

Pesticides and cancer – tracing the links

Cancer incidence rates are increasing worldwide and may rise by as much as 50% by 2020. At the same time we have been exposed to a complex mixture of novel chemicals. There is mounting evidence that persistent organic chemical contaminants such as pesticides, are involved in the aetiology of cancer and that these chemicals exert their effect during critical periods of development, at low, environmentally relevant levels. Elucidating cause/effect relationships allowing us to pinpoint the specific chemicals involved is improbable. John Newby and Vyvyan Howard suggest this may be an appropriate time for governments to adopt the precautionary principle.

Cancer incidence rates have increased in the last half of the 20th century; since 1990 worldwide incidence rates have increased by 19%. Eleven million people each year are now diagnosed with cancer and this rate is set to increase to 16 million cases per year by 2020¹⁻⁴. The developed world bears the highest cancer burden. The incidence in Europe represents over 25% of the world burden^{5,6}.

The causes of this increasing cancer rate are the subject of heated debate. The most common explanation holds it is a consequence of an ageing population⁹⁻¹². However, the increased incidence of cancer affects the whole age spectrum. Childhood and adolescent cancer rates have increased and accelerated over the past 30 years to a rate of 1% and 1.5% a year respectively in Europe and USA⁷. In England and Wales if the age-standardised incidence rate over the past 30 years is considered (1971–1999), the percentage change for some tumour sites is dramatic⁸ (see Figures 1 and 2). The risk of developing cancer in the UK is more than one in three; around 2% of the UK population (1.2 million people) are alive with a diagnosis of cancer⁹.

Environmental factors predominate in cancer aetiology^{13,14}. Could exposure to pesticides, play a role? Involuntary exposure to environmentally relevant levels of pesticides, particularly organochlorines and other persistent organic pollutants (POPs) has been hypothesised to be a major factor in cancer aetiology¹⁵⁻²⁰. This hypothesis is not incompatible with a rising incidence of cancer associated with increasing age. It is widely acknowledged that many environmental pollutants are carcinogens and cancer risk is related to length of exposure.

Novel xenochemicals and xenoestrogens

During the past half-century the chemical, nuclear and agricultural industries have produced toxic pollution and novel substances of unknown toxicity. Chemicals developed by the pesticide industry include halogenated molecules, organochlorines and organofluo-

rines, which are toxic to most forms of life. Evolution avoided incorporating these persistent halogenated molecules into the mainstream of biochemistry²². Natural organochlorines produced predominately by marine organisms and bacteria are not persistent^{23,24}.

Organochlorines such as pesticides and PCBs are almost wholly banned in most industrialised countries. However, due to their persistence they are still ubiquitous in the environment, are lipophilic and bioaccumulate in fat^{25,26}. The main source of organochlorine exposure is from the diet: the higher up the food chain, the higher the concentration of organochlorines present in living tissues²⁷.

Occupational exposure

Prostate cancer

Studies of occupational exposure to pesticides have shown an association with an increased risk of prostate cancer. Data taken from a multisite case-control study in five rural areas in

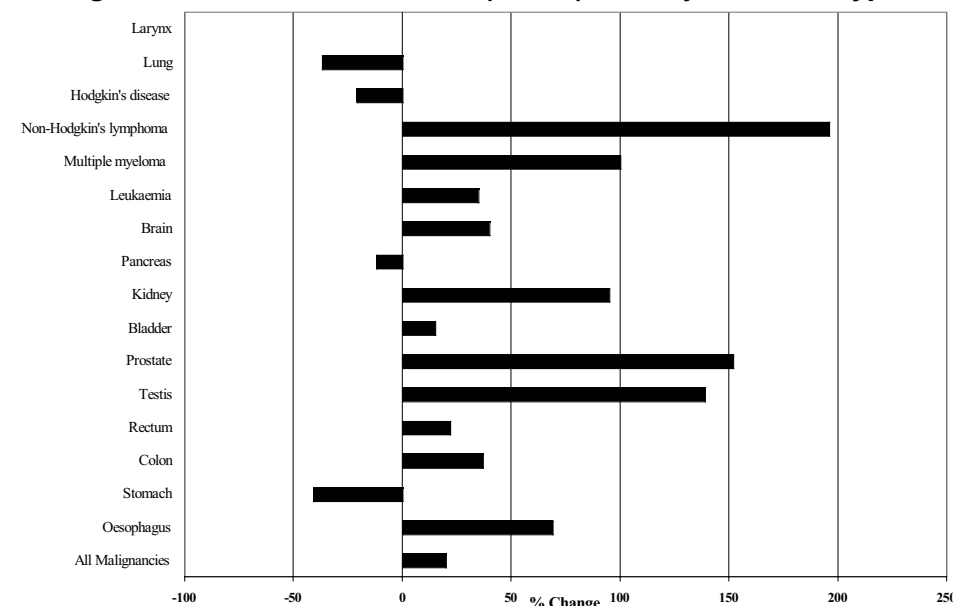
Italy showed that farmers and agricultural workers had an increased risk of prostate cancer. Farmers were especially vulnerable to organochlorine pesticides. Another study linking occupation and prostate cancer risk suggested that there is a significant excess risk for men in agriculture-related industries, and for farming in particular there was a significantly elevated risk for prostate cancer²⁸.

A meta-analysis reviewing 22 studies of occupational exposure to pesticides and prostate cancer estimated that the relative risk ratio was 1.13, meaning that exposed men are 1.13 times more likely to contract prostate cancer. This estimate is in agreement with three, previously published meta-analyses²⁹. A study cohort of 20,025 men who held a licence for pesticide application in Sweden had a significantly increased risk of prostate cancer³⁰. In a retrospective study, the effect of pesticides on aggressive prostate cancer in males younger than 50 years with prostate adenocarcinoma from rural/farming communities in the USA was investigated. The study showed preliminary evidence that pesticide exposure may lead to early development of prostate cancer and possibly to an aggressive form³¹. The third study found a significantly elevated risk for prostate cancer in men over 50 years who had occupational exposure to the fumigant methyl bromide. Exposure to organochlorines also increased the risk³².

Non-Hodgkin's lymphoma

In Nebraska, USA, exposure to the herbicide 2,4-dichlorophenoxy-acetic acid (2,4-D) was found to be associated with a 50% increased risk of non-Hodgkin's lymphoma (NHL). Organophosphate, carbamate and organochlorines were also associated with an increased risk³³. Other studies found that exposure to herbicides, particularly 4-chloro-2-methyl phenoxyacetic acid, and fungicides were associated with an increased risk of NHL^{34,35}.

Figure 1. Percentage change in age standardised incidence rates in England and Wales, 1971-1999 (males) for major tumour types.



Source: Office for National Statistics

Farm workers exposed to carbamate pesticides, particularly Sevin (carbaryl), have been shown to have a 30–50% increased risk of NHL. In this study, farmers not using carbamates showed no increased risk of NHL³⁶.

Non-occupational exposure

Occupational exposure to pesticides is somewhat voluntary. However, is involuntary exposure to environmental contaminants such as pesticides a factor in cancer aetiology?

Testicular cancer

A case-control study was carried out examining levels of DDE, hexachlorobenzene (HCB) and chlordane in men with testicular cancer and age-matched controls, and their mothers. Chlordane (cis-nonachlordane) was significantly raised in affected men. Moreover, their mothers had significantly increased levels of HCB and chlordanes compared to controls. The median age of the affected men was 30 years; they were born during the period of the highest concentrations of POPs in the population, the 1970s³⁷.

Childhood cancers

Environmental exposure to POPs such as PCBs, pesticides and other endocrine disruptors has been studied less in children and more epidemiological studies are needed. One study examining the critical windows of exposure to household pesticides suggested that exposure to these substances increased the risk of childhood leukaemia. The highest risk was during pregnancy and the lowest was at year three. The risk of leukaemia was associated with indoor but not outdoor household pesticides³⁸. The Children's Cancer Group found a significant risk for NHL was associated with the frequency of pesticide use in a domestic setting, and particularly with professional fumigations in the home. Increased risks were observed for different forms of

NHL, that is both T-cell and B cell lymphomas. The increased risks were found both in young children, less than six years old, and in older children. Risks for specific pesticides were not examined³⁹.

Prostate cancer

In a study of the possible relationships between 18 organochlorine pesticides and 30 PCBs with prostate cancer the pesticides dieldrin, p,p'-DDE, trans-nonachlor, oxy-chlordane, heptachlor epoxide were detected in at least 20% of the participants in the investigation. Oxychlordane was associated with an increased risk of prostate cancer. The authors concluded that long-term, low-dose exposure to specific organochlorine pesticides and PCBs in the general population may lead to an increased risk of prostate cancer⁴⁰.

Endocrine disruption

Organochlorines such as pesticides, PCBs, and dioxins can alter how human hormones act⁴¹⁻⁴⁴. Such endocrine disruptors may stimulate or inhibit enzymes responsible for the breakdown or synthesis of a hormone affecting hormone levels, or they may mimic or block hormone action by affecting the receptor which detects the presence of hormones.

In the human body DDT and the fungicide vinclozolin are broken down to metabolites which are able to bind the androgen receptor and alter how cells normally respond to testosterone *in vitro*^{45,46}. In cultured cell lines grown from human prostate tumours, an oncogene (a gene contributing to the formation of cancer) that is often over-expressed or amplified in prostate cancer, is 'switched on' by the pesticides β -HCH, o,p'-DDT and heptachlor epoxide (organochlorines), trans-permethrin and chlorothalonil suggesting that these pesticides may be able to play a role in prostate cancer aetiology⁴⁷. DDT stimulated one of these cell lines to proliferate showing a

possible mechanism by which pesticides may be involved in hormonal carcinogenesis. The chemical structure of pesticides such as DDT show some similarities to the female hormone oestrogen, and can bind the oestrogen receptor stimulating or inhibiting it^{48,49}.

There are many *in vitro* and *in vivo* studies on organochlorines that show endocrine disruption and carcinogenicity⁵⁰⁻⁶¹. However, are humans exposed at sufficient levels to be a major factor in cancer aetiology? This question divides scientists; pesticides have been shown to be carcinogenic in animals, however, many researchers believe that the background levels of these substances are insufficient to cause adverse effects.

Low level exposure

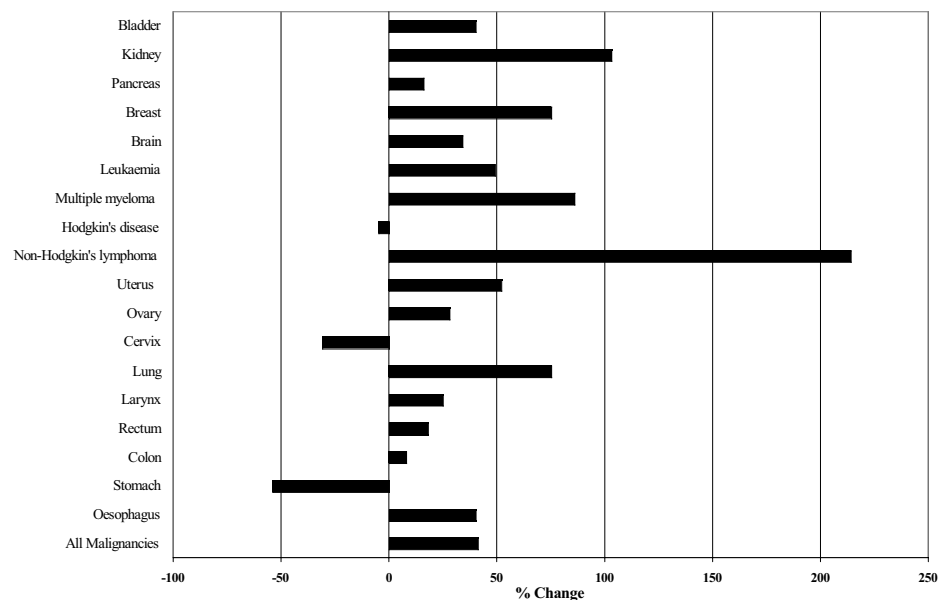
Traditional toxicological testing may not be adequate for assessing the carcinogenic risk of environmental chemicals such as pesticides. Most animal testing is carried out on adult animals and with single chemicals. However, humans are exposed to a 'cocktail' of chemicals in the environment. Mixtures of chemicals could potentially have synergistic or additive effects⁶². Low levels of pesticides similar to those which might be encountered in the environment have been shown to have effects below the no observed effect level (NOEL) observed by traditional animal testing models. The United States Environmental Protection Agency set up a panel to investigate experiments concerning low-dose effects. The definition of a low-dose effect was that the effect was deemed to have occurred when a non-monotonic dose response (U-shape) resulted in significant effects at a dose lower than the estimated NOEL. Low-dose effects were observed for oestradiol, DES, methoxychlor (insecticide), genistein (phytoestrogen) and nonylphenol (pesticide adjuvant). The review panel concluded that the current testing paradigm needs to be revised. Changes may be needed regarding dose selection, the age when animals are evaluated and the endpoints measured⁶³.

Three different *in vitro* and *in vivo* techniques used in one study showed that HCB weakly affects the activity of androgens, such as testosterone: low levels of HCB enhanced androgen action but high levels suppressed androgen action. A further *in vivo* study, in which transgenic mice with a prostate-specific androgen-responsive promoter upstream of a reporter gene were prenatally exposed to HCB, showed that HCB modulated androgen action. Following low-dose exposure to HCB in four-week-old male mice, the proportion of dilated prostate acini, a marker of sexual maturity, was increased, suggesting enhancement of androgen action. In high-dose HCB mice, androgen action was suppressed⁶⁴.

Prenatal exposure to pesticides

The intrauterine environment has been shown to be exquisitely sensitive to ambient hormone fluctuations at a few parts per trillion; this is approximately the same concentration that pesticides are found in serum. The high rates of cell proliferation and differentiation

Figure 2. Percentage change in age standardised incidence rates in England and Wales, 1971-1999 (females) for major tumour types.



Source: Office for National Statistics

in the foetus render the developing child's cells susceptible to mutagenic and epigenetic alteration. The blood-brain barrier and the placenta act as barriers to potentially harmful substances. There is abundant animal evidence suggesting that prenatal exposure to environmental carcinogens occurs⁶⁵⁻⁶⁹ and the hypothesis that early life exposure to environmental factors such as organochlorines may be involved in cancer aetiology is plausible. HCB can cross the placenta⁷⁰; the foetus, therefore, gets a huge dose compared with the dose adults receive from background levels.

POPs bioaccumulate in fat tissue and the female body burden reduces during pregnancy and breast feeding as POPs pass through the placenta and are present in breast milk. One study indicated that a woman's body burden of organochlorines can potentially reduce by as much as 69% over a 30-month period⁷¹.

Synthetic versus natural

It is suggested that the amount of synthetic chemicals, such as pesticides, in the diet pales into insignificance when compared with the amount of natural phytoestrogens ingested. Proponents of this argument point out that we ingest around 5,000-10,000 different natural plant pesticides and their metabolites in our diet. This amounts to approximately 1.5g of natural pesticides per day. Many of these natural pesticides are phytoestrogens (plant oestrogens) and, therefore, have some oestrogenic properties. The 1.5g of phytoestrogens ingested per day is 10,000 times the 0.01mg of synthetic pesticides ingested⁷².

However, it is feasible that the relatively tiny amount of synthetic pesticides (0.01mg/day) may be carcinogenic compared with the relatively huge amounts of natural oestrogenic pesticides (1500mg/day). Oestrogen metabolism proceeds down two mutually exclusive pathways: the catechol (oestrogen-2-hydroxyestrone) pathway and an alternative pathway that yields 16 α -hydroxyestrone. Oestrogen-2-hydroxyestrone is weakly anti-oestrogenic and non-genotoxic. However, 16 α -hydroxyestrone is a potent oestrogen, tumorigenic, genotoxic and induces cell proliferation. One study looked at the ratio of catechol / 16 α -hydroxyestrone in oestrogen-responsive cells after treatment with the positive tumorigenic controls, negative controls, and the organochlorine pesticides DDT, atrazine, γ -benzene hexachloride, kepone, endosulfans I and II. The results showed that the organochlorine synthetic pesticides decreased the amount of 2-hydroxyestrone and significantly increased 16 α -hydroxyestrone production three- to fourfold relative to negative control cells. DDT, kepone and atrazine treatment caused a greater conversion to 16 α -hydroxyestrone (seven-fold) and lower conversion to 2-hydroxyestrone than the positive controls, which were known carcinogens⁷³.

In another study 16 α -hydroxyestrone was shown to be genotoxic to normal mammary epithelium and that a raised ratio of 16 α -hydroxyestrone to oestrogen-2-hydroxyestrone is associated with breast and other can-

cers in animals⁷⁴. On the other hand oestrogen-2-hydroxyestrone (oestrogen metabolite) is weakly anti-oestrogenic, has not been found to be carcinogenic and may even mediate a protective effect⁷⁵. Studies have found that diets rich in compounds that stimulate oestrogen-2-hydroxyestrone, particularly cruciferous vegetables, which are high in indole-3-carbinol, are protective against cancers such as breast and colon cancer⁷⁶⁻⁸⁰.

Conclusions

There is mounting animal and human epidemiological evidence that environmental contaminants, particularly persistent organic chemical contaminants such as pesticides, are involved in the aetiology of cancer and that these chemicals exert their carcinogenicity at critical periods of development (prenatal, childhood, and adolescence). Thus, preventative measures to protect all people need to be put into place. Strategies for reducing overall exposure to bioaccumulative, persistent, carcinogenic and/or endocrine-disrupting chemicals should be put in place.

The incidence of cancer worldwide has increased over the past decades and during this period we have been exposed to complex mixtures of novel chemicals, some genotoxic, some acting as cancer promoters. The toxicity of these mixtures is beyond the current ability of toxicologists to analyse. Elucidating cause / effect relationship by epidemiology to specific environmental contaminants is improbable. We should not wait to take action. There is some evidence that measures taken to reduce environmental contaminants such as pesticides is producing positive effects.

The declining incidence in NHL seen in some developed countries may be a result of cancer prevention methods. In Sweden, between 1991 and 2000, NHL incidence declined in males and females by 20.8 and 20.2%, respectively. Phenoxyacetic acids and chlorophenols, which are pesticides, have been associated with NHL aetiology and these chemicals were banned in 1977. The change in incidence of NHL in Sweden could provide a good example of how regulation and precautionary measures to reduce exposure may be reflected in cancer incidence statistics in decades to come⁸¹.

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