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Background Briefing | In-Utero Exposures

Background

The prenatal phase of development is a time of rapid growth (1). Although the womb is traditionally exemplified as safe and protected, there is growing concern that prenatal exposures to harmful chemicals may lead to adverse health effects in children, some of which may not manifest until adulthood. Here, we explore the potential links between prenatal environmental chemical exposures and diseases that occur later in life, with a specific focus on breast cancer.

The role of chemicals in human development and disease

During early development, when cells are dividing rapidly and tissues and organs are forming, there is no immune system to fight infection; no detoxification system to remove toxins; and, no DNA repair systems to repair damage that may occur to genetic material. It is thus a period of "critical vulnerability" when cells are particularly sensitive to damage (5,6). Although the entire duration of foetal development is a highly susceptible period, different tissues and organs will have heightened vulnerability at different times, with varying sensitivities to different chemicals (7) (see box).

The growth of a baby inside the womb (*in utero*) and after birth, is mediated by hormones, such as oestrogens, progesterone, androgens, insulin and thyroid hormone, which are released from endocrine glands (including the placenta) into the bloodstream and transported to different tissues and organs. For normal growth and development

Overview of Foetal Development

The developmental stages of pregnancy are split into three, 3-month periods known as trimesters.

First trimester: The egg is fertilized and divides rapidly. Within 3-5 days it implants into the wall of the uterus. The dividing cells split into two sections, forming an embryo and placenta (2). At 5 weeks (3 weeks after conception), the brain, spinal cord and heart begin to form. At 6 weeks, arm and leg buds appear. Brain and spinal cord development continue throughout pregnancy. By 8 weeks all major organs and external body structures have begun to form, including sex organs and mammary glands.

Second trimester: Skin, muscle and bone continue to form, creating a more complete skeleton. At 14 weeks the baby's sex is apparent; ovarian follicles begin forming in girls and in boys the prostate appears. At 19 weeks, a vagina and uterus begin to form in girls. By 22 weeks, eyebrows, fingernails and toenails have formed and the baby can hear and swallow. At 24 weeks the bone marrow begins to make blood cells (3). Taste buds form and hair begins to grow. The lungs are formed, but do not yet function. In males, testicles begin to move from the abdomen into the scrotum and in females, eggs have formed in the ovaries.

Third trimester: Bones become fully formed, but are still soft. The lungs practice "breathing" movements. During the last few weeks of pregnancy, nipple and milk ducts begin to form. Breast development in boys stops following a surge of androgens (male hormones) just before birth (4). By the end of 37 weeks, organs

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to occur, tissues require specific concentrations of particular hormones at particular times (8). This is why early development is especially susceptible to those chemicals that disrupt the hormone (endocrine) system (so called endocrine disrupting chemicals or EDCs).

Chemicals and other agents which cause abnormal development of unborn babies are known as 'teratogens'. At their very worst, teratogens can cause a pregnancy to terminate, but they can also cause birth defects and cancers. There are a number of relatively well known teratogens such as the anti-morning sickness drug, thalidomide, used during the 1950s and 1960s (9) and responsible for multiple birth defects and rubella (German measles virus) which may lead to miscarriage or cause deafness or heart disease in children, especially if contracted by the mother early in pregnancy (10). Alcohol is also a teratogen which can affect the central nervous system (and so the brain and spinal cord) if exposure occurs anytime during pregnancy (11). Recent animal studies have shown that foetal exposure to alcohol increases mammary tumour susceptibility in adulthood (12). Teratogens that are toxins include methylmercury and lead (13). These metals are sometimes present in fish and seafood, which, if consumed in large quantities, may adversely affect neurological development.

Prenatal exposure to a range of different carcinogens can affect the health of unborn babies. Most carcinogens act by directly damaging DNA, the genetic material present in all our cells. For example, ionizing radiation exposure (via work

Prenatal exposure to some chemicals may affect the health of unborn children

related activity or from medical X-rays) has been linked with childhood cancers, neurological and growth abnormalities and an increased risk of spontaneous abortion (14). Polycyclic aromatic hydrocarbons (PAHs) are carcinogenic compounds formed following combustion of, for example, tobacco, wood and meat. Certain PAHs are known to cause mammary (and other) cancers in rodents (15), especially if exposure occurs during the first trimester (16).

Many factors determine how harmful the effects of a chemical will be, for example its structure, concentration, the duration of exposure to it, and whether it is excreted quickly or builds up in tissues of the body (bioaccumulation) (17). The mother or child's genetic make-up may also determine individual response. For example, the presence of the *BRCA1* breast cancer susceptibility gene makes some people more vulnerable to certain environmental exposures (18). Chemical compounds may have gender-specific effects, or be more damaging to one of the sexes (19).

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Exposure to mixtures of chemicals is of particular concern, as harmful effects may add up (20). In some cases, chemical mixtures may have adverse effects, even if each chemical is ineffective at an individual level (21).

in utero exposures and EDCs

EDCs can interfere with the body's normal hormone function (endocrine system), often by mimicking or blocking the action of hormones naturally produced by the body. Often, they are similar in structure to natural hormones. The endocrine system is important for regulating many physiological functions such as growth, metabolism, reproduction and stress response. EDCs therefore have the potential to disrupt the normal function of many body processes.

Suspected EDCs are present in a wide variety of everyday products including plastics, pesticides, personal care products and cleaners. Examples of suspected EDCs currently in use include bisphenol A (BPA) used in polycarbonate plastics, phthalates used in PVC plastics; pesticides such as chlorpyrifos and vinclozolin; parabens, used as preservatives in shampoo and cosmetics and the antimicrobial agent triclosan, found in personal care products (for further details see our website).

EDCs can affect the reproductive system of both sexes by interfering with hormones such as testosterone and oestrogens. Studies of wildlife and laboratory animals demonstrate that foetal exposure to EDCs may result in changes to sex ratios, deformed reproductive organs and decreased fertility in adult life (22, 23, 24). In human studies, EDCs have been associated with an increase in incidence of endometriosis, infertility and reproductive cancers (25).

EDCs are present in a wide range of products but may affect an unborn child's development.

Some changes induced by exposure to EDCs during early development may cause permanent alterations that can be passed on to future generations. Such changes may affect "epigenetic" control mechanisms, a means by which cells switch genes on or off, without altering the primary DNA sequence of a gene (26). Different cells require different genes to be active (switched on) at specific times; disruption may result in disease such as cancer or Alzheimer's in later life (27). Diethylstillbestrol (DES), used in the U.S. until the 1970s (and Europe until the 1980s) to help prevent miscarriage, is an example of an oestrogenic EDC which induces epigenetic changes in breast cells (28). In the U.S., daughters of exposed mothers have an increased risk of breast (29) and uterine cancer (30). Similarly, DDT, an insecticide once used widely in the U.S. until its ban in 1972, has been identified as an oestrogenic EDC (31). A recent U.S. study found that women whose mothers had been exposed to significant levels of DDT during pregnancy were four times as likely to have had breast cancer by the age of 52, as woman whose mothers were exposed to small quantities (32). Despite its toxicity, environmental persistence and worldwide restrictions on its use, DDT is still employed in some countries, due to its effectiveness against malaria-carrying insects (33).

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A number of reports highlight the potential problems following exposure to EDCs during pregnancy (e.g. 34,35,36). Numerous studies have demonstrated EDC effects on the immune system, central nervous system, reproductive system, urinary tract, thyroid function, behaviour and increased miscarriage (e.g. 37,38,39).

EDCs are commonly identified in animal and human body fluids and tissues (40). For example, BPA is routinely found in human urine, blood, amniotic fluid, breast milk, fat tissue and the placenta (41). Phthalates, parabens, synthetic musks (fragrances), pesticides and UV filters (42), have been shown to be present in breast milk, and polychlorinated biphenyls, dioxins and methylmercury in placenta (43).

in utero exposure to EDCs and breast cancer

There is increasing evidence that *in utero* exposure to certain EDCs may increase the risk of developing breast cancer later in life. EDCs may delay or inhibit post-natal breast development and cause a lack of response to hormones (44). They may also cause an increase in breast tissue density, a known risk factor in breast cancer, or increase sensitivity of the breast to carcinogens, thereby increasing breast cancer risk following carcinogen exposure (45). Some EDCs bind to oestrogen receptors and mimic the action of natural oestrogens (46). Binding of oestrogens to their receptors results in increased breast cell division which is thought to explain why lifelong exposure to elevated levels of oestrogens is a known breast cancer risk (47). Furthermore, oestrogen metabolites (break-down products) may increase mutations and promote cancer (48).

Prenatal exposure to EDCs no longer in use, such as DES (49) and DDT (50), is associated with increased breast cancer risk. Exposure to elevated levels of certain polychlorinated biphenyls (PCBs), may also be linked to increased breast cancer risk, specifically in young women (51). PCBs were once used widely in electrical insulating fluids and as plasticisers, and, like DDT and its metabolites, are common contaminants of soil and water. Exposure occurs following consumption of contaminated food and water.

Associations between currently used EDCs and an increased breast cancer risk are generally based on extrapolations from animal and cell culture studies. For example, studies in rodents suggest *in utero* exposure to BPA increases the risk of mammary gland tumours (52); enhances sensitivity of mammary glands to carcinogen-induced tumours (53); could cause epigenetic changes thought to contribute to the development of pre-cancerous and cancerous lesions (54); and may also induce mammary carcinogenesis by binding to oestrogen receptors present in foetal breast tissue (55).

Prenatal exposure of rats to benzyl butyl phthalate, (commonly used as a plasticiser in PVC plastics), alters the mammary gland morphology, resulting in changes in mammary tissue gene expression, previously associated with an increased susceptibility to carcer (56). Prenatal exposure to the pesticide vinclozolin was found to increase mammary cancer in offspring, and subsequent generations (57). Prenatal exposure to methoxychlor, a banned insecticide and persistent aquatic environmental pollutant (58), is also associated with increased mammary cancers (59). Prenatal exposure of rats to mixtures of common oestrogenic EDCs affected mammary gland development of prepubertal female offspring. When exposed to anti-androgenic EDCs mixtures

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mammary gland development of adult offspring was affected (60).

What can we do to reduce *in utero* exposures?

EDCs and other hazardous chemicals may be present in food and everyday products such as household cleaners, fabrics, cosmetics and medicines. There is uncertainty regarding the detrimental effects of some of these environmental contaminants. Nevertheless, we believe that pregnant and breast feeding woman should be made aware of the potential sources, possible risks, routes of exposure, and ways to reduce these. Currently, there are no UK government publications which provide advice for pregnant or breastfeeding women about the risks that environmental chemical exposures might pose for their unborn children (61). This contrasts to other countries such as Denmark, which publishes a guide for pregnant woman on how to reduce exposures to environmental chemicals (62). The Danish government also commissioned a study (63) which examined the effects on pregnant woman of EDCs present in food and the environment and concluded that these compounds may have anti-androgenic, oestrogenic and thyroid disrupting effects.

There are a number of ways that pregnant woman can minimize *in utero* exposures to EDCs (see our guides "Protecting you and your baby during pregnancy" and "Cosmetics and breast cancer information sheet"). For example, consuming fresh food and drink that is not pre-packaged may reduce intake of plasticisers such as BPA or phthalates, which can leach out of plastic containers upon heating. Avoid pesticides in the garden, buy organic where possible and minimize

exposure to paint fumes. Steps can be taken to reduce or avoid EDC-containing personal care products: such as those that include parabens, phthalates and triclosan. Taking these precautionary steps can do no harm and may help to protect your baby from future health problems.

Breast Cancer UK position:

- There is increasing evidence that *in utero* exposure to environmental pollutants is associated with disease and abnormalities in infancy and later in life, including breast cancer;
- Breast Cancer UK is calling for the Government and NHS advice services to publish a comprehensive guide for pregnant woman which explains the potential risk of *in utero* environmental exposures and their possible effects on the unborn child, and how they might minimise exposures, similar to the guide published by the Danish Environment Protection Agency; and,
- Breast Cancer UK believes greater investment should be directed towards research which helps us to understand the environmental causes of breast cancer in order that we can prevent the disease before it starts.

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