

Critical Windows of Susceptibility for Breast Development

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Peer reviewed by two members of Breast Cancer UK independent Science Panel

1. Summary

The normal growth and development of the human body is a critical and highly sensitive process. Despite humans continuously developing throughout life, there are certain periods of development which are more sensitive to adverse factors. These are known as critical windows of susceptibility and include development in utero (in the womb), the postnatal period, puberty, pregnancy and menopause. During these periods the mammary gland (breast) undergoes extensive development. Research suggests that exposure to harmful chemicals such as endocrine disrupting chemicals (EDCs) during these critical periods may adversely affect normal development. In the case of in utero exposure, these effects may be programmed during early development but not manifest until adulthood. Limited research is available on how chemical exposure during these periods affects breast cancer risk. Yet some studies suggest that risk may be increased, likely due to the altered development of the mammary gland.

2. Introduction

Human development is a process that starts in the first few weeks of foetal life and continues throughout life. The prenatal and postnatal periods, puberty, pregnancy and menopause are highly sensitive stages of life. These highly sensitive periods, largely part of normal growth and development, are also known as “critical windows of susceptibility” [1].

In humans, most of the internal organs and systems develop in the first 12 weeks of pregnancy (see Box 1), making this potentially the most crucial developmental period [2]. Even though the placenta acts as a protective barrier,

it cannot stop all substances from reaching the developing foetus [3]. This leads to concerns over what the foetus is exposed to in utero (in the womb), including harmful environmental chemicals.

Most tissues and organs continue their development after birth in the postnatal period. Others, including the breast, do not fully mature until puberty [4]. Therefore, these periods are also susceptible to exposure to harmful chemicals.

The human breast (or mammary gland) is a highly specialised tissue responsible

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Box 1: Overview of foetal development

Full-term pregnancies usually last for 9 months, with the developmental stages of pregnancy split into three 3-month periods known as trimesters.

First trimester [2,108]: The egg is fertilized and immediately begins to divide rapidly. 3-5 days after fertilization, the egg implants into the wall of the uterus. The dividing cells then split into two sections, with the embryo and placenta starting to form. At 5 weeks, the brain, spinal cord, and heart begin to form, with arm and leg buds appearing at 6 weeks. Towards the end of the first trimester, all major organs have begun to form, including the mammary glands.

Second trimester [109,110]: Bone, skin and muscle continue to mature, forming a more complete skeleton. By 14 weeks, the foetus' sex becomes apparent as ovarian follicles form in females and the prostate forms in males. By the middle of the second trimester eyebrows, fingernails, and toenails have formed, and the foetus can hear and swallow. Towards the end of this trimester, taste buds form and hair begin to grow. The lungs are also formed but are not yet functional.

Third trimester [111,112]: The skeleton is fully formed but it is still soft. The lungs are the final organ to mature completely. In the final few weeks of pregnancy, nipple and milk ducts within the mammary glands begin to form in females. For males, breast development stops following a surge of androgens (male hormones) [38]. Most babies also move to a head-down position in the uterus just before birth.

for milk production and secretion. Mammary glands distinguish mammals from all other animals and are unique as they primarily develop postnatally, meaning after birth [5].

The fully developed mammary gland is formed by a complex network of ducts terminating with lobules. The lobules (i.e., alveoli) are formed by two types of epithelial cells, the secretory luminal cells and the myoepithelial cells. The epithelial cells are responsible for milk production and are also the main target of cancer [6]. Surrounding these structures, there are fat cells, immune cells and fibroblasts. Fibroblasts are collagen-producing cells that help form a structural framework to support the main cellular structures [7].

The mammary gland development occurs in many different stages [4] (Figure 1). During foetal life (in utero, i.e., in the womb), the main duct structures are formed and are then significantly

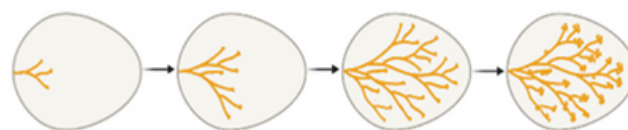


Figure 1. Development of the female mammary gland throughout life. At birth, the mammary gland is minimally developed with few main epithelial structures forming the ducts (long tubes), and consists of mainly fat cells. During puberty, the gland undergoes significant expansion and branching known as ductal morphogenesis, which fills the fat with ducts and lobules (the end of the branches, also known as acini or alveoli). These structures consist of epithelial cells and form what is known as the epithelial mammary tree. By early adulthood, ductal morphogenesis is complete. When pregnancy occurs, there is a significant increase in the number of alveoli as this is the site of milk production [7].

expanded during puberty. During pregnancy, the lobules reach full maturity allowing for milk production, which is regulated by the hormone prolactin. After lactation ends, the epithelial cells return to their non-functioning state. Further changes to the mammary gland occur later in life with atrophy of the tissue, where the glandular tissue is replaced by connective and fat tissue.

The development of the human breast primarily depends on hormones, in particular oestrogen and progesterone, making mammary gland development especially sensitive to any hormone imbalance [8]. This has led to concerns about exposure, during these critical periods of development, to some environmental chemicals which can alter the normal patterns of the hormonal release and action (endocrine system) known as Endocrine Disrupting Chemicals (EDCs).

Exposure to EDCs in utero may also pose significant threats to other aspects of foetal growth, including neurodevelopment [9], reproductive health [10,11] and obesity [12].

Many EDCs are synthetic chemicals frequently identified as environmental contaminants [3]. This means they are released into the environment, often unintentionally. Other EDCs are natural chemicals, such as phytoestrogens, that can be found in certain foods [13]. Previous research has shown that certain EDCs can affect various aspects of hormone function [14]. Chemicals can bind to hormone receptors, mimicking the natural hormones and leading to their activation or can suppress their activity. EDCs can also interfere with the synthesis of endogenous hormones or, via epigenetic changes, with the expression of hormone receptors (Figure 2). Given the reliance on the endocrine system for the growth and development of the breast, there is considerable concern about how these chemicals may affect the developing mammary gland [3]. Chemicals that mimic the natural hormone oestrogen (e.g., bisphenols) are of particular concern regarding breast cancer risk [15].

Humans are also exposed to multiple EDCs throughout life, which can build up in the body and cause adverse effects when they are in combination with other

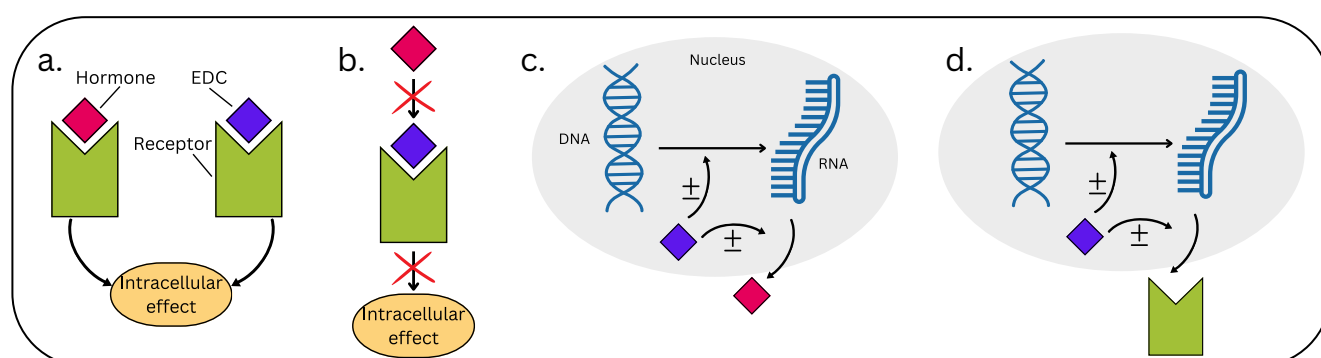


Figure 2. Endocrine disrupting chemicals (EDCs) modes of action [105]. EDCs can mimic the natural hormones and bind to the hormone receptor leading to (a) activation or (b) suppressing their activation. EDCs can (c) increase or decrease the synthesis of hormones or (d) increase or decrease the expression of hormone receptors.

chemicals compared to on their own [16].

In this review, we will discuss how exposure to EDCs during critical periods of development (in utero, postnatally, puberty, pregnancy, and menopause) may affect human health, including contributing to an increased breast cancer risk.

3. In utero

Foetal development in the womb is a time when cells are dividing rapidly, with the simultaneous development of various organs and tissues (Box 1). Therefore, it is considered by many to be the most critically vulnerable time regarding chemical exposure.

3.1 Chemicals and in utero development

During early foetal development, the foetus has no immune system to fight infection, although the mother's immune system does offer some protection throughout the pregnancy. Detoxification systems, to remove toxins, and DNA repair systems, to repair genetic damage, are also absent. Crucially for EDC exposure, no first-pass metabolism is present to metabolise and excrete chemicals [17,18]. For these reasons, the early foetal developmental stage is a period of heightened vulnerability to chemical exposure, including to concentrations considerably lower than what is generally accepted as 'safe' for adults.

EDCs have been detected in many bodily fluids, including blood and urine [19–22]. Concerningly, these harmful

chemicals have also been shown to cross the placenta [22] and have been detected in the amniotic fluid and foetal cord serum [19,22–24], as well as breast milk [19,21]. These biomonitoring studies (the measurement of chemicals in human tissues and fluids) demonstrate that exposure to potentially harmful chemicals occurs even prior to birth and at a time when the body and internal structures are rapidly developing.

Worryingly, foetal exposure to EDCs in utero may have significant repercussions on both short- and long-term health by making permanent changes in the foetus that may increase the risk of diseases later in life. This concept was first introduced by Barker in 1995 under the name of "Foetal Origin of Adult Disease" [25]. It later evolved into "The Developmental Origins of Health and Disease" (DOHaD) paradigm to include another period critical for development, the postnatal period. Exposure to certain environmental factors during the foetal or postnatal period may programme changes that will only manifest later in life [26].

Reproductive toxicants are chemicals that adversely affect fertility and the development of the offspring. Perhaps two of the most well-known reproductive toxicants are thalidomide and diethylstilboestrol (DES). Thalidomide was a drug prescribed to women in the 1950s and 1960s for morning sickness, and it caused birth defects, including limb deformities [27].

Diethylstilboestrol is an EDC with estrogenic properties. Between the 1940s and 1970s, it was prescribed to

women with high-risk pregnancies, as it was believed to be an anti-miscarriage drug [28]. It was the first chemical shown to cross the placenta and cause adverse effects that would only manifest later in life. In 1971, prenatal exposure to DES was linked to a rare vaginal cancer [28]. Since then, a higher incidence of hormone-related cancers has been observed in the offspring of women prescribed DES during pregnancy [29]. DES induces epigenetic changes (see section 3.2, “In utero exposure to EDCs”) and increases the risk of breast [30] and uterine [31] cancer in female offspring. DES has also shown multi and transgenerational characteristics impacting subsequent generations [13].

Alcohol can have a toxic and teratogenic effect due to its ability to pass through the placenta and reach the foetal organs. Foetal alcohol exposure can affect neurological (i.e., the brain and nervous system) and physical development [32]. This is known as foetal alcohol spectrum disorder (FASD). Many complications that arise due to FASD are permanent, with the severity of the symptoms linked to the quantity, frequency and timing of alcohol consumption [33]. Foetal alcohol exposure has also been linked to increased susceptibility to mammary tumours in the offspring in animal studies*[34].

Most research into the effects of EDCs in utero has been performed using animal studies. This is due to the ethical difficulties of conducting such

experiments in humans. However, epidemiological studies in humans are lengthier but possible. These studies involve measuring the chemicals to which women are exposed during pregnancy through regular urine or blood tests and subsequently monitoring the baby’s health throughout pregnancy and after birth [23].

3.2 In utero exposure to EDCs

The developing foetus and a baby’s growth immediately after birth depends on hormones, including oestrogens, androgens (such as testosterone), progesterone, insulin and thyroid hormones. These hormones are all released from the endocrine glands and transported via the blood to various target tissues and organs at specific times. This reliance of the developing foetus on the endocrine system makes this the most susceptible and sensitive period to EDC exposure.

Given that EDCs are used worldwide in many everyday products, they are almost impossible to avoid (Table 1). For further details, please see the [Chemicals and environment](#) page on our website.

EDCs differ in their origin, structure, and potency. These are some of the factors that determine how harmful their effects will be, alongside the duration of exposure and whether they can build up in the body (bioaccumulation). In addition, EDCs can act via different mechanisms in different combinations. Some EDCs can mimic the

*Breast Cancer UK does not support research projects which involve animal experiments or materials derived from animals.

activity of hormones and display androgenic or oestrogenic activity, whilst others have anti-androgenic or anti-oestrogenic properties [14].

EDC exposure during early development may also cause permanent harmful effects via epigenetic mechanisms. Epigenetics are changes affecting gene expression and function without altering the DNA sequence [13]. There are different types of epigenetic modifications. The DNA can undergo methylation, where CH₃ groups are added to the nucleotides blocking the transcription of the gene [13]. DNA methylation usually results in downregulation of gene expression. Other epigenetic alterations include changes to the chromatin and long non-coding RNAs. The chromatin is responsible for compacting the DNA, changes to this can alter the transcription of genes. Long non-coding RNAs also regulate the transcription of genes [13]. Altered gene transcription can modify expressions of genes associated with tumour progression.

Epigenetic changes are heritable changes and can affect multiple generations (multigenerational effect) and also future generations that were not directly exposed to the EDC (transgenerational effect). This is consistent with the DOHaD paradigm [13].

Exposure to ethanol through maternal alcohol consumption can cause epigenetic changes. Studies show that alcohol can alter DNA methylation on genes essential for early development, which may contribute to the

developmental abnormalities associated with offspring whose mothers consume high levels of alcohol during pregnancy [35].

Altered epigenetic programming due to in utero exposures to environmental chemicals can also cause the offspring to be more susceptible to altered neurobehavioural outcomes, obesity, impaired immune function, reproductive problems, and certain types of cancer, with these likely not manifesting until adulthood [12,36].

3.3 In utero exposure to EDCs and breast cancer

Development of the female mammary gland begins during the latter stages of the first trimester of pregnancy. This is characterised by nipple formation and branching of the first epithelial structures that will facilitate milk production in the future (Figure 1) [4]. Interestingly, much of this development does not involve oestrogen signalling, with only one area of the developing mammary gland expressing oestrogen receptors (ERs) [37]. Critical periods of susceptibility to EDCs during in utero mammary gland development also exist and may increase the risk of developing breast cancer later in life [38].

Other ways in which EDCs may increase breast cancer risk include promoting already established risk factors such as early onset of puberty and increased mammographic density [39].

In both epidemiological and animal studies, perinatal (in utero and immediately after birth) exposure to

some EDCs, including bisphenols (e.g., BPA, BPAF, BPS), was associated with early thelarche (breast development) in females [40,41], which has been associated with an increased risk of breast cancer [42]. However, for other chemicals, animal studies are less

conclusive. Adverse effects from phthalate exposure, for example, appear to depend more on the timing of exposure, dose and chemical species (i.e., the molecular weight of chemicals) [39].

Table 1. List of endocrine disrupting chemicals (EDCs)[†], their use, sources, exposure routes and whether their use is banned or restricted [3].

EDC	Use	Sources	Exposure route	Restriction or ban
Bisphenols (e.g., BPA, BPAF, BPS)	Plasticiser	Plastics bottles, toys, food cans, till receipts	Ingestion, inhalation, dermal absorption	Restricted
Diethylstilbestrol (DES)	Synthetic oestrogen, anti-miscarriage drug	Contaminated water	Ingestion, inhalation, vaginal suppository	Banned as anti-miscarriage drug
Dioxins (e.g., TCDD) [101]	Byproduct of herbicide production, paper bleaching, waste incineration	Occupational exposure, contaminated food and water	Ingestion, inhalation	Not applicable, as it is never intentionally produced
Parabens	Preservatives in personal care products and cosmetics	Personal care products, cosmetics, food	Ingestion, dermal absorption	Restricted [102]
Per- and polyfluoroalkyl substances (PFAS) (e.g., PFOA, PFOS, EtFOSAA)	Firefighting foams, food packaging, waterproof and stain-resistant clothing and furniture, non-stick cookware	Contaminated food and water, dust, consumer products	Ingestion, inhalation	Some PFAS (e.g., PFOA and PFOS) are banned or heavily restricted [103], many others are unregulated
DDT and DDE	Pesticides	Contaminated water, crops, fish	Ingestion, inhalation, derma absorption	Banned
Phthalates	Plasticiser in PVC plastics, medical devices, personal care products,	Contaminated food, consumer products, dust	Ingestion, inhalation, derma absorption	Restricted
Polyaromatic hydrocarbons (PAHs) [104]	Byproduct of fossil fuel. Present in material to make plastic and rubber	Contaminated air, food and water	Ingestion, inhalation, dermal absorption	Restricted
Polychlorinated biphenyls (PCBs)	Paint, electrical equipment	Contaminated air, food, old electrical equipment	Ingestion, inhalation, dermal absorption	Banned
UV filters (e.g., benzophenones, cinnamate and camphor derivatives)	Sunscreen and preservatives in personal care products	Personal care products	Dermal absorption	Restricted

[†]This is not a comprehensive list of all EDCs. For a more comprehensive list visit the [Chemicals and environment page](#) on our website.

For mammographic density, experiments are limited to animal studies. Markers of increased mammographic density include stiffening of the mammary gland, higher levels of collagen (a structural support protein found in the matrix between and surrounding all breast cells) and potentially an increase in the amount of stromal (e.g., fibroblasts) and epithelial cells that make up the fibroglandular component of mammographic density. Studies in rodents have shown prenatal exposure to BPA [43], 2,4 dichlorophenol (used in herbicide production) [44], and perfluorooctanoic acid (PFOA; non-stick coating) [45] can promote some of the above markers of increased mammographic density. However, more research in this area is required [39].

For bisphenols, which are EDCs known to mimic the hormone oestrogen, animal studies suggest that exposure to low concentrations of BPA between embryonic day 12.5 and 18.5 (embryonic days are measured from the day of conception) can cause developmental defects in the mammary gland [46]. BPA exposure in mice beyond this period has also been shown to affect gene expression and result in dysregulated mammary gland development [47]. These time points correspond to the end of the first trimester in humans, where the mammary gland begins to form [48], demonstrating this may be a critical period of exposure to oestrogenic agents.

In utero exposure to other EDCs has also been associated with an increased risk of breast cancer. EDCs no longer in use due to their adverse health effects,

such as DDT (an insecticide), have been associated with an increased risk of breast cancer in offspring [49].

Other factors already known to increase the risk of breast cancer in an individual may also increase the risk of developing breast cancer during adulthood if exposed in utero. Epidemiological studies have found foetal exposure to tobacco smoke may be linked to breast cancer risk [50]. Meanwhile, cell culture studies (using cells grown in a lab) have indicated foetal alcohol exposure affects mammary epithelial cells, making them more vulnerable to cancerous transformation. This could drive the formation of mammary tumours [51].

Fewer studies have documented the effects of in utero exposures to other EDCs such as PFAS, a range of chemicals found ubiquitously and used to make products stain resistant/flame retardant. An epidemiological study looked at the breast cancer risk in daughters of mothers who, during pregnancy, had high cholesterol levels and were exposed to PFAS [52]. High levels of N-ethyl-perfluorooctane sulfonamido acetic acid (EtFOSAA - a precursor of PFOS) were found to increase breast cancer risk in daughters. In contrast, high levels of PFOS were linked to a decreased risk. The association between PFAS and cholesterol is interesting, given that several studies have cited that exposure to PFAS in adults and children can elevate serum cholesterol levels [53,54]. However, the mechanisms relating to PFAS, cholesterol and breast cancer are still unclear.

4. Postnatal period

After birth, most organs and tissues continue their development. On the other hand, the breast tissue goes into a quiescent (dormant) phase until puberty onset [4].

4.1 Postnatal exposure to EDCs

Postnatally infants and children can be exposed to EDCs from the environment (e.g., toys) and through breast milk. Even though the presence of many EDCs in breast milk has been confirmed [55], exposure to EDCs through lactation and its adverse health effects has attracted limited attention.

So far, epidemiological studies have focused on postnatal exposure to EDCs and neurodevelopmental consequences. Exposure to phthalates from breast milk has been associated with neuropsychological developmental delays in infants [55,56]. Children are also exposed to phthalates from toys and dust (where phthalates accumulate) [57]. Their high hand-to-mouth and crawling behaviours make them particularly exposed to these EDCs, with levels of phthalates believed to be higher in children than in adults [38].

Regarding the effect of EDCs on breast development and breast cancer risk, epidemiological and animal studies have not analysed exclusively postnatal exposure. The vast majority of studies that have considered postnatal exposure, have investigated the whole perinatal period (in utero and infant) [3,39], making it hard to attribute adverse effects to postnatal exposure.

5. Puberty

Puberty is a time of significant physical change for both females and males and includes growth spurts, changes in body composition and further development of sexual characteristics. For females, the latter encompasses breast development (also known as thelarche). Girls tend to begin puberty earlier than boys, with onset usually occurring between 8 and 13 years old for girls, and between 9 and 14 years old for boys [58].

Thelarche is one of the most important milestones of puberty, as it usually marks the onset and is the first physical change [59].

Pubertal onset depends on genetic and environmental factors and is a period of hormone-sensitive development. In the breast, the epithelium continues to develop and branch outwards into the fat (Figure 1). This process is predominantly mediated by oestrogens [5,60]. Therefore, puberty represents another critical window of exposure for EDCs, with thelarche being a highly sensitive time for EDC exposure that may have further implications later in life, such as an increased breast cancer risk.

5.1 Pubertal exposure to EDCs and breast cancer risk

Investigating whether exposure to EDCs during puberty affects breast cancer risk in adulthood requires epidemiological studies with a significantly extended follow-up. Given that the potential adverse effects of EDCs have only become more prominent in the past 20 years, limited research has been

published on this possible link. So far, studies have mainly focused on whether exposure to EDCs in early life affects pubertal timing.

A recent study has shown the timing of pubertal onset in girls has decreased (i.e., came earlier) by an average of 3 months each decade from 1977 to 2013 [61]. Starting menstrual periods early (early menarche), i.e., before 12 years, is linked to an increased breast cancer risk in girls [62,63]. Early thelarche also correlates with an increased risk of developing breast cancer. Research suggests this association is stronger than other aspects of puberty, including early menarche. Both processes rely on hormones, including oestrogen. When these processes start at a younger age, the exposure to oestrogen throughout life is lengthened. Prolonged exposure to this hormone is considered to be a factor that can increase breast cancer risk [63,64].

Therefore, exposure to EDCs before and during puberty is also of considerable concern. Numerous EDCs have been investigated regarding early menarche, with human epidemiological studies often reporting inconsistent results [65]. Due to its ubiquitous uses in numerous everyday products, BPA is one of the most studied EDCs. Some studies have correlated serum or urinary BPA levels with early puberty, including premature thelarche and other physical aspects of pubertal development [41,66,67]. However, others have demonstrated no association between the two [65], and some have even reported the opposite effect [68,69]. Critical review studies (which account for all available data on a

given topic) on BPA's effects on pubertal timing have concluded that due to the conflicting results, it is still unclear exactly what effect BPA has on this critical development period [65,70].

A similar story is seen with phthalates, certain pesticides (DDT/DDE), dioxins and flame retardants; however, data is limited for the latter two groups. Various studies have reported conflicting results, including early and delayed puberty or no association (reviewed in [65]). One study focused on the association between EDC exposure in childhood and adolescence and high breast density (a strong breast cancer risk factor). They identified a correlation between EDC exposure during this period and elevated markers of breast density [71]. Whether this translates into an increased breast cancer risk requires long-term follow-up.

Studies have shown that phthalates with different chemical structures affect puberty in different ways [65]. Furthermore, when considering the impact of exposure to BPA and phthalates on pubertal timing, it may be important to account also for high BMI or obesity [72,73]. High BMI or obesity has been linked to early puberty, but how the combination of high BMI and EDC exposure affects puberty still needs to be clarified.

Animal studies have shown that faster mammary gland development or earlier thelarche increases the risk of mammary tumours. Thus, clarifying the effects of EDCs on breast development is crucial for determining breast cancer risk [39].

6. Pregnancy

The mammary gland undergoes a significant period of development during pregnancy, known as alveologenesis. This process is denoted by a major expansion in the main epithelial structures known as ducts, which terminate in milk-secreting buds (alveoli or lobules, Figure 1) [5]. This allows for sufficient milk to be produced for the newborn. Many hormones are implicated in this process.

Progesterone has been shown to be a critical mediator for alveologenesis, with rodent studies demonstrating that the mammary glands of mice who lack the progesterone receptor are unable to undergo this process [5,74–76]. This is similarly true for the prolactin receptor, revealing a critical role for this hormone, which is responsible, amongst many functions, for milk production [5,76–78]. Interestingly, there appears to only be a minimal need for direct action of oestrogens during this period. However, its presence in the mammary gland is thought to still be critical [79]. Oestrogen increases the secretion of prolactin from the anterior pituitary in the brain and induces the expression of prolactin and progesterone receptors in the mammary gland. This demonstrates oestrogen action is crucial for alveologenesis [76,80].

6.1 Maternal effects of exposure to EDCs during pregnancy

Exposure to EDCs during pregnancy may not only be singularly harmful to the developing foetus but may also be

detrimental to the mother, given the significant physical changes the body goes through during this period.

Exposure to chemicals has been shown to be higher in pregnant women. For example, one study estimated that pregnant women have a significantly higher BPA intake than the general adult population [81]. The reasoning behind this may be due to the increased food and water consumption by pregnant women, as ingestion is the most common route of exposure to bisphenol compounds [76]. This, therefore, raises concern as to whether an increase in the levels of other chemicals whose main route of exposure is through consumption of food and drink (e.g., phthalates, pesticides and polyaromatic hydrocarbons (PAHs)) would also be seen in these women.

Unfortunately, most research on chemical exposure during pregnancy focuses on foetal exposure, and how this impacts the risk of developing diseases later in life. Few studies have focused on the maternal effects of EDC exposure during pregnancy. Interestingly, women previously prescribed DES to help prevent miscarriage had pregnancy-related issues, including premature labour and a higher chance of spontaneous abortion and neonatal death [82,83]. Follow-up studies of these women also found that exposure to this now-banned EDC also promoted an increased risk of breast, endometrial and ovarian cancers later in life [76,82–84].

For chemicals such as phthalates, bisphenols and certain pesticides,

epidemiological and animal studies have shown their exposure to be associated with pregnancy-related issues, including preterm birth, increased risk of pregnancy loss and fertility problems. However, not all studies agree, likely due to the variation in human samples used and parameters selected for analysis (e.g., animals used, duration of exposure and concentration) [76].

More recently, countries worldwide have produced information targeting pregnant women that contains the risks of EDC exposure during pregnancy and encouraging healthier choices [85,86]. Assessment of pregnant women's current knowledge of EDCs and whether they currently make specific changes to reduce their exposure has found some interesting results. A study in France found that over half of the 300 women surveyed had never heard of EDCs. Those that had, generally could only name between 0-4 chemical groups with BPA, pesticides and parabens as the most common answers given. Other interesting statistics include that less than half (40.3%) were reducing their use of products containing chemicals during pregnancy [87].

In another study, 45% of pregnant women regarded cosmetic use as not a significant risk during pregnancy, and few were prepared to change their current habits. However, 65% of women surveyed did say that they would have appreciated receiving information and advice on cosmetic use during their pregnancy, including the potential risks they pose [88].

For all these assessment studies above,

it was found that birthplace, socio-economic status and level of education all played a significant role in whether women changed their habits with regards to EDC exposure during pregnancy [76,87,88].

There is a demonstrable need for increased research into exactly how EDC exposure during pregnancy affects the mother, not only regarding pregnancy outcome, which of course is a crucial consideration; but also concerning maternal short- and long-term health. This can help better inform women about their habits and choices surrounding products containing EDCs and their exposure to them during pregnancy.

7. Menopause

Another critical stage in a woman's life is menopause, including perimenopause and post-menopause. The perimenopause is a transition period that starts with the onset of irregular menstruation and leads to menopause. Menopause is defined as at least 12 months without menstrual activity. In the UK the average age at which menopause occurs is 51 years old [89].

A woman's body during menopause undergoes multiple changes, mainly ovarian and hormonal alteration. The breast also changes. In a process that starts around 40 years of age, the mammary gland undergoes atrophy, with the glandular tissue being replaced by connective tissue and fat [4].

Postmenopausal women have an increased risk of breast cancer

compared to other age brackets. A 2022 US study showed that 83% of all breast cancer diagnoses are in women aged 50 or above [90].

7.1 Menopause and exposure to EDCs

As for the pubertal period, so far studies have only looked at whether exposure to EDCs influences menopause timing.

Persistent EDC exposure throughout life has been linked to earlier menopausal onset [91,92]. Postmenopausal EDC exposure may also have slightly different effects, given that the responsibility of producing oestrogens is shifted from the ovaries to fat tissue, where many EDCs preferentially accumulate.

So far, studies have focused on the link between hormone replacement therapy (HRT) and breast cancer. HRT is a treatment prescribed to alleviate menopausal symptoms, such as hot flashes and night sweats [89]. Almost all HRT formulations have been linked with an increased risk of breast cancer, with a greater risk for formulations containing both oestrogen and progesterone [93].

8. Exposure to chemical mixtures

Early studies into exposure to EDCs with respect to human health primarily focused on the effects of single chemicals. This is in contrast to real-world exposure. We are exposed to a range of different chemicals and

chemical classes, all of which have slightly different effects on the endocrine system. Exposure to chemical mixtures during critical periods of development poses a significant risk and is of considerable concern, particularly for how this may affect health later in life.

The effects of mixtures are also known as 'cocktail effects' whereby a mixture of EDCs produces adverse health effects that each chemical, on its own and at the same dose, would not cause. Therefore, the effects of an EDC mixture are greater than the sum of the adverse effects seen for each EDC individually [16,94]. In the body, mixtures of EDCs may work cooperatively in activating receptors and the subsequent response [95].

Unfortunately, limited studies focus on the effects of human-relevant chemical mixtures, meaning that studies focusing on these mixtures in utero are even more limited. This was highlighted by a 2022 critical review [96]. Most studies that do focus on this topic report effects on reproductive health and function in both male and female offspring [96].

One study exposing ewes (female sheep) throughout pregnancy to a 'real-life environmental chemical mixture' found that male offspring had altered testis development which lasted into adulthood [97]. A study in young men has investigated the associations between maternal levels of PFAS in plasma samples and male offspring reproductive health in adulthood. Maternal exposure to PFAS was associated with reduced semen quality

in adult offspring [98].

Exposure to human-relevant chemical mixtures has also revealed changes to the maternal metabolome (the collection of molecules that help regulate a biological species' growth, maintenance, and normal function) of sheep [99]. A relatively high percentage (39%) of these molecules were lipid (fat compound)-based. This may have implications for foetal health as maternal lipids are significantly important in foetal development. Interestingly, the authors also observed a greater number of metabolome-related changes in mothers who had female offspring compared to those who had male. Female offspring reproductive health has also been investigated, with adverse effects on ovarian development reported in sheep when mothers were exposed to chemical mixtures [100].

In humans, exposure to a mixture of phthalates, bisphenols and organic pollutants, during foetal development was found to affect foetal weight. The authors found that growth in the early stages of pregnancy was susceptible to lower concentrations of EDCs; however, higher concentrations were required in the later stages to affect overall birth weight [101].

Few studies have been conducted regarding breast cancer risk in response to prenatal exposure to chemical mixtures. However, studies examining prenatal exposure to single chemicals have observed disruption to mammary gland development, which could influence breast cancer risk during adulthood [1,102]. Making it plausible

that exposure to chemical mixtures may promote similar or potentially even more significant adverse effects on the mammary gland.

9. Conclusions

The findings presented in this brief demonstrate that critical periods of growth and development have increased susceptibility to environmental chemicals and may increase breast cancer risk.

Given that development begins in utero, this is where most research has focused, with animal and epidemiological studies highlighting correlations between chemical exposure and adverse effects at birth. However, such studies now need to go further and have enhanced follow-up of offspring to evaluate the long-term effects of prenatal exposures, including how this affects breast cancer risk. Studies have shown that EDCs can affect mammary gland development, but how this affects offspring during adulthood and whether this increases breast cancer risk is still unclear.

Other periods of significant development for the breast tissue are puberty, pregnancy, and menopause. However, the consequences of chemical exposures during these periods on long-term health are still significantly understudied. It is noted that these studies would require many resources, but this should be balanced against the potential knowledge and benefits that could be gained from such research.

Whilst the life stages mentioned in this review are significant periods of

development and hormonal activity, it should not be forgotten that exposure to EDCs throughout life, outside these critical windows, may still increase the risk of serious health implications, including breast cancer.

The combined exposure to the chemicals in mixtures throughout life is another important consideration. Collectively, we need to move away from research that investigates a single chemical effect and move towards exposure to human-relevant chemical mixtures. This will provide a much more realistic and 'real-life' scenario for chemical exposure.

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About Breast Cancer UK

Who we are?

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. And 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 please visit our website www.breastcanceruk.org.uk

To view this information in a more accessible format or to provide feedback, please contact us.

This review 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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We welcome your feedback, if you have any comments or suggestions about this review please contact us at info@breastcanceruk.org.uk or on 0208 1327088.

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