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Protecting humans and wildlife from harmful chemicals

A REVIEW OF THE ROLE PESTICIDES PLAY IN SOME CANCERS: CHILDREN, FARMERS AND PESTICIDE USERS AT RISK?

A CHEM Trust report by Gwynne Lyons and Professor Andrew Watterson

CHEM (Chemicals, Health and Environment Monitoring) Trust's aim is to protect humans and wildlife from harmful chemicals. CHEM Trust's particular concerns relate to chemicals with hormone disrupting properties, persistent chemicals that accumulate in organisms, the cocktail effect and the detrimental role of chemical exposures during development in the womb and in early life.

Both wildlife and humans are at risk from pollutants in the environment, and from contamination of the food chain. CHEM Trust is working towards a time when chemicals play no part in causing impaired reproduction, deformities, disease, deficits in brain function, or other adverse health effects.

Human exposure to pesticides may arise from contamination of the food chain and from pesticides in the air or in water.

CHEM Trust is committed to engaging with all parties, including regulatory authorities, scientists, medical professionals and industry to increase informed dialogue on the harmful role of some chemicals. By so doing, CHEM Trust aims to secure agreement on the need for better controls over chemicals, including certain pesticides, and thereby to prevent disease and protect both humans and wildlife.

about the authors

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A REVIEW OF THE ROLE PESTICIDES PLAY IN SOME CANCERS: CHILDREN, FARMERS AND PESTICIDE USERS AT RISK?

overview

Section 1 of this report provides a summary of the epidemiological and related data linking exposure to pesticides with certain cancers. It notes several studies suggesting that exposure to pesticides seems to confer a greater risk of several specific cancers including, but not limited to, Non-Hodgkin's Lymphoma (NHL), soft tissue sarcoma, leukaemia, prostate cancer and brain cancer.

Moreover, it provides a summary of the growing body of research indicating that pesticide exposure may play a role in hormone-related cancers including prostate, breast and testicular cancers. Studies of death registries in some parts of the world suggest that farmers and agricultural workers are more likely than the general population to die from several cancers including NHL, leukaemia, multiple myeloma, prostate cancer, Hodgkin's disease, pancreatic cancer and brain cancer. Some studies strongly indicate an association between pesticide exposure and NHL, leukaemia and prostate cancer.

The increasing incidence of cancer in children gives weight to the suggestion that environmental exposures play a role in certain cancers, and some researchers have confidently stated that there is at least some association between pesticide exposure and childhood cancer. Some studies have reported an increased risk of childhood cancer and pesticide exposure prior to conception, during

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pregnancy or during childhood, with maternal exposure during pregnancy being most consistently associated with childhood cancer.

Table 1 outlines the pesticides suspected of playing a role in various human cancers that have been implicated in epidemiological studies examining either occupational exposures or environmental (that is, unrelated to occupation) exposures. Our aim is not to undertake a full systematic review of the literature, but to highlight epidemiological studies raising important concerns that pesticides have played an influential role in some human cancers.

Section 2 summarises some mechanisms of cancer aetiology. It shows the emerging awareness that all factors influencing cancer must be taken into account, and that there is a need to give greater consideration to cancer prevention via the control of exposures. This section also notes the difficulties with epidemiological studies and underlines the fact that in order to deliver a precautionary and preventative approach, action needs to be based on toxicity studies in the laboratory.

Section 3 sets out the current regulatory context, and notes the need for effective screening and testing of chemicals to identify those which might cause cancer. It highlights that the new EU pesticides Regulation (1107/2009) will bring in 'cut-off' criteria for both carcinogens and endocrine disrupting pesticides, which will result in the phase-out of such substances.

The case for considering that chemicals, including pesticides, play an important and preventable role in many cancers is based on a large and growing body of in-vitro (test tube), animal and epidemiological research. CHEM Trust considers that all suspected carcinogenic pesticides should be phased out. Therefore, there should be a precautionary interpretation of the data to decide when a substance can be presumed to have a carcinogenic potential for humans.

Section 4 sets out conclusions and recommendations. Of most importance is the conclusion that exposure to certain pesticides may interact with other chemical exposures and other life circumstances (such as those causing a weakened immune system) and genetic factors to increase the risk of cancer. Furthermore, the unnecessary use of pesticides should be eliminated and those with endocrine disrupting properties or those with known or suspected human carcinogenic properties should be substituted with safer alternatives. A key recommendation is therefore that all EU member states should support the strict implementation of the 2009 Pesticides Regulation (1107/2009), which imposes 'cut-off' criteria that will result in pesticides with carcinogenic, mutagenic or endocrine disrupting properties no longer being approved for use.

Annex 1 summarises the rapidly increasing incidence of several cancers in the general population, including the increase in childhood cancer. The rate of increase in some cancers, including testicular cancer, breast cancer and NHL, is such that they must have an environmental cause (which includes lifestyle and/or exposure to chemicals etc.) rather than being largely due to genetic make-up, because genes in a population do not change that quickly.

Annex 2 is an introduction to chemicals causing cancer, the susceptible windows of exposure in humans, and discusses the proportion of cancers that are considered to be related to occupation.

Annex 3 provides information on how pesticides that cause cancer are currently identified, and outlines EU pesticides legislation, particularly summarising the 2009 EU Pesticides Regulation and the likely implications of its implementation. It notes that there have been some alarmist claims suggesting that this Regulation will threaten EU crop yields, but considers there are sufficient provisions to prevent this. Moreover, research suggests that considerable financial and health benefits are likely to accrue from better regulation of pesticides.

Annex 4 briefly sets out the criteria used for categorising CMR (carcinogens, mutagens or reproductive toxicants), as these are needed to understand the implications of the 2009 EU Pesticides Regulation.

At the end of the report, glossaries of abbreviations and technical terms are provided. Listed in alphabetical order are definitions or explanations of some of the words used in this report, including carcinogen (cancer causing), mutagen (mutation causing) and pesticide.

section 1

summary of data linking pesticide exposure with cancer

Throughout this report, the term 'pesticide' is used to include insecticides, insect and plant growth regulators, fungicides, herbicides, molluscicides, algaecides etc. Such chemicals are designed to be toxic to living organisms, so it should not be surprising that they have been linked with a range of adverse health effects, including cancer, neurological,[1] respiratory and dermatological diseases.[2] However, this report specifically highlights the role that pesticides are suspected of playing in some cancers.

The proportion of cancers linked to pesticides via all exposure routes, including the workplace, the food chain and the general environment, is unknown. Nevertheless, even if pesticides are involved only in a relatively small proportion of all cancer cases, securing more effective regulation of pesticides may prevent significant numbers of people from being diagnosed with cancer (see Annex 2).

[Credit: Forting/iStock]

Farmers are not at increased risk of developing cancer per se – indeed, perhaps in part because they have historically smoked less and exercised more than most people, their risk of contracting some cancers is less. [3, 4] Even so, it appears that exposure to pesticides, in some situations, confers a greater risk of several specific types of cancer. For example, (and see also Table 1) research indicates that pesticide exposure can increase the risk of:

- non-Hodgkin's lymphoma (NHL);[6, 7, 8, 9]
- soft tissue sarcomas;[10, 11, 12]
- leukaemia in pesticide manufacturing workers,[13] agricultural and forestry workers;[14, 15, 16, 17]
- leukaemia in children whose mothers were exposed to pesticides occupationally,[18] or during pregnancy in the home,[19, 20] or in children themselves exposed in the home;[21]
- prostate cancer;[22, 23,24, 25, 26, 27, 28]
- brain cancer in adults,[29] and in children of exposed parents[30] (although not all studies have found an increased risk of brain cancer in agricultural workers).[31]

It also seems that pesticides and/or farming might be linked with several other cancers,[32] including (but not limited to) bladder,[33, 34] stomach,[35] pancreatic,[36, 37, 38, 39] lung,[40] multiple myeloma,[41, 42] Hodgkin's disease,[43] colorectal cancers,[44] ovarian,[45] and oesophageal cancer (with the latter particularly in cider-growing areas).[46] For skin cancer too, exposure to certain pesticides appears to increase the melanoma risk.[47]

Furthermore, a growing body of research into hormone disrupting chemicals provides a firm foundation for suggesting that exposure to pesticides can increase the risk of breast and testicular cancer – particularly exposure to pesticides with endocrine disrupting properties at critical windows of exposure, such as during development in the womb.

Farmers and agricultural workers are more likely to die from certain cancers

Compared with the general population, farmers (including pesticide applicators) do seem to be more likely to die from several cancers,[48] including NHL,[49, 50] leukaemia,[51, 52] multiple myeloma,[53, 54] prostate,[55, 56, 57] Hodgkin's disease,[58] pancreatic[59, 60] and brain cancer.[61, 62, 63]

Overall, as outlined in this report, we consider that several studies provide a strong indication of an association between pesticide exposure and NHL, leukaemia and prostate cancer. Indeed, a review conducted in 2004 concluded that there is "compelling evidence of a link between pesticide exposure and the development of NHL."[64] Other studies to support the suggestion that pesticides may play an important role in hormone-related cancers are discussed below.

Childhood cancer and pesticide exposure

The growing number of studies and the increasing incidence of cancer in children gives weight to the suggestion that environmental exposure, including exposure to pesticides, plays a role in some cancers. In industrialised countries, one child in 500 develops a cancer before the age of 15, and before the age of six in almost half the cases.[65] Moreover, childhood cancers appear to have increased by about 1% a year in some European countries (see Annex 1). Several studies (though not all)[66, 67] have linked parental[68, 69] and/or a child's pesticide exposures to higher risks of childhood cancer,[70] including leukaemia, brain cancer,[71, 72, 73] lymphomas,[74, 75] (including NHL),[76] Ewing's sarcoma[77] and Wilms' tumour.[78]

Another study has highlighted that children living in counties in the US with moderate to high levels of agricultural activity have a greater risk of being diagnosed with various cancers.[79] In 2007, some researchers reviewing the data concluded that it could confidently be stated that there was at least some association between pesticide exposure and childhood cancer, and that maternal pesticide exposure during pregnancy was most consistently associated with childhood cancer.[80] Similarly, a 2009 review of childhood leukaemia and parental pesticide exposure found that maternal exposure prenatally was most strongly associated with increased risk.[81]

Table 1: Pesticides suspected of playing a role in certain human cancers as identified in epidemiological studies examining either occupational exposures or non-occupational (environmental) exposures

Cancer Type	Pesticides
Hodgkin's disease	Chlorophenols.[82] Phenoxy acid herbicides.[83, 84] Other pesticides – perhaps including DDT.[85] Triazole fungicides and urea herbicides.[86] Increase in children of pesticide exposed parents.[87]
Non-Hodgkin's Lymphoma (NHL)	Increased risk of NHL in men who had farmed at some time in their life,[88] and in long-term farmers[89] and forestry workers.[90] Also, some evidence of increase in exposed children or children of pesticide-exposed parents.[91, 92, 93, 94] Lawn care pesticides, but small numbers in study.[95] Phenoxy acid herbicides,[96, 97] including MCPA,[98] dicamba,[99] 2,4-D[100,101] and mecoprop.[102] Triazines,[103, 104] including atrazine.[105] Chlorophenols,[106, 107] possibly dioxins in pentachlorophenol.[108] Organochlorines[109] including DDT,[110, 111, 112] lindane[113, 114, 115] and aldrin,[116] β-HCH,[117] chlordane,[118, 119, 120, 121] trans-nonachlor,[122] HCB,[123] mirex,[124] heptachlor,[125] toxaphene,[126] dieldrin.[127, 128, 129] Technical grade HCH, and lindane used in sheep dipping.[130] Metribuzin.[131] Butylate.[132] Terbufos.[133] Other organophosphates,[134] including diazinon[135, 136] dichlorvos,[137] malathion,[138, 139] coumaphos and fonofos.[140] Carbamate insecticides[141, 142] including carbaryl.[143, 144] Fumigants,[145] including carbon tetrachloride.[146] Methyl bromide, ethylene dibromide, carbon disulphide, phosphine.[147, 148] Nicotine.[149] Glyphosate,[150] sodium chlorate.[151] Arsenic compounds[152] including copper acetoarsenite.[153] Amide fungicides including captan.[154] Sulphur compounds.[155] Immuno-suppression, possibly in combination with viruses, has been speculated as a possible causal mechanism for some of these pesticides.[156] It seems that there may be an interaction with pesticides exposure and antibodies to Epstein-Barr virus.[157] Also, some molecular research supports the suggestion that pesticides are involved.[158, 159]
Multiple Myeloma	Pesticide exposures are associated with multiple myeloma[160] including dieldrin, chlorothalonil, and carbon tetrachloride / carbon disulphide fumigant mixture.[161] Permethrin – but data not strong.[162] Alachlor,[163] glyphosate[164] – suggestion. Phenoxy herbicide producers reported to have increased risk of multiple myeloma, with the stronger association for those exposed to multiple agents, including dioxins, during production.[165] DDT.[166]
Lung cancer	Occupational exposure to pesticides,[167] including those used to control pests in buildings.[168] Organochlorines, although inconsistent findings.[169] Dieldrin – but based on small numbers.[170] High exposures to chlorpyrifos, diazinon, metolachlor, pendimethalin possibly implicated.[171] Amitrol,[172] phenoxy herbicides,[173] dicamba,[174] terbufos,[175] carbofuran[176] – weakly suggestive. Mosquito coil smoke.[177] Arsenic compounds.[178, 179]
Pancreatic cancer	Pendimethalin, EPTC (a thiocarbamate herbicide, S-ethyl-N,N-dipropylthiocarbamate).[180] Area with high use of 1,3-dichloropropene, captafol, pentachloronitrobenzene and dieldrin reported with increased death rate due to pancreatic cancers.[181] Arsenical pesticides.[182] DDT – long-term exposure in chemical manufacturing workers.[183]
Colorectal cancer	Chlorpyrifos, aldicarb,[184] chlordane,[185] dicamba,[186] EPTC,[187] – but needs further study. Alachlor.[188] Dieldrin and aldrin – some suggestion some years ago,[189] but later follow-up did not support this.[190] Imazethapyr, a heterocyclic aromatic amine herbicide.[191] Trifluralin – but small numbers and inconsistencies.[192]
Liver cancer	Exposure to pesticides, including DDT[193, 194] and arsenic compounds.[195]
Soft tissue sarcoma	Increased in workers exposed to pesticides, including farmers, forestry workers and gardeners.[196] Organochlorine insecticides.[197, 198] Chlorophenols.[199, 200] Phenoxy acid herbicides.[201, 202, 203, 204, 205]
Stomach cancer	Agricultural workers in areas with heavy use of 2,4-D, chlordane or propargite.[206] Atrazine in drinking water at levels of 50-649ng/l.[207]

Cancer Type	Pesticides
Leukaemia	Pesticide exposure of parents seems to increase the risk of leukaemia in offspring,[208, 209, 210] as does exposure of children themselves to pesticides in the home.[211, 212] Having parents engaged in animal husbandry, particularly pig farming, also seems to increase the risk of some types of acute leukaemias (where exposure may be to animal viruses or insecticides).[213] Similarly, some suggestion that children living on or near farms might be at increased risk of leukaemia.[214, 215] Use of insecticidal shampoos for head lice associated with acute leukaemia in children - but results need to be replicated.[216] Increased risk in adults working in forestry[217] and/or agriculture[218, 219, 220, 221] and men[222] and women[223] specifically exposed to pesticides. Fungicides, including nitro derivatives and dinocap, and weak data for an association with dithiocarbamate exposure in women, also cyclohexane insecticides, triazine and amide herbicides, and organotin.[224] In areas where toxaphene and mancozeb were heavily applied, leukaemia risk was doubled.[225] DDT.[226, 227] Chlordane/heptachlor.[228] Alachlor,[229] metribuzin,[230] – but needs further study. Crotoxyphos, dichlorvos,[231] famphur, pyrethrins, methoxychlor, nicotine.[232] Diazinon,[233] fonofos,[234] EPTC[235], terbufos[236] but again authors caution further studies needed. Propoxur [237] and mosquitocidals[238] which may initiate changes predisposing to leukaemia when exposure occurs in the womb. Organophosphate insecticides in non-smoking farmers.[239]
Brain + CNS (central nervous system) cancers	Farming, including exposure to pesticides,[240, 241, 242, 243, 244] or being the offspring of a parent exposed to pesticides[245] or of a farmer engaged in animal husbandry[246] may increase the risk of brain cancer. Some suggestion also that pesticides used in the home,[247] on golf courses,[248] or in vineyards may play a role.[249] Another study to investigate the role of pesticides found increased rates of brain tumours in young and middle-aged horticulturalists.[250] Exposure to flea and tick control products suggested to increase the risk of brain tumours in children.[251]
Bladder cancer	Employment in farming, particularly long-term, appears to confer a risk.[252] Imazethapyr, a heterocyclic aromatic amine herbicide.[253]
Ovarian cancer	As this is a hormone-related cancer, substances with endocrine disrupting properties might impact risk.[254] Some evidence to suggest increased risk in female pesticide sprayers[255] Weak suggestion that triazines,[256] such as atrazine,[257] might increase risk, but an expanded study was unsupportive.[258]

Cancer Type	Pesticides
Breast cancer	Organochlorine pesticides, including aldrin and lindane,[259] hexachlorbenzene (HCB),[260] DDT/DDE,[261, 262, 263] hexachlorocyclohexane (including lindane),[264] dieldrin[265, 266] heptachlor epoxide.[267, 268] Chlordane, malathion, and 2,4-D, and chemical-related risk was greater in younger women.[269] Areas with heavy use of 2,4-D, chlordane,[270] methoxychlor or toxaphene.[271] Also, areas with use of aldicarb, lindane and the triazine herbicide, atrazine, but data not strong,[272, 273] and another study was unsupportive.[274] Some suggestion of increased risk associated with use of 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP) and possibly use of dieldrin, captan, and 2,4,5-TP, but small numbers. Risk slightly increased among women whose homes were closest to areas of pesticide application, but this needed follow-up.[275] Hormone disrupting pesticides have been conjectured to be a possible factor in the increased incidence of breast cancer on Martinique island.[276] A study in Canada found increased risk of breast cancer in women of 55 or under who had worked in farming.[277, 278] Total body burden of oestrogen-mimicking pollutants implicated.[279]
Testicular cancer	Men with testicular cancer had mothers with higher levels of some organochlorine pesticides, including HCB, trans- and cis nonachlordanes.[280] Another study found men with testicular cancer had higher levels of some organochlorines.[281] Elevated risk found in pesticide applicators.[282] Methyl bromide.[283] Persistent organic pollutants, including pesticides with endocrine disrupting properties suggested to be involved in some cases.[284]
Prostate cancer	Studies of farmers and those applying or coming into contact with pesticides,[285, 286] fairly consistently suggest pesticide exposure confers an increased risk,[287, 288, 289, 290, 291, 292] although not all studies find an association with pesticide exposure.[293, 294] Exposure to organochlorine pesticides and acaricides, including heptachlor,[295] lindane,[296] DDT and dicofol[297], has been implicated. Studies have also reported that elevated levels of some organochlorines, including oxychlordane,[298] HCH, trans-nonachlor and dieldrin,[299, 300] in men's bodies may be associated with an increased risk. Atrazine.[301] Simazine (but data weak).[302] Methyl bromide.[303, 304] Phenoxy herbicides.[305] Dichlorvos.[306] Terbufos.[307] Butylate,[308] chlorpyrifos,[309] permethrin,[310] coumaphos,[311] fonofos,[312] or phorate[313] – all associated with higher risk in farm workers with a relative with prostate cancer. Hormone disrupting pesticides conjectured to be a factor in the increased incidence of prostate cancer on the island of Martinique.[314] Manufacture of benzothiadiazin herbicide,[315] although these and some other findings in industry workers were suggested to be related to better screening and earlier detection.[316]

Explanatory notes to Table 1

Some of the pesticides for which epidemiological studies have raised suspicions that they play a role in some cancers are outlined in Table 1. A full systematic review of all the literature on the role of pesticides in cancer is beyond the scope of this review. Rather, the aim is primarily to highlight epidemiological studies that raise important concerns that pesticide exposures have played an influential role in certain cancers.

In some instances there may be several studies which provide the basis for this concern – although there may also be other studies that have not found an association. Also, some of the studies included here are considered to provide quite preliminary data because, for example, they may be rather small studies or the particular pesticide exposure may be associated with only a relatively small increase in the expected number of cancers. The table should therefore be viewed with these caveats in mind. Moreover, some of the cancers listed in the table comprise several different types of cancer – so this exercise should be regarded as providing an initial broad-brush picture rather than a definitive database, as narrower definitions of certain cancers might better elucidate those pesticides potentially involved in causation.

For some pesticides implicated in Table 1, it may be that unintentional contaminants within them,[317] such as dioxins, contribute to adverse effects.[318] Similarly, for some pesticide formulations it is thought that some ingredients, other than the main active pesticide (i.e. adjuvants and surfactants), may play a role. For example, although in 2005 new pesticide formulations were not allowed to contain nonylphenol ethoxylate (NPE),[319] this legislation did not affect the existing national authorisations of pesticide products containing NPE,[320] where it is used to make the product perform better.

Nonylphenol, the breakdown product of NPE, is an oestrogen-mimicking, hormone disrupting chemical which is now found in human body fat with unknown consequences,[321] although there are now concerns about the potential role of such substances in breast cancer (see below). Other chemicals used in agriculture which fall within the definition of pesticides include plant growth regulators; and for example, some years ago gibberellin A3 was reported to cause cancer in animal tests.[322]

[Credit: iStockphoto/Kemter]

Pesticides with hormone disrupting properties and cancer

There is a good basis for suggesting that hormone disrupting substances, including pesticide formulations with oestrogenic and/or anti-androgenic properties (i.e. those that mimic the female hormone, oestrogen, and/or block the male hormone, testosterone, an androgen), may play a role in hormone-related cancers, such as those of the breast, testicle or prostate. Indeed, the highly respected international Endocrine Society has noted that "the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong".[323]

A brief summary of the reasons for concern is provided here, but more lengthy discussions can be found in the following CHEM Trust publications authored by internationally respected experts in the field. For breast cancer, see *Breast cancer and exposure to hormonally active chemicals: An appraisal of the scientific evidence* by Professor Andreas Kortenkamp,[324] and for testicular cancer see *Male reproductive health disorders and the potential role of exposure to environmental chemicals* by Professor Richard Sharpe.[325]

It should be noted that hormonally active substances which may have profound developmental effects on the risk of developing hormone-related cancers are not mutagenic and will therefore be missed during regulatory screening for carcinogens. Moreover, the testing of chemicals, including pesticides, for possible carcinogenic effects in laboratory animals is carried out after they are born, thereby missing the in-utero developmental period, which may be particularly sensitive to effects due to hormonal disruption.

Breast cancer and exposure to oestrogen-mimicking pesticides

It is well known that the risk of breast cancer is influenced by a woman's lifetime exposure to her own oestrogen. Factors that increase her lifetime exposure, including early puberty, late menopause, not having children and not breast feeding, all increase breast cancer risk. So does being a twin of a sister (where in-utero oestrogen exposure is increased),[326] taking the contraceptive pill,[327] hormone replacement therapy,[328, 329, 330] and other lifestyle factors which give rise to increased oestrogen levels, including alcohol consumption[331] and being overweight.[332]

Several pesticides have been found to have oestrogen-mimicking properties, and it is hypothesised that exposure to such substances add to a woman's total oestrogen exposure, thereby increasing her risk of breast cancer. When epidemiologists looked at the total man-made oestrogenic activity in women, arising from oestrogen-mimicking chemicals, to see if those with higher levels of these contaminants were at greater risk of breast cancer, they did indeed find this in leaner women.[333]

Earlier epidemiological studies, looking at whether certain organochlorine pesticides were involved in breast cancer, did not reveal a consistent association. They may have missed finding a link because they only looked at the role individual substances might play, rather then that played by the total man-made oestrogenic burden arising from exposure to such chemicals. It is now well accepted that when exposure occurs simultaneously to many hormone mimicking-chemicals, they can act together and cause an 'additive effect', far greater than would occur with each chemical by itself.[334]

Additive effects have been reported for oestrogen-mimicking, anti-androgenic[335, 336, 337] and thyroid hormone disruptors,[338] with some indication that there may be synergistic (more than additive) effects in some cases.[339] It is the sheer volume of contaminants with hormone disrupting properties, including pesticides, which raises the concern that those with oestrogen-mimicking properties might be adding to the burden of breast cancer cases.

It should be noted that only around one in 20 cases of breast cancer is believed to be due to genes – therefore most women acquire this cancer during their lifetime. It is also clear that genetic susceptibility is not the only factor that influences breast cancer risk, in that among women who carry the damaged BRCA1 and BRCA2 genes – the so-called 'breast cancer genes' for women born before 1940 – the risk of developing breast cancer by the age of 50 was 24%, whereas women with these genes who were born after 1940 have a much higher risk (67%) of being diagnosed by the age of 50.[340] So over time, some environmental factor(s) are exacerbating the risk in these genetically highly susceptible women.

[Credit: Benjamin Ealovega/WWF-UK]

In humans, it seems that the breast is particularly at risk from cancer-causing influences during development in the womb,[341] or during childhood or puberty.[342, 343] A study of girls born to women who were misguidedly prescribed an oestrogenic drug called diethylstilboestrol (DES) during pregnancy has shown that they are more prone to breast cancer – which again highlights the vulnerability of the unborn child.[344]

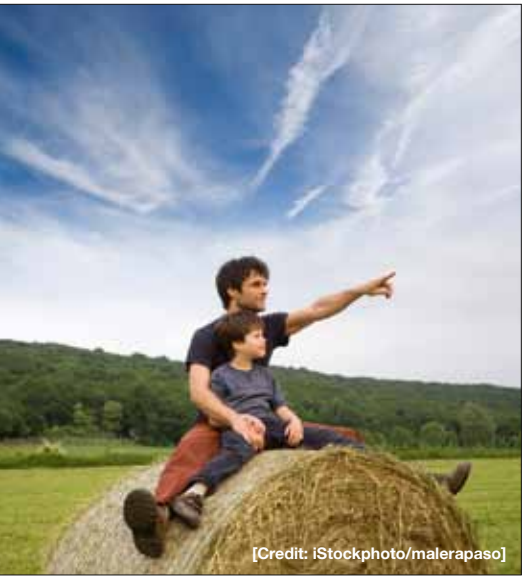
Similarly, further research designed to examine whether age at exposure to contaminants plays a crucial role has shown that exposure to DDT before puberty, but not after, increases the risk of breast cancer.[345] Before birth, oestrogen levels influence the number of end buds in the primitive duct structure of the foetal breast tissue, with higher oestrogen levels inducing the growth of more end buds, thereby enlarging the number of cells from which cancer cells can arise.[346] In line with this, studies have shown that if rodents are exposed to an oestrogen-mimicking chemical via their pregnant mother prior to birth, they are far more likely to contract mammary cancer[347] when exposed after birth to another cancer-causing substance.[348]

Another study has also shown that when rodents are exposed to atrazine (a herbicide) in-utero, it causes a delay in the development of the mammary gland in female offspring, which is suggested to confer an extended window of sensitivity to cancer-causing agents after maturity.[349] In mice, it has also been shown that dieldrin exposure of female offspring via their mothers during pregnancy and lactation, causes mammary tumours.[350] Both dieldrin[351] and atrazine are considered to have oestrogen-disrupting properties.

Timing of exposure to contaminants can therefore be seen to be crucial for some cancers. This means that epidemiological studies that look for associations between a woman's exposure to various substances at the time of breast cancer diagnosis are seriously flawed, because they miss consideration of exposure at sensitive time windows possibly decades earlier in life.

With regard to breast cancer, there is a need to evaluate the role that cumulative exposure to oestrogenic pesticides and other man-made hormone disrupting chemicals may play, and it is also necessary to evaluate and assess more thoroughly those chemicals which have been shown to cause mammary tumours in rodents. A 2007 review noted that more than 200 such chemicals had been identified, including ten pesticides (1,2-dibromo-3-chloropropane, atrazine, captafol, chlordane, clonitralid, dichlorvos, fenvalerate, nifurthiazole, simazine, sulfallate).[352]

Testicular cancer and exposure to anti-androgenic pesticides


[Credit: iStockphoto/malerapaso]

Similar to the role that cumulative exposures to man-made oestrogenic chemicals are suspected to play in breast cancer, it is considered very likely that cumulative exposures to chemicals with anti-androgenic (de-masculinising) properties increase testicular cancer risk. This form of cancer has increased dramatically over the last 40 years. Furthermore, the fact that the children of immigrants to a country take on the testicular cancer incidence rate of the country in which they are brought up, rather than that of their fathers' country of origin, provides compelling evidence indicating that some environmental factor(s), as opposed to genetic factors, are at play.[353]

It is known that boys with undescended testicles are at greater risk of developing testicular cancer, and several scientists now consider that a spectrum of symptoms including birth defects of the genitals, low sperm counts and testicular cancer (together called testicular dysgenesis syndrome – TDS) are likely to be caused by chemicals which block androgen action in-utero.[354, 355, 356, 357] Several pesticides have the ability to block androgen, and/or act as an oestrogen mimics.[358] Animal studies provide a wealth of data to show that anti-androgenic chemicals can cause birth defects in male genitals and low sperm counts; and undescended testes and carcinoma in situ-like (CIS) testicular lesions (an early form of cancer) have been reported in rabbits treated during development with p,p'-DDT or p,p'-DDE.[359]

Similarly, several human epidemiological studies have reported an association between a mother's exposure, or her baby's exposure, to certain chemicals and undesirable effects reported in baby boys. These include birth defects of their genitals, reduced testosterone levels, or effects related to reduced testosterone action.[360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370]

Furthermore, a mother's exposure to oestrogenic pharmaceuticals during pregnancy is associated with testicular cancer risk in her baby boy.[371]

The experience of pregnant women misguidedly given DES certainly illustrates that great care should be taken during pregnancy, because it was found that the baby boys of these women were more likely to be born with genital abnormalities[372,373] and have damaged sperm later in life.[374] There is also some suggestion of increased risk of testicular cancer later in life.[375] Another study has found that baby boys with undescended testes or hypospadias were more likely to have detectible levels of man-made organochlorine oestrogen-mimicking chemicals in their placentas than boys without such defects. More pesticides were also detected in the placentas of the baby boys with these birth defects, and mothers engaged in agricultural activities were at greater risk of having a baby with these defects. The increased risk for male urogenital malformations was related to the combined effect of environmental oestrogenic contaminants in the placenta.[376, 377]

Another study has found that men with testicular cancer had higher levels of pp'DDE (a contaminant and breakdown product of DDT insecticide) and some chlordane compounds when tested much earlier in life.[378] Exposure may occur via the mother when the baby is in the womb and during lactation, as well as direct exposure later in life. It does seem that very early life exposures play a part, and that a mother's exposure to certain pollutants may increase her son's risk of testicular cancer.[379] In line with this, a study of breast milk in Denmark and Finland found significantly higher levels of chemicals, including dioxins, PCBs, and some pesticides in Danish mothers: this was hypothesised to account for the higher prevalence of testicular cancer and other reproductive disorders in Danish men.[380]

Prostate cancer and exposure to hormone disrupting pesticides

Prostate cancer is another cancer which is influenced by hormonal action.[381] For example, a study has suggested that oestrogens and aromatase (an enzyme which converts testosterone to oestrogen) may play a role in this cancer.[382] In rodent experiments, exposure to an anti-oestrogenic substance appears to reduce the number of mice developing the disease.[383] Moreover, an in-vitro (test tube) study using human prostate cancer cells has shown that several pesticides (including beta-HCH, o,p'-DDT (a constituent of DDT insecticide), heptachlor epoxide, trans-permethrin and chlorothalonil) can cause these cells to proliferate, demonstrating a possible mechanism for cancer causation.[384]

Hexachlorobenzene, another organochlorine pesticide, has also been implicated in test tube experiments, and has been reported to disrupt androgen regulation in the prostate.[385] Researchers have noted that some of the substances suggested to play a role (shown in Table 1) might act by altering the metabolism of sex hormones.[386] For example, chlorpyrifos, fonofos[387] and phorate[388] strongly inhibit CYP1A2 and CYP3A4, which are the major p450 enzymes in the liver responsible for the metabolism of oestradiol, oestrone and testosterone.

More research is needed to help determine during which stages of life the prostate is most under threat from chemical exposures, but laboratory experiments give weight to the suggestion that hormone disrupting chemicals may particularly play a role in prostate cancer.

Farmers appear to be at a greater risk of prostate cancer, and pesticide exposure (including those with endocrine disrupting properties) may be involved.[389] In 2004, the UK Government's advisory committee on cancer noted that there was some evidence of a small increase in the risk of prostate cancer among farmers and farm workers using pesticides, but the evidence did not point clearly to any single pesticide or group of pesticides that might be responsible. In 2007, the committee recommended that this should be kept under review, and noted that although a meta-analysis (which combines the results of several studies) by Van Maele-Fabry et al (2006)[390] provided some evidence of a weak association between pesticide-related occupations and prostate cancer, causality could not be inferred from the available data.[391]

Since then, more data from the large Agricultural Health Study in the US (see Table 1) suggest that exposure to pesticides might influence prostate cancer susceptibility in men with a genetic predisposition.

It also seems that even when the disease is already manifest, it could be wise to avoid exposure to endocrine disruptors, because another in-vitro study has suggested that exposure to chemicals with endocrine disrupting properties might affect the successful treatment of prostate cancer.[392]

section 2

cancer aetiology and cancer prevention policies

[Credit: iStockphoto/flashgun]

Teasing out the role of pesticides in cancer is difficult. The disease is known to be caused by complex interactions of a number of factors including genetics, diet, lifestyle, stress, occupational and non-occupational exposures to chemicals (including pesticides), physical and biological agents, and in some cancers, infections. Cancer causation is therefore very complex as it is a multi-factorial and multi-stage process.

Damage to DNA plays a role in carcinogenesis, but also important is inadequate functioning of the DNA repair mechanisms and other protective cellular processes. Some chemicals are not mutagenic or genotoxic at low exposures, but can turn on or off specific genes that alter a person's susceptibility to genotoxic agents or perhaps somehow affect the progression of cancer. Some chemicals therefore act as epigenetic carcinogens – substances that do not themselves damage DNA, but cause alterations that predispose to cancer (see glossary). Pesticides may thus increase the risk of cancer through a variety of mechanisms including genotoxicity, tumour promotion, epigenetic effects, hormonal action and immunotoxicity.

Authorities in the US estimate that overall, at least two thirds of cancer cases are due to environmental factors, with smoking being the single most important preventable factor[393] (although it needs to be recognised that tobacco is not linked to the majority of cancers). Recent studies have revised the assessment of 'environmental factors' to include a much larger fraction of cancers due to exposures to chemicals.[394] It is also noteworthy that in 1994 the US National Cancer Advisory Board reported that inadequate acceptance of the importance of contaminants in food and the environment had been an obstacle in cancer prevention.[395] In a similar vein, in 2010 the US President's Cancer Panel was concerned that the true burden of environmentally induced cancer had been grossly under-estimated and highlighted the unacceptable burden of cancer resulting from environmental and occupational exposures which could be prevented.[396]

Similarly, the European Parliament has noted that cancer prevention is the most cost-effective response and has urged that more resources be systematically and strategically invested in prevention. In addition, the Parliament has noted that a new cancer prevention paradigm is required to address genetic, lifestyle, occupational and environmental factors on an equal footing, and in a manner that reflects the combination effects of different factors, rather than focusing on isolated causes. The Parliament specifically mentions the role of exposure to chemical contaminants in food, air, soil and water, including exposure arising from industrial processes, agricultural practices or the content of such substances in, for example, construction and consumer products.[397] (Annex 2 further discusses the role of workplace exposure and environmental factors in cancer.)

Life circumstances determined by socio-economic factors often control many lifestyle choices that affect the incidence and prevalence of some cancers. Beyond stopping smoking, other lifestyle changes advocated as reducing cancer risk include avoiding excessive exposure to the sun, avoiding obesity, increasing exercise, reducing alcohol intake, and ensuring that all health and safety instructions on substances, including chemicals which may cause cancer, are followed.[398] However, although people may choose their diets, they do not usually know about the environmental carcinogens, including pesticidal contaminants, which may be present in food and water.

Pesticide usage and exposure concerns

Pesticides are rightly suspected of being implicated in ill health, because they are specifically designed to be toxic to certain organisms. Furthermore, it is difficult to achieve the goal of selective toxicity, whereby the pesticide just targets the pest organism. Therefore, concerns are high because pesticides are often very toxic to humans and exposure can be widespread.

The production of synthetic pesticides has increased dramatically since the 1950s, with global pesticide use virtually doubling every ten years between 1945 and 1985, when it reached three million metric tons.[399] As the bulk of these pesticides have been spread on the land, vast numbers of people have been exposed to a variety of these chemicals – often unknowingly and albeit often at very low levels – in the food they eat, the water they drink and the air they breathe, and also possibly via skin contact.

Difficulties with epidemiological studies

Given the large number of chemicals to which workers and the general population are exposed, and the difficulty in acquiring good data on all such exposures, epidemiological studies which look for associations can sometimes produce weak findings or false positives or negatives. With false negatives, chemicals that are hazardous may be cleared for use, which will benefit chemical producers and users but may have potentially significant adverse public health impacts.[400, 401, 402] False positives may identify safe chemicals as hazardous, which will have adverse economic effects on chemical producers. Some researchers consider that there are a significant number of false positive epidemiological studies which have been too readily accepted.[403] Others dispute this and have found few false positive studies and little evidence of bias in favour of such studies in regulatory decision-making.[404]

Nevertheless, in studies where the cancer is rare and the increased numbers of cancers is small, it is difficult to be sure whether this is due to the exposure under examination or due to chance. Similarly, if the cancer is not rare, increased incidence due to a particular exposure may not be recognised as such at an early stage, as happened initially with lung cancer due to asbestos exposure. Bearing this in mind, epidemiological studies, implicating various pesticides in disease, need to be viewed cautiously, as do those which have failed to confirm associations. Discrepancies in findings may arise due to several factors, including:

- chance variation;
- bias in the study methods;
- confounding exposures; and
- differences in the quality, quantity and timing of exposures.

Given these difficulties, and coupled with the fact that epidemiological studies are always a case of 'shutting the stable door after the horse has bolted', it is clear that to deliver a precautionary and preventative approach, action needs to be based on toxicity studies in the laboratory.

section 3
regulatory issues

[Credit: iStockphoto/Maica]

Are the pesticides implicated now banned?

Some of the pesticides in Table 1 (p6-7), shown in epidemiological studies as implicated in cancer causation, have now been banned in the EU. But some are still in use, and a database identifying which are in use and which have been banned can be found on the following website, where information on uses can also be found by looking at the maximum residue limit (MRL) for the substance (http://ec.europa.eu/food/plant/protection/evaluation/database_act_subs_en.htm). Pesticides banned in the EU can often still be found as contaminants in imported produce, where MRLs would apply.

The need to regulate on the basis of screens and tests

Given the inherent difficulties with epidemiological studies, and that a more ethical approach is cancer prevention in the first place, it is imperative that screening and testing to identify carcinogens is undertaken, so that those pesticides found with such properties are not authorised for use. However, there can often be debate on whether the cancer seen in animal tests is caused by a mechanism that operates in humans and whether or not the animal test data are sufficient for the substance to be presumed as carcinogenic for humans.

The new EU Pesticides Regulation 1107/2009 will require the phase-out of any pesticides classified as Category 1A (known to have carcinogenic potential for humans, largely based on human evidence) and Category 1B (presumed to have carcinogenic potential for humans, largely based on animal evidence). However, if the evidence is not sufficiently convincing, a pesticide could not be phased out on the basis of its carcinogenic properties alone, because Category 2 pesticides are not covered by so-called carcinogen 'cut-off criteria'. A substance can be placed in Category 2 on the basis of evidence obtained from human and/or animal studies, when that evidence is not sufficiently convincing to place the substance in Categories 1A or 1B, based on strength of evidence (See Annex 3 and 4).

CHEM Trust considers that all suspected carcinogenic pesticides should be phased out wherever possible, and that there should be a precautionary interpretation of the data to decide when a substance should be presumed to have carcinogenic potential for humans. Unfortunately, the concern and controversy about the ongoing use of substances can last for many years.

For example, 2,4-D was first under the spotlight in the 1970s, when it was often used with 2,4,5-T, which was subsequently withdrawn from the market.

Since then, several epidemiological studies have suggested that the phenoxy acid herbicides (also called chlorphenoxy herbicides) are implicated in cancer (see Table 1). Now, several organisations, including the Canadian Cancer Society, are calling for 2,4-D to be banned.[405] However, the International Agency for Research on Cancer's (IARC's) position of 2002 shows the difficulties with some of the epidemiological data implicating pesticides. In that year, an IARC spokesperson is quoted as noting that:

> *"The epidemiological data on 2,4-D as a separate compound were inadequate to evaluate its carcinogenicity to humans, because no data on human exposure to the single compound were available. The animal carcinogenicity data for 2,4-D were inadequate. The chlorphenoxy herbicides showed limited epidemiological evidence for increased occupational risk in pesticide applicators, and were evaluated as possibly carcinogenic to humans, Group 2B. Because 2,4-D belongs to this group of substances, the compound has been given the same classification, in the absence of data that would make a full evaluation of 2,4-D possible."*[406]

Here it should be noted that the IARC classification system[407] is different from that of the EU, but nevertheless, this statement shows the difficulty in getting definitive data. This pesticide is still used in the EU, with the 2001 EU review noting that there was "no evidence of carcinogenicity".[408]

The burden of proof

Looking at the research, several studies strongly indicate that pesticides play a role in some cancers. However, due to the many factors involved and what is often a long time-lag between exposure to causal factors and the disease becoming apparent in humans, it will be immensely difficult to establish with a very high degree of scientific proof that pesticide exposures play a role in many human cancers, particularly including breast, testicular and prostate cancers.

In order to prevent cancer, it is clear that pesticides and other chemicals need to be subjected to tough regulation on the basis of laboratory studies indicating a carcinogenic potential. Reducing society's reliance on toxic substances will be key to achieving a reduction in cancer. Therefore, putting in place policies which seek to reduce the use of harmful substances, including finding options that don't require the use of potentially harmful substances or by substituting hazardous substances with less hazardous substances, will all be part of the solution. Given the large numbers of people exposed to pesticides, public health considerations should be paramount and the use of potentially harmful pesticides minimised as soon as possible.

Agencies around the world are now acknowledging the potential benefits of reducing pesticide usage; for example, it is noteworthy that the UN Food and Agriculture Organisation is promoting Integrated Pest Management (IPM) – this is an ecosystem approach to crop production and protection that combines different management strategies and practices to grow healthy crops minimising the use of pesticides.

Geoffrey Rose, chair of epidemiology at the London School of Hygiene and Tropical Medicine, noted that rather than an approach which targets people at high risk of disease, a more powerful strategy should aim to shift the whole distribution of a risk factor in a favourable direction.[409] Reducing overall exposures by minimising the use of potentially toxic pesticides would deliver such a goal, and there needs to be the political will to deliver this shift towards a wider preventative approach.

Unfortunately, changing policy or making decisions on whether there is a need to reduce exposure to a particular substance can often get tied up with whether compensation should be paid to individuals for a disease they have contracted. For example, the level of proof required by the UK Industrial Injuries Advisory Council is arbitrary and high: it generally seeks robust epidemiological (population-based) evidence that the risk of the disease is more than doubled in relation to certain occupational exposures before it recommends that an addition to the list of prescribed diseases for which Industrial Injuries Disablement Benefit is payable (http://www.iiac.org.uk/). This can sometimes help skew the statistics on disease causation. Internationally, some governments appear to take a more enlightened view than others as to when compensation is paid to workers.[410]

Given the inherent difficulties in establishing proof of cancer causation in epidemiological studies, perhaps official advisory committees should move towards giving advice based on expert judgement as to the probability that the substance in question is involved in certain cancers. They should then try to ensure appropriate and meaningful application of the precautionary principle, rather than, for example, report that causality cannot be established from the available data.

The European Parliament, in its resolution of 10 April 2008 on combating cancer in the enlarged European Union, has officially recognised that exposure to certain chemicals may be the cause of many cancers.[411] The case for considering that chemicals, including pesticides, play an important and preventable role in many cancers is based on a large growing body of in-vitro, animal and epidemiological research.

section 4
conclusions and recommendations

[Credit: iStockphoto/digital planet design]

Conclusions

- Exposures to certain pesticides may interact with other chemical exposures and life circumstances (e.g. those causing a weakened immune system) and genetic factors to increase the risk of cancer.
- Extensive data highlight the role pesticide exposures are suspected to play in several cancers.
- There are studies which strongly suggest an association between pesticide exposure and NHL, leukaemia and prostate cancer. In addition, there are strong reasons to consider that pesticides can play an important role in breast and testicular cancer. Moreover, some researchers consider it can also confidently be stated that there is at least some association between pesticide exposure and some childhood cancers.
- Some studies suggest pesticide exposure prior to conception, during pregnancy or during childhood seems to increase the risk of childhood cancer, with maternal pesticide exposure during pregnancy often being most consistently associated with childhood cancer.
- Given the available evidence of the role pesticides play in ill health, substantial financial and future health benefits are likely to accrue from the better regulation of pesticides.
- Pesticides with endocrine disrupting properties, or those with known or suspected human carcinogenic properties, should be substituted with safer alternatives. This is particularly because of the overwhelming evidence showing that simultaneous exposure to chemicals with endocrine disrupting properties can cause additive effects – and similarly, evidence to show that carcinogenic substances can work together to exert tumorigenic responses after sequential or simultaneous exposures.[412]

Recommendations

- With regard to pesticides used in agriculture, the goal should be to reduce the cancer burden and other pesticide-related health effects, while maintaining the security of food supplies, by giving due regard to integrated and sustainable pest management systems.[413]

- Unnecessary use of pesticides should be avoided. Significant pesticide-use reduction should be achieved through integrated pest management, which requires non-chemical options to be explored and, if chemical control is necessary, then the lowest risk pesticides are to be used in a manner to reduce human exposure. Such a regime provides opportunities for the creation of healthy green jobs.[414]

- An important aim must be to ensure that current pesticides do not lead to cancer a decade or two hence. Adequate screening and testing of chemicals must therefore ensure that those with cancer-causing or hormone disrupting properties are identified, and safer replacements found. A precautionary interpretation of data is needed to identify human cancer-causing or hormone disrupting substances. Due regard must also be given to developing non-animal test methods that can reliably identify such chemicals.

- All EU member states should support strict implementation of the 2009 EU pesticides legislation, which imposes so-called 'cut-off' criteria that will result in pesticides with carcinogenic, mutagenic or endocrine disrupting properties no longer being approved for use.

- Epidemiological studies need to give greater consideration to the timing of exposure, and more research should be undertaken to provide a better understanding of susceptible windows of exposure.

- Where pesticides are used, better technologies should be developed and used in ways to limit spray drift and human and non-target organism exposures. This is because there is a need to prevent other health effects and, moreover, it can be anticipated that not all pesticides which play a part in cancer will be identified and eliminated from use.

- In order to protect the public, where possible buffer zones should be established which, under proper spraying conditions, should ensure no spray drift reaches homes, schools and other public buildings.

- People living in houses bordering agricultural land should have a legal right to be notified in advance of any pesticide spraying operations, if they so request. This would give them the option to reduce their families' exposure by, for example, bringing their children in from the garden, not hanging clothes out to dry on that day, or shutting their windows.

- There should be a legal and enforced duty to display notices on footpaths before, during and after pesticide application.

- The use of pesticides in municipal and recreational settings for 'cosmetic' reasons should be phased out, and non-chemical options should always be used in public areas, where possible.

annex 1

EU cancer numbers and trends

[Credit: iSto[illegible]to/brozova]

The International Agency for Research on Cancer (IARC) estimates that one in three Europeans is diagnosed with cancer during their lifetime and one in four Europeans dies from the disease. In 2006, in the European Union (EU25), 2.3 million cases of cancer were diagnosed. In men, prostate cancer was the commonest form (accounting for 24% of all incident cases) followed by lung cancer (15.5%) and colorectal cancers (13%). In women, breast cancer was by far the most common form (31% of all incident cases), while colorectal cancer was second (13%). Cancer of the uterus was less common and accounted for 8% of cancers in women.[415]

Good trend data for specific cancers are available in some countries. In Great Britain, for example, in the 30-year period 1977 to 2006, the overall age-standardised incidence rate for cancer increased by 25%; and while in the 10-year period of 1997-2006 the overall incidence trends remained fairly constant, the highest increase was among young people aged 15 to 34.[416]

The cancers that have increased dramatically should be the focus of particular attention. Some have some well known causal factors, including melanoma of the skin (sun exposure), lung cancer (where the increase is in women smokers), liver cancer (alcohol) and mesothelioma (asbestos). Prostate cancer also seems to have undergone a real increase, although a large proportion of the reported tripling in incidence during the last 30 years[417] is thought to be due to better diagnostic techniques.[418]

Other cancers that have shown big increases[i] in Britain over the last 30 years (1975/6 to 2005/6) include the following:

- Testicular cancer - doubled[419]
- Breast cancer in women - increased by about two thirds (64%)[420]
- Breast cancer in men - more than quadrupled[421]
- Non-Hodgkin's lymphoma - more than doubled (an increase of 153%)[422]
- Kidney cancer - doubled[423]
- Multiple myeloma - increased by 60%[424]
- Brain and other CNS - up by a third (32%)[425]

Cancer rates in children have also been rising. In Britain, incidence rose by 0.8% per year on average between 1962 and 1998, making a total increase of 35% (although to what extent this increase may result from an under-diagnosis in the early years is not known).[426] A large analysis of trend data in 15 European countries found a similar annual percentage increase of 1.1% for the period 1978-1997. It was concluded that the increased incidence could only partly be explained by changes in diagnostic methods and registrations, and that the magnitude of the increase suggested that other factors – changes in life circumstances and exposure to a variety of agents, for example – had contributed to the increase in childhood cancer.[427]

Within the total increase in childhood cancer in Britain between 1962 and 1998, there were differences in trends between various cancers. For example, from 1963 to 1997 the average annual increase was 0.6% per year for leukaemias and lymphomas, 1% for brain and spinal tumours and 1.4% for bone and soft tissue sarcomas.[428]

[i] It should be noted that these increases are not due to population ageing, as cancer rates are age adjusted.

annex 2

introduction to chemicals causing cancer, susceptible windows of exposure, and occupation-related cancers

Chemicals causing cancer

Many chemicals are known to cause cancer. For example, it is well known that smoking cigarettes or exposure to asbestos, benzene, arsenic or vinyl chloride increase a person's chances of getting certain cancers.

Since 1971, more than 900 agents and chemicals have been evaluated for their ability to cause cancer, some 400 of which have been identified by the International Agency for Research on Cancer (IARC) as carcinogenic or potentially carcinogenic to humans.[429] However, with thousands of chemicals traded in volumes of over 100 tonnes a year, many of which have not been thoroughly tested, it can reliably be predicted that many chemicals which cause cancer have not yet been identified.

It is known that globally the acute effects of pesticides give rise to 355,000 people being unintentionally fatally poisoned each year.[430] But just how many die from chronic effects such as cancer is not known with any certainty, although one researcher (Schottenfeld) has estimated that in the US pesticides might be linked to less than 1% of total cancer cases.[431] Even working with a figure of 0.5% of all cancers, this would amount to some 11,500 cancers a year in the EU – which shows the potential benefits of better pesticide regulation.

Identifying which chemicals (particularly which pesticides) can cause cancer should be an important part of any cancer prevention strategy. There is currently much research into which genes may make a person more susceptible to cancer. Perhaps what deserves more attention is which chemicals can cause cancer, which carcinogenic exposures are preventable, and during what time of life people are particularly susceptible to carcinogens.

[Credit: iStockphoto/Hofmeester]

Susceptible windows of exposure

Better understanding of susceptible windows of exposure could greatly improve epidemiological studies and cancer prevention strategies.

It may be during early life when potentially harmful exposures can particularly cause most damage. Exposure to X rays in the womb, especially during the first trimester, increases the risk of leukaemia in children.[432] Similarly, animal data suggest that prenatal exposure to some hormone disrupting chemicals may affect later breast cancer risk.[433] Prostate cancer, too, appears to be possibly linked to in-utero exposure altering gene behaviour leading to cancer in later life.[434] Childhood may also be an important time, and it is noteworthy that with regard to several cancer sites, a review has suggested that children may be particularly sensitive to the carcinogenic effects of pesticides.[435]

For some cancers, the time around puberty may also be a critical period: research some years ago showed elevated numbers of breast cancer cases in women who were exposed before or during puberty to the massive levels of radioactivity from the bombing of Hiroshima and Nagasaki.[436] Similarly, evidence suggests that exposure to DDT before puberty, but not after, increases the risk of breast cancer.[437] Ageing may also bring about a higher risk – for example, it seems that older workers at nuclear power plants are more susceptible to radiation-related cancer.[438, 439, 440]

Taking due account of the timing of exposure is vital in epidemiological studies, or false assumptions may be made about the safety to humans of particular chemicals. It may also mean that extrapolating the safety or otherwise of chemicals from studies on people exposed in the workplace will grossly underestimate the total cancer burden due to chemicals in the population at large – particularly if in-utero, pre-pubertal or indeed later life exposures are most problematic. Moreover, in some instances, unprotected rural populations might be exposed to higher levels of pesticides than those found in the workplace, where protective clothing and other controls may be in place.

Occupation-related cancers

Occupational exposures tend to be relatively better known than those of the general population, so they lend themselves more easily to epidemiological study. Overall, the World Health Organisation considers that occupation-related cancers account for 10% of all cancers, and indeed many researchers have produced estimates that this figure is in the range of between 2-10% of all cancers.[441, 442, 443, 444] However, there are very good reasons to suggest that this figure may be in excess of 13%.[445]

Some time ago, Doll and Peto suggested that only around 4% of cancer deaths were due to occupation.[446] But their work has since been disputed (and, some feel, discredited) due to data limitations[447] and recent reports about the industry funding received by Doll.[448, 449] Also, many cancer experts now challenge the concept of 'attributable fractions', and are particularly concerned that this early work has led to cancer policy largely ignoring many of the preventable cancers and addressing only those agents, such as tobacco and asbestos, known to play a part in large numbers of cancers.[450]

Thus, many cancer experts now argue that due to the interwoven nature of cancer causation, it is impossible, futile and erroneous to try to add up all the possible factors to which cancer can be attributed to provide a summation of 100%. For example, Montagnier from the Pasteur Institute is quoted as challenging the view of those clinging to the old paradigm: "And what my colleagues often don't understand is that there's an accumulation of these doses – they all add up. A little dose of radiation here, and exposure to some chemical there, a bit of something in your food, and so on... All of this adds up to create an oxidant field and it's the totality of this field which does all the damage and may bring about a cancer."

Therefore, when considering the following discussions, it needs to be firmly borne in mind that official estimates are fraught with over-simplification in terms of the cancer causation pathways, so are likely to grossly underestimate the role that chemical exposures may have in cancer. In Britain, the official estimate is that 5.3% of cancer deaths were attributable to occupation in 2005; this was derived in a 2010 published study for the UK Health and Safety Executive (HSE), which considered 24 cancer sites, 41 separate carcinogens and 60 industrial sectors. This same study suggested that the overall burden of occupational cancer in Great Britain was around 8,000 deaths and 14,000 cancer registrations a year[451] and it included cancer caused just by occupational factors (including sun exposure, environmental tobacco smoke (i.e. 'passive smoking'), shift work and chemical exposures etc. The report only touched on a small number of pesticides linked to cancer – mainly insecticides and one category of herbicides – and to a relatively small number of cancers linked to work in agricultural and horticultural activities. Thus, this study for the HSE did not cover all pesticides linked to cancer cited in this review. Its estimates are therefore very limited and seriously underplay the cancer risk from pesticides posed both to those working and living in rural areas.

This HSE study also suggested that occupational exposures causing just six cancers – bladder, lung, non-melanoma skin, sino-nasal, leukaemia and mesothelioma – made up 4.9% of total cancer deaths in 2004.[452, 453] But this research, suggesting that occupational cancer accounts for around 1 in 20 cancer deaths, has several methodological problems which, in addition to the 'totality of the oxidant stress' issue, is also likely to result in underestimation of the overall true occupational cancer burden.

For example, the research was largely based on studies of workers with high exposure to known or likely human carcinogens and it disregarded the widespread low exposures to human carcinogens, exposures to suspected carcinogens without good human data, and general air pollution. Some experts have noted that the HSE figure of 4.9% is likely to be a gross underestimation, not only due to these limitations, but also because the HSE work did not take into account the effects of simultaneous exposures to certain compounds. Nor did it consider 'unknown' carcinogens – and certainly many chemicals have not been adequately tested for their ability to cause cancer.[454]

Other flaws in the HSE's estimate will arise because there are many methodological challenges, particularly in terms of estimating exposed populations in agriculture, horticulture, forestry and gardens, estimating exposures, and attributing the risks. Even where known carcinogens are used in UK workplaces, there are inaccurate estimates of those exposed and weak control standards may be ineffectively or never enforced, especially in small and medium-sized enterprises.

The UK also lacks a comprehensive list of occupational and wider environmental carcinogens. This means populations exposed to carcinogens, the number of carcinogens they are exposed to, and the years of exposure to carcinogens that may occur in those working up to and beyond 65, can all be seriously under-estimated. In an attempt to rectify the under-estimation that is considered to exist, some public health experts believe that, for example, one in five UK workers is exposed to carcinogens.[455]

Leaving aside the difficulties of acquiring good data on the role occupational exposures play in cancer, exposures in the wider environment also play an important part. However, what proportion of cancer cases might, in addition, be caused by chemical exposures in the population at large is even more difficult to determine – not least because it's at present impossible to evaluate with accuracy what role low-level exposures play in the development of cancer. Nevertheless, according to the American Cancer Society, "there is reason to be concerned about low-level exposures to carcinogenic pollutants because of the multiplicity of substances, the involuntary nature of many exposures, and the potential that even low-level exposures contribute to the cancer burden when large numbers of people are exposed". Expressing similar concerns, the US President's Cancer Panel noted the growing body of evidence linking environmental exposures to cancer, which had hitherto been grossly underestimated.[456]

Concerns about the role of pesticides in cancer arise not only because of their toxicity, but also because their diffuse use (on crops grown on farms, on animals used for meat and milk production, on allotments or in the garden and on pests in the home) means there is potential for widespread exposure of susceptible populations from spray drift, contamination of soil, water and the indoor environment, and from food chain contamination. These vulnerable people include the elderly, pregnant women and pre-pubertal children.

Occupational exposures of adults tend to be more studied than those of the general public, and therefore this review includes several epidemiological studies of pesticide manufacturers and farm workers. However, we know that 'quadruple jeopardy' will apply to many exposed to pesticides, in terms of pesticide exposures at work (eg. pest control in offices), leisure (eg. pesticides used in the country or on sports fields), in the home (eg. pesticides on carpets, fabrics and pets) and for example, via food.[457]

Studies of families on farms may provide more useful data because these are more likely to capture vulnerable windows of exposure, and because pregnant mothers and young children will be exposed via pesticide residues that find their way into their home.[458] A large study of farming families in the US is now shedding light on some of the long term-health concerns associated with farming. This initiative, the Agricultural Health Study, has 89,000 participants, including farming families and professional sprayers. It is sponsored by the US National Institutes of Health (specifically the National Cancer Institute and the National Institute of Environmental Health Sciences) and the Environmental Protection Agency, with the work being done at the University of Iowa and Battelle Centers for Public Health Research and Evaluation. Children in general may be particularly vulnerable to the effects of pesticide exposure, and it also seems that they may be exposed to higher levels of certain pesticides than adults in the general public.[459]

annex 3

identifying pesticides causing cancer, and EU legislation on pesticides

[Credit: iStockphoto/Radiant Byte]

To secure cancer prevention, chemicals which cause the disease need to be identified so that they can be prevented from being marketed in the first place. However, the unfortunate reality is that many industrial chemicals have not been tested before being widely brought into use, and others have not been adequately tested. The new EU REACH legislation (Regulation 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals) for industrial chemicals is now being implemented – but even so, it will only require substances produced above certain tonnages to be tested for carcinogenicity.

Previously, many pesticides had also been inadequately tested for their cancer-causing properties prior to marketing. For example, in 1991 in the US National Cancer Institute and the National Toxicology Programme, only 47 pesticides had been tested on rodents, with evidence of carcinogenicity for half of these.[460] In the EU, a similar 'catch-up' testing programme was brought in as laid down in Directive 91/414/EEC, and by March 2009, this pesticide review programme was eventually completed. About 1,000 existing pesticides on the market prior to 1993 were subject to this review programme, but only some 250 passed the harmonised EU safety assessment. Most substances (67%) were eliminated because dossiers were either not submitted, were incomplete or were withdrawn by the industry. About 70 substances failed the review and were removed from the market, because evaluation showed they were not safe enough for use.[461]

The European Commission has now created a list of approved active substances and member states may authorise only plant protection products containing such substances (a database is available on the European Commission website).[462] Even so, concern remained that some pesticides warrant better regulation – which is why new legislation on pesticides, outlined below, was agreed in 2009.

Currently, to test for the cancer-causing properties of a substance, the primary experimental approach is to expose rats and mice to relatively high doses of the substance for a couple of years. The vast majority of substances that are carcinogenic in humans are also carcinogenic in laboratory animals,[463] so relying on animal tests is a useful option in some cases until equally robust non-animal test methods are available. However, as noted earlier, a problem with these test methods is that they do not include the period during development in-utero, although there is evidence that this would increase the sensitivity with which cancer-causing agents could be detected. Some fast and cheap in-vitro test methods which can identify genotoxicants are already available.

To minimise animal testing, developing and implementing non-animal test methods to reliably identify cancer-causing substances should be a priority.

EU Pesticides Regulation 1107/2009

The new EU Plant Protection Products Regulation (EC No 1107/2009)[464] seeks to protect human health and wildlife. It will be used to eliminate exposure to pesticides which are PBT (persistent, bioacccumulative and toxic), vPvB (very persistent and very bioaccumulative), persistent organic pollutants (POPs), mutagenic, carcinogenic, or have endocrine disrupting properties. This new Regulation applies from 14 June 2011, and brings in so-called 'cut-off criteria' for pesticides with certain properties. Specific cut-off criteria include:

- mutagens Category 1A or 1B;
- carcinogens Category 1A or 1B, unless human exposure is negligible;
- reproductive toxicants Category 1A or 1B, unless human exposure is negligible; and
- pesticides with endocrine disrupting properties, unless human exposure is negligible.
  (See Annex 4 for explanation of Categories).

It is therefore expected that several pesticides will, in future, no longer be approved for use.

There have been some alarmist claims about the consequences of this new Regulation – that it will threaten crop yields, lead to increased food prices,[465] and will result in the inability to grow some crops in certain parts of the EU.[466, 467] However, the Regulation ensures that where there are valid concerns about there being no alternative to contain a threat to crops, exceptions can be made.

It allows temporary authorisation of pesticides not complying with provisions related to endocrine disrupting properties or suspected cancer-causing properties (provided there is a threshold for effects) because of a danger or threat to plant production or ecosystems which cannot be contained by any other reasonable means (see Preamble 32 & Art 4(7) & Art 53). Furthermore, there are transitional provisions, whereby existing approvals are valid for 5-10 years following the date when they were granted under earlier legislation (Directive 91/414/EEC – see Article 80). So not all pesticides with such undesirable properties will come under the hammer straight away.

The Regulation stipulates that use of a pesticide will not be allowed if it has endocrine disrupting properties that may cause adverse effects in humans, unless human exposure is negligible. Similarly, the pesticide will not be allowed if it has endocrine disrupting properties that may cause adverse effects on non-target organisms, unless their exposure to that active substance is negligible (see Annex II, 3.8.2).

However, the Regulation does not provide specific scientific criteria for the assessment and decision on which substances can be judged to have endocrine disrupting properties. Such criteria are to be presented by the European Commission by mid-December 2013. Until such time as criteria for endocrine disruption are brought forward, any pesticide classified as a Category 2 carcinogen (C2) and a Category 2 reproductive toxicant (R2) or R2 with toxic effects on the endocrine organs, will be considered to have endocrine disrupting properties.

Relevant parts of Annex 2 of the text of the Regulation (1107/2009) are reproduced below, and it can be seen that the provisions apply to all substances in the pesticide formulation, not just the active ingredient. Annex 4 of this report provides extracts from the classification and labelling legislation and explains the definitions and categories of mutagens, carcinogens and reproductive toxicants.

"3.6.2. An active substance, safener

EU Pesticides Regulation 1107/2009 *(cont)*

or synergist shall only be approved if, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as mutagen category 1A or 1B.

3.6.3. An active substance, safener or synergist shall only be approved, if, on the basis of assessment of carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1) (b) of Regulation (EC) No 396/2005. [ii]

3.6.4. An active substance, safener or synergist shall only be approved if, on the basis of assessment of reproductive toxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.

3.6.5. An active substance, safener or synergist shall only be approved if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not considered to have endocrine disrupting properties that may cause adverse effect in humans, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No 396/2005.

By 14 December 2013, the Commission shall present to the Standing Committee on the Food Chain and Animal Health a draft of the measures concerning specific scientific criteria for the determination of endocrine disrupting properties to be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 79(4).

Pending the adoption of these criteria, substances that are or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogenic category 2 and toxic for reproduction category 2, shall be considered to have endocrine disrupting properties.

In addition, substances such as those that are, or have to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 2 and which have toxic effects on the endocrine organs, may be considered to have such endocrine disrupting properties."

[ii] The default value set in accordance with point (b) of Article 18(1) of Regulation (EC) No. 396/2005 is 0.01 mg/kgfood.

Just how many pesticide active ingredients might be impacted by the cut-off criteria for CMRs and endocrine disruptors in this new Regulation is not known with certainty, but an initial study suggested it might be around 7%. For example, the Swedish Chemicals Agency (KEMI) examined 271 active substances and considered that seven met the criteria for CMRs and fifteen might be considered to be endocrine disruptors, with some overlap between the two, such that this was nineteen pesticides in total. Those listed as potentially meeting the cut-off criteria for both their CMR and endocrine disrupting properties include linuron, flusilazole and flurprimidol. Those listed for just their CMR properties are glufosinate, carbendazim, dinocap and flumioxazin, while those listed for their endocrine disrupting properties are amitrole, ioxynil, molinate, tepralozydim, tralkoxydim, epoxiconazole, iprodione, mancozeb, maneb, metconazole, tebuconazole and thiacloprid.[468] However, this assessment should not be taken as a definitive.

In December 2008, the UK Pesticides Safety Directorate published an update of their earlier assessment of a selection of almost 300 pesticide active ingredients, and identified those which might be caught by various cut-off criteria. This suggested that a greater number of pesticides might be impacted.[469] In 2008, another impact assessment (Blainey et al.) was also published and this outlined an amalgamated list of pesticides which might not be approved for use in future, based on the assessments of the UK Pesticides Safety Directorate and environmental non-governmental organisations. However, the impact of the Regulation will ultimately depend on the scientific criteria for the determination of endocrine disrupting properties that are yet to be agreed, although a subsequent summary impact assessment has been published. (see http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/Outcomes_paper_-_summary_impact_assessment_(Jan_09).pdf).

The names of chemicals (including pesticides) known or suspected to have endocrine disrupting properties can also be found in reports on the European Commission's website.[iii] The EC now has a list of around 200 substances which show clear evidence of endocrine disrupting effects. Given the possibility of additive effects from simultaneous exposure to several hormone disrupting chemicals, any exposure – even to low levels of a particular hormone disrupting pesticide – might be expected to potentially contribute to an effect. Therefore, it would be wise to ensure the EU legislation is strictly implemented in order to try to eliminate exposure to hormonally active pesticides. Indeed, the new Regulation requires that cumulative effects are considered, and for example, that residues should

> *"not have harmful effects on human health, including that of vulnerable groups, or animal health, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available, or on groundwater." (Article 4(2)(a))*

The reality is that exposure to endocrine disrupting chemicals from all sources, not just pesticides, might contribute to cumulative effects. Exposure to multiple chemicals by multiple routes needs to be taken into account, and given the complexity of this, the practical option of regulating pesticides on the basis of certain hazardous properties, rather than just a formal individual pesticide risk assessment approach, has been adopted.

There are likely to be considerable financial and health benefits from more tightly regulating pesticides by ensuring that, where necessary, safer substitutes are used. Such benefits will accrue not just with respect to cancer reduction. For example, a World Bank study[471] estimated that in developed countries, pollution from agro-industrial chemicals and chemical pollution from diffuse sources caused around 1.5% (that is between 0.6% and 2.5%) of the total disease burden (deaths and general ill health).

The financial and health benefits from banning certain pesticides are not easy to attribute because of the difficulty in establishing causation of health effects. Nevertheless, a study commissioned by the UK Pesticides Safety Directorate estimated the potential benefits of banning just seven active pesticide ingredients to be at least somewhere in the region of £93 -186 million as a result of avoiding cancer in spray operators alone, and perhaps up to as much as £354 -709 million in the case of the most exposed farm workers over 30 years.[472] Blainey et al (2008) noted that if these figures were scaled up to apply to the EU, which is roughly eight times the size of the UK, the benefits of withdrawing approvals for those substances could be as much as €3,568 - 7,160 billion over 30 years in the case of the maximum exposed farm population.[473] Such estimates illustrate that the new pesticides legislation has the potential not only to alleviate much suffering, but also provide significantly reduced health spending due to a reduction in the burden of cancer.

[iii] http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm

annex 4

classification of CMRs in the EU

Table 2: Hazard categories for germ cell mutagens

Categories	Criteria
CATEGORY 1 Category 1A Category 1B	Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans. The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans. The classification in Category 1B is based on: • positive result(s) from in-vivo heritable germ cell mutagenicity tests in mammals; or • positive result(s) from in-vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity / genotoxicity tests in germ cells in-vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or • positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.
CATEGORY 2	Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: • positive evidence obtained from experiments in mammals and/or in some cases from in-vitro experiments, obtained from: • somatic cell mutagenicity tests in-vivo, in mammals; or • other in-vivo somatic cell genotoxicity tests which are supported by positive results from in-vitro mutagenicity assays. Note: Substances which are positive in in-vitro mammalian mutagenicity assays, and which also show chemical structure activity relationship to known germ cell mutagens, shall be considered for classification as Category 2 mutagens.

For the purposes of the EU pesticides legislation, the definition and categorisation of carcinogenic, mutagenic and reproductive toxicant (CMR) substances are laid down in EU Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances.[474]

A crucial element for assessing the predictive value of rodent tumours for human cancer hazard is whether data are adequate to exclude a genotoxic mode of action.

For the purpose of classification for germ cell mutagenicity, substances are allocated to one of two categories shown in Table 2. Test results are considered from experiments determining mutagenic and/or genotoxic effects in germ and/or somatic cells of exposed animals. (The germ cells are the cells which give rise to the gametes – sperm and eggs – while the somatic cells are other cells in the body.) Mutagenic and/or genotoxic effects determined in in-vitro tests are also considered.

Table 3: Hazard categories for carcinogens

Categories	Criteria
CATEGORY 1 Category 1A Category 1B	Known or presumed human carcinogens A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as: Category 1A, known to have carcinogenic potential for humans; classification is largely based on human evidence, or Category 1B, presumed to have carcinogenic potential for humans; classification is largely based on animal evidence. The classification in Category 1A and 1B is based on strength of evidence together with additional considerations. Such evidence may be derived from: • human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or • animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
CATEGORY 2	Suspected human carcinogens. Placing a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

A carcinogen is a substance or a mixture of substances which induces cancer or increases its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans. For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and weight of evidence considerations. These are shown in Table 3.

Reproductive toxicity includes adverse effects on sexual function and fertility in adults, as well as developmental toxicity in offspring. In this classification system, reproductive toxicity is subdivided under two main headings:

- adverse effects on sexual function and fertility; and
- adverse effects on development of the offspring.

For the purpose of classification, the hazard class Reproductive Toxicity is differentiated into:

- adverse effects
  - on sexual function and fertility, or
  - on development;
- effects on or via lactation.

Adverse effects on sexual function and fertility includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that depend on the integrity of the reproductive systems.

Adverse effects on development of the offspring includes any effect which interferes with normal development of the baby, either before or after birth, and results from exposure of either parent prior to conception, or exposure of the developing offspring

Table 4: Hazard categories for reproductive toxicants

Categories	Criteria
CATEGORY 1 Category 1A Category 1B	Known or presumed human reproductive toxicant. Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans, or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B). Known human reproductive toxicant. The classification of a substance in Category 1A is largely based on evidence from humans. Presumed human reproductive toxicant. The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2	Suspected human reproductive toxicant. Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for future parents. Therefore, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes such effects are treated separately. This is because it is desirable to classify substances causing an adverse effect on lactation so that a hazard warning can be given to breast-feeding mothers.

Classification of reproductive toxicants is made on the basis of the appropriate criteria, outlined in Table 4, and an assessment of the total weight of evidence. This means that all available information that bears on determining reproductive toxicity is considered together, such as epidemiological studies and case reports in humans, and reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs.

Evaluation of substances chemically related to the substance under study may also be included, particularly when information on the substance is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, the level of statistical significance for inter-group differences, the number of endpoints affected, the relevance of route of administration to humans, and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification.

glossary of abbreviations

CIS	Carcinoma in situ is an early form of cancer. 'In situ' means it is before any invasion of the surrounding tissue.
CMR	Carcinogen, mutagen and/or reproductive toxicant
DDT	Dichloro diphenyl trichloroethane, a persistent insecticide, now banned. Commercial DDT is a mixture of several closely related compounds. The major component (77%) is the pp isomer but the o,p' isomer is also present in significant amounts (15%).
DDE	Dichloro diphenyl dichloroethylene, a contaminant and breakdown product of DDT insecticide.
DNA	Deoxyribonucleic acid (see below in Terms and definitions).
EPTC	S-ethyl-N,N-dipropylthiocarbamate, a thiocarbamate herbicide.
HCB	Hexachlorobenzene, a persistent fungicide, now banned.
HCH	Hexachlorocyclohexane, an insecticide. Technical grade contains a mixture of isomers including alpha, beta and delta HCH (α,β and - HCH), as well as the gamma (γ) isomer. Technical grade HCH has long been banned in the EU.
γ HCH	Gamma hexachlorocyclohexane is lindane, an insecticide.
HSE	The UK Health and Safety Executive.
IARC	International Agency for Research on Cancer
MRL	Maximum residue limit (see https://secure.pesticides.gov.uk/MRLs/)
NHL	Non-Hodgkin's lymphoma.
OCs	Organochlorine chemicals.
TDS	Testicular dysgenesis syndrome.

glossary of terms

Active ingredient
The substance in a pesticide formulation that is biologically active as a pesticide.

Anti-Androgenic
A hormone disruptor which works against the male hormone, androgen.

Aromatase
An enzyme involved in the production of oestrogen that acts by catalysing the conversion of testosterone (an androgen) to oestradiol (an oestrogen). Aromatase is located in oestrogen-producing cells in the adrenal glands, ovaries, placenta, testicles, adipose (fat) tissue, and brain.

Biocides
In the EU, biocidal products are defined as *"active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, deter, render harmless, prevent the action of or otherwise exert a controlling effect on any harmful organism by chemical or biological means."*

The scope of the EU biocidal products directive is very wide, with four main groups containing 23 different product types. The four main groups are: (i) disinfectants - for home and industrial use; (ii) preservatives - for manufactured and natural products; (iii) pest control products; and (iv) other biocidal products, e.g. vertebrate control and other specialised products. In the EU, 'biocide' does not, however, include plant protection products, human medicines, veterinary medicines, medical devices or cosmetics. Therefore plant protection products, such as herbicides and insecticides, are regulated separately from biocides. (However, see below under Pesticides - throughout this report, the term pesticides includes plant protection products and biocides).

Carcinogen
A substance or a mixture of substances which induces cancer or increases its incidence.

Cancer promoter
This causes cells with DNA mutations to multiply and become tumours.

Clastogen
A substance that can cause breaks in chromosomes, leading to sections of the chromosome being altered. This is a form of mutagenesis and can lead to carcinogenesis, as cells that are not killed by the clastogenic effect may become cancerous.

Co-carcinogen
A chemical that promotes the effects of a carcinogen in the production of cancer. Usually, the term refers to chemicals that are not carcinogenic on their own. A chemical can be co-carcinogenic with other chemicals or with non-chemical carcinogens, such as UV radiation.

Dioxins
Polychlorinated dibenzodioxins (PCDDs). Dioxins are unwanted by-products of combustion, and they may be found as a contaminant in certain chlorinated compounds.

DNA
DNA (Deoxyribonucleic acid) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms. The main role of DNA molecules is the long-term storage of information, and as such it is considered to be the blueprint, containing the instructions needed to construct other components of cells such as proteins and other molecules. The DNA segments that carry this genetic information are called genes, and within cells, DNA is organised into long structures called chromosomes.

EDCs
The term 'endocrine disrupting chemicals' is interchangeable with 'hormone disrupting chemicals' or

'hormone disruptors'. Hormone disruptors are substances, not naturally found in the body, that interfere with the production, release, transport, metabolism, binding, action or elimination of the body's natural hormones, which function as chemical messengers.

Epigenetic
An epigenetic effect is an inherited change in the appearance or gene expression of an organism's offspring caused by mechanisms other than changes in the underlying DNA sequence, hence epi- (Greek: over, above) genetics. These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism, but non-genetic factors cause the organism's genes to behave (or 'express themselves') differently.

Furans
Polychlorinated dibenzofurans (PCDFs). Like dioxins, furans are unwanted by-products of combustion.

Genotoxic
This applies to agents or processes which alter the structure, information content or segregation of DNA, including those which cause DNA damage by interfering with normal replication processes, or which in a non-physiological manner temporarily alter its replication. Genotoxicity test results are usually taken as indicators for mutagenic effects.

Hodgkin's Disease or Lymphoma
Hodgkin's lymphoma is named after Dr Thomas Hodgkin, the first person to document it back in 1832. It is a cancer of the lymphatic system characterised by cells called 'Reed-Sternberg cells'.

Leukaemia
A cancer of the blood or bone marrow characterised by an abnormal increase of blood cells, usually leukocytes (white blood cells). Leukaemia is a broad term covering a spectrum of diseases.

Melanoma
Melanoma is a tumour of melanocytes which are found predominantly in skin and are responsible for the production of the dark pigment melanin. Melanoma is one of the less common types of skin cancer but causes the majority of skin cancer related deaths.

Multiple myeloma
A cancer of the white blood cells known as plasma cells, which are a vital part of the immune system responsible for the production of antibodies.

Mutagen
A mutagen causes a permanent change in the amount or structure of the genetic material in a cell. The term 'mutation' applies both to heritable genetic changes (can be transmitted to offspring) that may be manifested in the organism and to the underlying DNA modifications when known (including specific base pair changes and chromosomal translocations). 'Mutagen' is the term used for agents giving rise to an increased occurrence of mutations in populations of cells and/or organisms.

Mutagenicity
In the narrow sense of the word, this can be defined as the induction of heritable changes in the DNA sequence of the affected organism, whereas genotoxicity is often used in an overlapping but wider sense, including chromosome mutations, chromosomal aberrations and sister chromatid exchanges.

Non-Hodgkin's Lymphoma (NHL)
Lymphoma is a cancer that begins in the lymphatic cells of the immune system and shows as a solid tumour of lymphoid cells. NHL is a diverse group of cancers that include any kind of lymphoma except Hodgkin's lymphomas.

Oestrogenic
A hormone disruptor which mimics the female hormone, oestrogen.

Pesticide
The term 'pesticide' in this report includes biocides, and all plant protection products such as insecticides, insect growth regulators, herbicides, fungicides, molluscicides, algaecides etc. As defined by the UN Food and Agricultural Organisation, 'pesticide' includes "any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. The term includes substances intended for use as a plant growth regulator, defoliant, desiccant or agent for thining fruit or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport".

Safener
Certain agents are sometimes used to 'safen' the action of some pesticides – for example, a substance added to a pesticide formulation to eliminate or reduce phytotoxic effects of the pesticide to certain crops.

Soft tissue sarcoma
Cancers that develop from cells in the soft, supporting tissues of the body. They can occur in muscle, fat, blood vessels or in any other tissues that support and protect the body's organs. Soft tissue sarcomas can also develop in specific organs, such as the uterus, stomach, skin and small bowel.

Synergist
A chemical that is added to a pesticide product, in addition to the active and inert ingredients, to increase the potency of the active ingredient.

references

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