BCUK Background Briefing | Pesticides, Organic Food and Breast Cancer

SUMMARY: Exposure to certain organochlorine and organophosphate pesticides, now banned in the UK, has been shown to increase breast cancer risk in women. Residues of these are still present in the environment and in human body tissues. Pesticides which are currently used may also increase breast cancer risk. Examples of these include the insecticide malathion and the herbicide glyphosate. Pesticides and herbicides may act as mammary carcinogens or increase breast cancer risk by disrupting hormones, especially oestrogen. Consumption of organic food reduces pesticide exposure.

Introduction

Breast cancer is the most common cancer in women globally (1). In the UK, in 2017, there were around 54,700 new cases of breast cancer in women and 390 in men (2). A person's risk of developing breast cancer depends on many factors, including those associated with age, hormones (in particular oestrogen), genetics, lifestyle and the environment. Environmental exposures which affect risk include exposure to chemicals such as pesticides. For example DDT and dieldrin have been shown to initiate development of breast cancer (3) and are now banned in the EU (4). This raises questions as to whether pesticides used currently could also increase breast cancer risk and if eating organic food, which contains less pesticide residue, could reduce risk. This brief will consider these questions.

Pesticides

Introduction to pesticides

Pesticides are substances used to kill harmful insects, fungi, weeds, and other pests, and are grouped according to their target organisms (5), see table 1. Over 1000 pesticides are in use globally (6). This brief will focus on insecticides, fungicides, and herbicides, the most commonly used by members of the public.

Pesticides may be potentially toxic to other organisms, including humans (6). Environmental exposure, which is contact with chemical substances found in air, water, food, or soil that may have a harmful effect on a person's health (7), may occur via the skin, inhalation, or ingestion; the most common being via consumption of contaminated food or drinking water. Significant exposure may also occur as a result of application of pesticides in the home or in agricultural settings. Pesticide factory workers and pest exterminators may also be affected through occupational exposure (8).

Table 1: Classification of common pesticides

Pesticide	Function
Insecticide	Kills insects
Herbicide	Kills weeds
Fungicide	Kills fungi
Rodenticide	Kills rodents

Pesticide residues

Pesticide residues may remain in or on food after pesticides are applied to food crops. The highest level of pesticide residue allowed in or on food or feed - known as the maximum residue level or MRL (9) – aims to ensure a large gap between the level permitted and the level that may lead to undesirable effects, as identified in animal experiments (10). Results from the UK government's monitoring of pesticide residues in food showed half of the tested samples contained none of the pesticides investigated, 47.6% contained a residue at or below the MRL and only 2.9% of the samples contained a residue over the MRL (11). Although MRLs for individual pesticides are generally adhered to, in many agricultural products residues of more than one pesticide are present (12). The

"maximum concentration of a pesticide residue" defined by an MRL could underestimate possible health risks if simultaneous exposures occur, that cause additive effects (13). In the EU more than 25% of conventionally grown food samples contain multiple residues; there is some evidence that suggests these may be particularly harmful to human health (14). Animal studies[1] demonstrate that mixtures of 'oestrogenic' chemicals (see box on page 3) can act together to exert an effect even when the level of each individual chemical is below the level needed for an effect on its own (15). The Pesticide Action Network UK has produced lists of the 'dirtiest' and 'cleanest' fruit and vegetables, based on how many samples contained multiple pesticide residues (see here).

Pesticides and Organic Farming

Organic farming is a system of farm management and food production "that contributes to the preservation of natural resources and applies high animal welfare and production standards" (see here) and is regulated by the *European Organic Regulation*[2]. It minimises use of fertilisers and prohibits use of most synthetic pesticides, to minimise negative environmental effects (16). All foods in the EU marketed as organic are subject to strict controls that cover the entire production chain.

There are currently 490 substances approved for use as pesticides in the EU (see here). Of these, only 28 are approved for use in organic agriculture (17), e.g. spearmint oil and citronella (see here). Organic farming relies largely on preventative and indirect measures to control pests and diseases, such as choosing species less susceptible to disease, biological control, and mechanical weeding. Pesticide application to an organic crop requires prior approval (16). Although organic produce may contain some pesticide residues, these are generally below MRLs and rarely include multiple residues (18).

Pesticides and human health

Many pesticides have been associated with detrimental health and environmental effects and are now banned. A famous example is DDT, which was banned in most developed countries after it was shown to harm or kill species beyond those targeted (19). Many factors determine the effect of a pesticide on human health, including the type of pesticide, the duration and route of exposure and an individual's health status. In humans or animals, pesticides can be broken down, excreted, or build up, in the body. Different pesticides have been detected in human breast tissue (20), breast milk, blood, cord blood, placenta, and urine (21). There are particular concerns around prenatal exposure to pesticides and the impact on development and long-term health of children (22).

Numerous health effects have been associated with pesticide exposure, including damage to endocrine (hormone), nervous, reproductive and respiratory systems and cancers (23), especially non-Hodgkin lymphoma, leukaemia and kidney, prostate, ovarian, colorectal, and breast cancers (24).

The International Agency for Research on Cancer (IARC) has classified five currently used pesticides as either 'probably' (Group 2A) or 'possibly' (Group 2B) carcinogenic to humans. Malathion, diazinon (insecticides) and glyphosate (herbicide) belong to Group 2A and tetrachlorovinphos and parathion (insecticides) belong to Group 2B (25). Of these, malathion and glyphosate are approved for use in the EU and UK (26).[3]

[1] Breast Cancer UK do not support research projects which involve animal experiments or materials derived from animal experiments.

2 Following the UK's EU departure, the UK Government is responsible for making its own decisions on whether to align with future EU bans/ restrictions or to diverge potentially allowing more pesticides onto the UK market. Visit PAN UK website here to find out more.

[3] Note: As very few pesticides have been evaluated these classifications do not necessarily imply these are more toxic than other pesticides.

Pesticides and breast cancer

How could pesticides play a role in increasing risk?

Pesticides play a role in the development of breast cancer in several ways. Animal studies demonstrate certain pesticides, e.g. the insecticide parathion (27), can act as a mammary carcinogen (cancer causing agent) by causing gene mutations (28), chromosomal damage, or forming free radicals (unstable molecules that may damage DNA) that can lead to or promote growth of cancer (29).

Pesticides may also increase breast cancer risk by acting as endocrine disrupting chemicals (EDCs), especially those that affect oestrogen signalling pathways (see box). Some mimic the actions of oestrogen (e.g. DDT, heptachlor and lindane) (30), stimulate the manufacture of oestrogen receptors (proteins that bind and activate oestrogen pathways, e.g. linuron and vinclozolin (31)), bind proteins in the blood that transport oestrogen, increasing circulating oestrogen levels, e.g. DDT, endosulfan (32, 33), or interfere with the elimination or metabolism of oestrogen, e.g. DDT (34) and endosulfan (35). Other pesticides, e.g. terbuthylazine (36) and thiamethoxam (37), increase levels of oestrogen in the body by increasing activity of the enzyme aromatase, which converts androgens (male hormones) to oestrogens. Certain pesticides can bind to other hormones and affect breast cancer risk. The DDT metabolite DDE can bind to androgen (male hormones) receptors and prevent their activation (38). As androgens can inhibit breast cancer cell growth (39), pesticides that are anti-androgenic may increase breast cancer risk. Other pesticides may interfere with the pituitary-ovarian axis (e.g. atrazine) and affect levels of oestrogen-regulated hormones associated with breast cancer risk (3). Pesticides can increase levels of growth factors, e.g. methoxychlor increases insulin-like growth factor 1 (40), which affects breast cancer development (41).

DDT can increase breast density, which is a significant risk factor for breast cancer (19). Other pesticides (e.g. chlorpyrifos) may compromise the immune system thereby increasing breast cancer risk (42).

Endocrine Disrupting Chemicals and Breast Cancer

Endocrine disrupting chemicals (EDCs) are substances that interfere with the functioning of the endocrine (hormone) system in humans and animals, altering hormone action, and resulting in harm to the health of an individual or that of subsequent generations. The mechanisms by which EDCs affect breast cancer are complex. Those best understood are EDCs that mimic the hormone oestrogen, described as "*oestrogenic*". These may increase breast cancer risk. Oestrogens (a group of female sex hormones) have essential physiological roles in both females and males. Exposure to high levels of these hormones is associated with an increased risk of breast cancer. They increase the number of cell divisions and thus the opportunity for random genetic errors which may lead to cancer. Oestrogens enter target cells, where they bind with receptor proteins, which then bind to specific regulatory DNA sequences (known as ERE), activating or suppressing oestrogen responsive genes that control cell growth and differentiation. Oestrogenic EDCs may initiate similar actions. Furthermore, many breast cancers grow in response to oestrogen therefore oestrogenic EDCs may increase growth of these types of cancers. EDC mixtures can exert a greater effect than that of individual chemicals (38).

Banned pesticides linked to breast cancer

Historically, one of the most significant groups of chemicals associated with breast cancer is organochlorine compounds, frequently used as insecticides or herbicides (70). These can persist for extended periods in the environment and in the body. They have been detected in food (43) and body fluids, including breast milk (44), and persist in adipose tissue

of animals and humans, including breast adipose tissue (20, 45).

The EU has banned several organochlorine pesticides, due to growing evidence of human or environmental harm (4). Some of these have links to breast cancer (see Table 1). For example DDT, an oestrogenic EDC, was banned in 1986, due to a number of health concerns, including an increased risk for breast cancer (46). Dieldrin, banned due to its toxicity in 1998, also increases the risk of aggressive breast cancer (47). Atrazine, a pyrethroid herbicide and oestrogenic EDC with the potential to cause mammary and prostate cancers (48), was banned in 2005 because of ubiquitous and unpreventable water contamination (49). In 2019, the EU voted not to renew approval of the organophosphate insecticide chlorpyrifos (50), which is a suspected EDC and may be associated with breast and lung cancer (24).

Although many pesticides were withdrawn from use many years ago, some associated with breast cancer are still found in the environment, for example DDT and atrazine, which continue to present a potential health risk (30).

Pesticides that increase incidence of mammary tumours in animals and/or are known, or suspected EDCs which affect sex hormones are listed below. Evidence of endocrine disruption has been reported by EFSA, MS analysis (analytical technique), by the EU's Joint Research Centre and/or by scientific literature. The list should not be regarded as definitive.

Table 1: Banned Pesticides that are EDCs and/or have been shown to cause mammary tumours. Yellow: Insecticide, Blue: Herbicide, Green: Fungicide.

UK/EU banned pesticide	EDC; effect on sex hormones	Mammary tumours	Type of Pesticide
	Organochlorines		
Aldrin (51)	Yes, oestrogenic		Insecticide
Chlordane (52)	Yes, oestrogenic		Insecticide
DDT/DDE (53)	Yes, oestrogenic		Insecticide
Dieldrin (30)	Yes, oestrogenic		Insecticide
Endosulfan (54)	Yes, oestrogenic		Insecticide
Endrin (55)	Yes, competitive binding to androgen receptors	Yes	Insecticide
Heptachlor (30)	Yes, oestrogenic		Insecticide
Lindane (30)	Yes, oestrogenic		Insecticide
Methoxychlor (56)	Yes, oestrogenic	Yes	Insecticide
	Organophosphates		
Chlorpyrifos (57)	Yes, oestrogenic		Insecticide
Dichlorvos (58)		Yes	Insecticide
Parathion (59)		Yes	Insecticide
	Carbamates		
Aldicarb (60)		Yes	Insecticide
Carbofuran (30)	Yes, oestrogenic		Insecticide
Methiocarb (35)	Yes, oestrogenic		Insecticide
	Nicotinoids		
Imidacloprid (37)	Yes, increases aromatase activity		Insecticide
Thiacloprid (37)	Yes, increases aromatase activity		Insecticide
Thiamethoxam[4](37)	Yes, increases aromatase activity		Insecticide
	Pyrethroids		
Atrazine (30)	Yes, oestrogenic	Yes	Herbicide
Cyfluthrin (61)	Yes, oestrogenic		Insecticide
Deltamethrin (62)		Yes	Insecticide
Fenarimol (63)	Yes, oestrogenic		Fungicide
Fenvalerate (64)	Yes, oestrogenic	Yes	Insecticide
Vinclozolin (65)		Yes	Fungicide
	Others		
Alachlor (53)	Yes, oestrogenic	Yes	Herbicide
Acetochlor (66)	Yes, oestrogenic		Herbicide
Captafol (67)		Yes	Fungicide
Etyhlene Oxide (68)		Yes	Fungicide
Linuron (69)	Yes, oestrogenic		Herbicide
Mancozeb (70)		Yes	Fungicide
Paraquat (70)		Yes	Herbicide
Propiconazole (36)	Yes, oestrogenic		Fungicide
Prothioconazole (36)	Yes, oestrogenic		Fungicide

[4] A pesticide containing thiamethoxam was granted emergency authorisation by the UK government in January 2021, but this was withdrawn in March 2021. The product is banned in the EU because it is harmful to bees. Link

Pesticides in current use that may be linked to breast cancer

Many pesticides which are currently used are suspected of being oestrogenic EDCs (see box) or cause mammary cancer in animals (see table 2). All may potentially increase breast cancer risk. Examples include commonly used organophosphates such as the insecticide malathion and the herbicide glyphosate, which may induce mammary tumours in rodents (59, 71), affect oestrogen signalling (72, 73). In 2015 both were classified as probable human carcinogens (27).

Epidemiological studies linking pesticides with breast cancer

Most epidemiological studies suggest past exposure to specific pesticides can increase breast cancer risk, including dieldrin, captan (87), malathion (88), (89), chlordane, 2,4-D (89) and chlorpyrifos (90). Studies that investigated a link between glyphosate and breast cancer risk found no association (87),(91).

Several studies examining general pesticide exposure with breast cancer incidence showed an elevated breast cancer risk (92–96), whereas one did not (97).

Obtaining results showing causative links from epidemiological studies is challenging. Limitations are associated with small sample size, difficulties in measuring exposures and correlating blood pesticide levels to breast cancer development, and lag-time between pesticide exposure and diagnosis (98). Furthermore, pesticide levels in blood or urine may not directly relate to what is present in breast tissue. Studies that measure pesticides in breast tissue may be more informative (20). Breast cancer can start many years before symptoms appear and measurements are only one snapshot in time which may not reflect what happened initially. Additionally, breast cancer is associated with numerous risk factors which need to be accounted for before any causal relationship between pesticide exposure and breast cancer can be found.

Table 2: EU/UK approved pesticides in current use that are EDCs and/or cause mammary tumours. Yellow: Insecticide Blue: Herbicide Green: Fungicide

UK/EU approved pesticides	EDC; effect on sex hormones	Mammary tumours	Type of Pesticide
Organochlorines			
Abamectin (74)	Yes, increases progesterone		Insecticide
Cyproconazole (75)	Yes, inhibits aromatase activity, decreases oestrogen production; increases androgen availability		Fungicide
Etridiazole (67)		Yes	Fungicide
Folpet (67)		Yes	Fungicide
Organophosphates			
Glyphosate (76, 77)	Yes, affects oestrogen	±Yes	Herbicide
Malathion (67, 73)	Yes, oestrogenic	Yes	Insecticide
Phosmet (67)		Yes	Insecticide
Carbamates			
IPBC (iodopropynyl butylcarbamate) (67)		±Yes	Fungicide
Fenoxycarb (75)	Yes, interferes with testosterone metabolism		Insecticide
Pyrethroids			
Cypermethrin (78, 79)	Yes, oestrogenic	±Yes	Insecticide
Deltamethrin (75, 79)	Yes, oestrogenic	±Yes	Insecticide
lambda-Cyhalothrin (75)	Yes, oestrogenic		Insecticide
Others			
2,4-D (2,4-dichlorophenoxyacetic acid) (80, 81)	Yes, oestrogenic	±Yes	Herbicide
Difenoconazole (82)	Yes, oestrogenic		Fungicide
Oryzalin (83)		±Yes	Herbicide
Pendimethalin (84)	Yes, oestrogenic		Herbicide
Prochloraz (85)	Yes, antiandrogenic activity		Fungicide
Prosulfuron (86)		±Yes	Herbicide
Pyriproxyfen (75)	Yes, oestrogenic		Insecticide
Tebuconazol (75)	Yes, inhibits aromatase activity, decreases oestrogen production; increases androgen availability		Fungicide
Terbuthylazine (67)		Yes	Herbicide
Thifensulfuron-methyl (85)	Yes, oestrogenic		Herbicide
Thiabendazole (85)	Yes, oestrogenic		Fungicide
Tolclofos-methyl (85)	Yes, oestrogenic		Fungicide
Triclopyr (67)		±Yes	Herbicide
Trifloxystrobin (85)	Yes, oestrogenic		**Fungicide**

± based on one *in vivo* study.

Organic Food and Breast Cancer

The few human studies that have investigated the effects of organic food on breast cancer risk have so far yielded mixed results. According to a 2018 French study, people who stated that they consumed more organically grown products, were less likely to develop various cancers, including post-menopausal breast cancer and non-Hodgkin's lymphoma, in the following years. People with the highest organic food score were 25% less likely to develop cancer than the quarter that had the least organic food (99). The authors of the US Sister Study found a lower risk of breast cancer with higher frequency of organic food consumption in almost 40 000 women, particularly oestrogen receptor-negative cancer (100).

The Million Women Study, which follows the health of middle-aged UK women, found avoiding food grown with pesticides made no difference to overall cancer risk, other than a reduced risk for non-Hodgkin lymphoma, after a follow-up time of 9.5 years (93).

It is unclear why findings of these studies vary. A potential protective effect from organic food consumption may be associated with lower exposure to pesticide residues associated with organic food, including pesticides that may affect breast cancer risk, as discussed earlier. The French study, has been criticised for not providing empirical evidence that pesticide exposure was actually lower amongst participants who ate organic food (101). This criticism could also be made regarding the Million Women Study and highlights the difficulty of interpreting results from studies based on surveys.

Is Organic Food generally "healthier"?

Many studies have assessed whether organic foods have higher levels of vitamins, minerals, and phytochemicals compared to the same foods grown conventionally. Some studies do show certain organically grown food products provide significantly higher levels of vitamin C, iron, magnesium, phosphorus and polyunsaturated fatty acids compared with the same non-organic food-products (102). In addition, organic foods were found to provide higher levels of important antioxidant phytochemicals (anthocyanins, flavonoids, and carotenoids) (103). However, despite these differences, nutritional intervention studies have not shown a clear association between antioxidant levels in humans and whether or not food consumed was organically produced (104).

Several observational studies have described beneficial effects of organic food on allergic, atopic, eczema and asthma symptoms, as well as other hypersensitivity diseases (105). The use of antibiotics as a prophylactic treatment is forbidden in organic farming. The misuse of these drugs has contributed to antibiotic resistance (106), where potentially harmful bacteria are no longer susceptible to antibiotics.

There is one risk factor around nutrition that has been proven to influence the risk of breast cancer: being overweight/obese. Many pesticides (e.g. DDT) dissolve in fat (lipophilic) rather than water and therefore more body fat (which includes the breast, which has a very high fat content) will enable a greater body burden of fat-soluble pollutants (107). Even more importantly, higher body fat and weight gain are well-recognised risk factors for breast cancer in post-menopausal women. +The current dietary guidelines, which recommend eating more fruit, vegetables and plant foods, should be followed, even if organic produce is unavailable.

Conclusion

In this brief we have highlighted how different pesticides have the potential to increase the risk of breast cancer. Several legacy pesticides have been

shown to be carcinogenic. Many pesticides in current use increase mammary cancer in animals and are EDCs which exert weak oestrogenic effects individually, but when present as mixtures, may have significant effects.

Organic food contains lower pesticide residues than conventionally grown food. While the impact of reduced pesticide exposure from organically produced foods on breast cancer risk is not clear, we know that some pesticides no longer in use increase breast cancer risk. So, as a precautionary measure, we recommend reducing pesticide exposure by growing or buying organic produce, washing, and brushing fruits and vegetables before use. Peeling removes pesticides that have seeped into fruit and vegetable skin, however non-peeled produce contains higher amounts of vitamins, minerals and other beneficial plant compounds, compared to peeled counterparts.

Many studies on pesticide exposures and cancer do not examine breast cancer or do not include women. There is a need for more multidisciplinary research based on *in vitro* technologies identifying EDCs and assaying mixtures, combined with epidemiological studies (including measurements of pesticides in breast tissue) that investigate women's exposure to pesticides and other environmental pollutants and breast cancer risk. Only then will we gain a better understanding of risk and the underlying mechanisms linking pesticides to breast cancer.

About Breast Cancer UK

Who are we?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. We fund scientific research that helps to better understand what risk factors contribute to breast cancer and how to address them.

For further information on breast cancer risk factors visit our website www.breastcanceruk.org.uk
To view this information in a more accessible format or to provide feedback, please contact us.

Disclaimer

This brief is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing, but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

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