolff et al., 2000). A recent study of workplace exposures and male breast cancer also failed to find any association with pesticide exposure (Cocco et al., 1998).

Other hormonally sensitive cancers include cancer of the endometrium and prostate. Two case-control studies have explored the possibility that DDT may be related to endometrial cancer with neither finding a significant association (Sturgeon et al., 1998; Weiderpass et al., 2000).

On the other hand, an Italian hospital-based multisite case-control study of prostate cancer found an increased risk among farmers exposed to DDT (Settimi et al., 2003). However, exposure assessment in this study relied on self-report, leaving these findings susceptible to recall bias. Rates of prostate cancer were also found to be increased among male applicators using chlorinated pesticides in the Agricultural Health Study cohort (Alavanja et al., 2003) and in a Swedish cohort of pesticide applicators (Dich and Wiklund, 1998).

2.6. Pancreatic cancer

Pesticides have been associated with pancreatic cancer and deaths from diabetes in cohort studies in pesticide-exposed flour millers, although not generally among other cohort studies in farmers (Alavanja et al., 1990). A large Norwegian prospective study of lifestyle factors and pancreatic cancer identified a higher risk among men occupied in farming, agriculture or forestry (Nilsen and Vatten, 2000). A recent cohort study (Cantor and Silberman, 1999) also identified increased mortality from pancreatic cancer when aerial pesticide applicators were compared to controls, but not when compared to the U.S. population. Diabetes has also been associated with organochlorine exposure in at least one study (Wong et al., 1984). Recent research lends a physiological plausibility to a possible association between DDT and pancreatic cancer by suggesting

that DDT may modulate oncogene expression or provide a growth advantage to mutated cells, for example, through its actions as an endocrine disrupter (Porta et al., 1999).

Pancreatic cancer has been associated with pesticide use as a whole by case-control studies using municipal and other records to identify pesticide users (Forastiere et al., 1993) and relying on self-report (Ji et al., 2001). DDT has also been associated with pancreatic cancer in a case-control study based on self-report (Fryzek et al., 1997). However, methodological problems limit the weight that can be placed on these studies.

The strongest evidence for an association between DDT and pancreatic cancer comes from a case-control study of twenty-eight verified cases nested in a cohort mortality study of chemical manufacturing workers (Garabrant et al., 1992). This study used work records and interviews with co-workers to determine chemical exposures and found a significant association with DDT exposure that persisted after controlling for smoking. The risk increased with both duration of exposure and latency since first exposure.

More recently, an Australian cohort study of mortality in staff working as part of an insecticide application program also found increased mortality from pancreatic cancer in DDT-exposed subjects and from diabetes in subjects working with any pesticide (Beard et al., 2003).

Few studies have so far used biological monitoring to explore this potential relationship. One case-control study examined serum levels at study enrolment and found median concentrations of DDE to be significantly raised in cases (Hoppin et al., 2000). However, there was no significant dose response relationship for DDE and the relationship became non-significant when PCBs were included in the analysis.

2.7. Other cancers

Case control studies using self-reported exposure have found significant associations between DDT exposure and lung cancer (De Stefani et al., 1996), leukaemia (Flodin et al., 1988) and non-Hodgkins lymphoma (NHL). However a nested case-control study using stored serum identified a dose response relationship for NHL with PCB exposure but not DDT (Rothman et al., 1997). A small case-control study using serum levels drawn at diagnosis has suggested an association between DDT exposure and colorectal cancer (Soliman et al., 1997).

2.8. Neurological effects

Animal studies have suggested DDT may cause central nervous system (CNS) toxicity (Eriksson and Talts, 2000). A recent review of epidemiological studies also concluded that exposure to DDT may be associated with a permanent decline in neurobehavioral functioning and an increase in psychiatric symptoms but that the few studies and limited exposure information made it impossible to be confidant about this potential relationship (Colosio et al., 2003). These findings are also complicated by potential confounding from exposure to other pesticides, such as organophosphates, that are known to have neurological effects.

One recent case study suggested that DDT may be related to neurological impairment (Hardell et al., 2002). Another recent study of retired malaria-control workers found various neurobehavioral functions and performance deteriorated significantly with increasing years of DDT application (van Wendel de Joode et al., 2001). Subjects exposed to pesticides including DDT also scored worse than non-exposed subjects on a self-reported neuropsychological questionnaire of surviving members of a historical cohort of pesticide applicators (Beard et al., 2003).

2.9. Immune function

At least one cross-sectional study has associated DDT and other pesticide exposures with suppression or induction of several immune parameters (Daniel et al., 2002).

3. Discussion

DDT is a chemical that has been widely used for over 60 years and to which we are all exposed. It is therefore somewhat surprising that there is such limited evidence on its safety. This is even more curious since, unlike most currently used pesticides, biological samples give a good indication of past exposure to these substances.

Significant methodological flaws weaken the majority of studies considered in this review. Common pitfalls include problems with study size, length of follow-up, multiple comparisons, loss to follow-up, outcome ascertainment, the "healthy worker effect", comparison populations and lack of information on confounders. However, despite the availability of biological monitoring, the most prevalent weakness remains exposure assessment.

Historical studies have often relied on occupational or general records to define subjects into exposure categories. Not only are such records often unreliable, but these categories also often include considerable heterogeneity of exposure. Both would tend to make it more difficult for a study to identify a true association. On the other hand case-control studies are often subject to recall bias or misclassification bias resulting from reliance on biological specimens taken at, or after, diagnosis. Both of these biases would tend to make it more likely to identify potential associations when in fact these were not real.

These problems are well demonstrated by studies of soldiers potentially exposed to dioxin during the Vietnam War. When subject categorization based on records and recall was matched with biological sampling, there was little correlation between the former and actual exposure (Wolfe et al., 1995).

The pervasive influence of these methodological problems means that, for many individual studies, neither positive nor negative findings can be taken at face value. The best way of dealing with this uncertainty is to take a weight-of-evidence approach that considers both the quality of individual studies and the consistency of the findings across study types.

Cohort and ecological studies suggest a number of potentially adverse outcomes of DDT exposure, although there is little consistency in the findings of these studies. More commonly suggested associations include breast cancer, pancreatic cancer, adverse birth outcomes, and leukaemia.

Among these, only breast cancer can really be considered to have been tested by rigorous research. While there is still some inconsistency in the results, the overwhelming evidence is that there is no causative association with DDT exposure.

Of the other possible associations, the current evidence for pancreatic cancer, adverse birth outcomes and neuropsychological outcomes appears most suggestive. These appear a worthwhile area for application of the research models more recently applied to breast cancer.

Despite their profile as some of the best known 'xeno-estrogens', there remains little epidemiological evidence supporting an association between exposure to DDT or its metabolites and endocrine disruption in humans. This is not surprising given the relatively minor role environmental estrogens play in the diet, although the lipophilicity and slow elimination of DDT and DDE mean this exposure may extend over prolonged periods.

Overall, the current evidence suggests that DDT exposure may potentially be associated with a number of adverse outcomes. In most cases, this evidence is only weak and the risk attributable to the exposure is relatively small. Most of the positive findings identified in this review are also based on research in subjects facing either occupational or community exposures far greater than those currently experienced in the developed world. Nevertheless, even a small increase in risk for some of these outcomes has the potential to cause a significant increase in disease burden at a population level.

The current evidence is insufficient to refute a number of other potential associations. Until rigorous methodological approaches are applied to these outcomes, we should not interpret this absence of evidence as indicating the absence of an effect.

The highest current exposures to DDT are experienced in countries still using the pesticide for vector control. While our lack of knowledge makes it impossible to accurately estimate the human health risks of exposure in those communities, these would also need to be balanced against the potential benefits from malaria control. It would seem unlikely that the direct risks of controlled DDT usage would outweigh the enormous benefits in individuals at risk of malaria should no other control agent be as effective. Of course, the negative environmental consequences of uncontrolled DDT use also need to be considered when setting policy on the use of DDT in these settings.

Recent methodological approaches in relation to breast cancer provide a good model for future research in this field. Indeed, it is questionable whether future studies relying on historical exposure categorization or using biological specimens taken after or close to diagnosis can add much to our current level of

knowledge. However, when combined with the potential for DNA testing to account for genetic susceptibility, rigorous approaches using historical samples will not only increase our understanding of the health effects of DDT exposure, but they may also provide a benchmark by which to measure other studies in the field of environmental health.

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