Links between Endocrine Disrupting Chemicals (EDCs) and breast cancer

Many thanks for your time in meeting with us on 9th March to discuss the UK Chemical Strategy, and our 12 Key Asks for it. We were really encouraged by your interest in addressing chemical pollution. Thank you for agreeing to speak at a future parliamentary event on the strategy, once you are able to share the Government’s initial thinking on it with NGO stakeholders. We also really appreciate the offer of a regular meeting with us.

We are writing to follow up on your question about the links between endocrine disrupting chemicals (EDCs) and hormone related cancers, to share with you peer-reviewed evidence literature and international publications demonstrating the links between exposure to EDCs and increased risk of breast cancer, as well as to other diseases.

The Impacts of Endocrine Disrupting Chemicals on Human Health

Synthetic chemicals play an important role in everyday life and can be found in an array of consumer products, industrial settings and the wider environment. An endocrine disrupting chemical (EDC) is defined as “an exogenous chemical, or mixture of chemicals, that interferes with any hormone action, resulting in harm to the health of the individual or that of subsequent generations” [ii]. We ingest EDCs through food and drink, inhale them in the air and absorb them through our skin.

We are exposed to a cocktail of hazardous chemicals in the course of our daily lives. Low dose exposure to EDCs can trigger reactions in the body that increase our chances of suffering from illnesses such as hormone dependent cancers, reproductive problems and neuro behavioural difficulties. EDCs not only impact our health but also that of subsequent generations. Poor regulation of EDCs falls more heavily on the public purse, in increased costs to health services and environmental protection.

Links between EDCs and Breast Cancer - Peer-Reviewed Literature

Breast cancer is a multifactorial disease linked to lifestyle and genetic factors, compounded by social and economic factors. According to the WHO, approximately half of breast cancers develop in women who have no identifiable breast cancer risk factor other than being female and over 40 years. There is considerable evidence linking breast cancer with environmental and occupational exposures (see referenced scientific papers below) to toxic chemicals such as EDCs, and work practices such as night shift work. While there is more we need to know about the mechanisms, we know enough about certain EDCs and other substances of concern to act now to prevent future harm.
Numerous studies have linked EDCs found in everyday products, the workplace and the environment to breast cancer risk (see references in Table 1). Examples of such chemicals include parabens, used as preservatives; phthalates used as plasticisers and as solvents in fragrance, bisphenols used in manufacture of polycarbonate plastics, resins and thermal ink, certain types of flame retardants, per-and polyfluorinated substances used as waterproofing and anti-greasing agents and UV filters used in sun-screen and in products to prolong shelf-life.

Peer-Reviewed Literature linking EDCs to Other Health Conditions
Evidence suggests exposure of the human population to EDCs is leading to an increase in the incidence of many human diseases (see references in Table 2). Examples include:

- Obesity, type 2 diabetes and cardiovascular disease following exposure to BPA, certain phthalates, the dioxin TCDD, some PFASs, some PCBs and persistent organic pollutants (Le Magueresse-Battistoni 2018; Gore et al. 2015; Kahn et al. 2020; Eales et al 2022).
- Female reproductive health problems and adverse pregnancy outcomes have been linked to exposure to BPA, phthalates and some pesticides (Gore et al. 2015, Sifakis et al. 2017; Eales et al 2022).
- Male reproductive health problems, testicular and prostate cancer have been associated with exposure to BPA, certain phthalates, certain pesticides, and dioxins (Sifakis et al. 2017; Garcia et al. 2017; Kahn et al. 2020; Eales et al 2022).
- Thyroid disruption and thyroid cancer has been linked to PCBs, certain flame retardants, dioxins, triclosan, BPA, and phthalates (Alsen et al 2021; Molehin et al. 2016; Eales et al 2022).
- Developmental, neuro-behavioural and cognitive difficulties have been linked to BPA, organophosphate pesticides, PCBs and phthalates (Mossa et al 2018; Kahn et al. 2020; Eales et al 2022).

UK and International Publications on Policy Measures to Support Disease Prevention
Chemical pollution is increasing our chances of suffering from lethal diseases. International agencies, scientists, and public health experts have called for urgent policy measures to strengthen chemical protections to support disease prevention and a non-toxic environment (see references in Table 3).

UK Chemicals Strategy: Our Calls to action
The UK Chemicals Strategy is an opportunity to minimise the adverse impacts of exposure to hazardous chemicals on the nation’s health. The harmful impacts of EDCs have been recognised for decades, yet regulatory action has been too little too late. The strategy must deliver an action plan to support a non-toxic environment and reduce deaths and illnesses from hazardous chemicals. That’s why 29 health and environmental NGOs have come together to develop 12 key priorities for the strategy. We would like to see close alignment between the UK Chemicals regulation, regulation on pesticides, worker health and safety, and all cancer plans and strategies.
In 2020, the EU published its ‘Chemicals Strategy for sustainability’ [v] and ‘Europe Beating Cancer Action plan’ [vi] committed to update the EU’s regulatory framework to support a zero-pollution ambition by speeding up EDC identification and banning their use in products. The UK Chemicals Strategy must take similar steps with timelines to prevent and minimise public exposure to EDCs.

The Chemicals Strategy has a vital role to play in reducing the 40% of preventable cancers [viii] and delivering on the Government’s public health objective of making the 2020s the decade of prevention [ix]. We need binding targets to phase out hazardous chemicals ensuring public health and precaution are the cornerstones of the strategy. That’s why we’re calling for the strategy to:

- Acknowledge health risks of EDCs and recognise them as chemicals which may increase cancer risk
- Implement criteria to systematically identify EDCs and suspected EDCs, with associated timelines to minimise and phase out exposure.
- Honour the UK’s commitment to the precautionary principle, prioritising public and workers health over commercial interests and supporting the phase out of EDCs in consumer products.
- Treat EDCs as non-threshold substances and a category of concern under UK REACH.
- Adopt a cross-governmental approach to chemicals management with DEFRA, HSE and the Department of Health working together to align commitments within the chemicals and cancer strategies to address hazardous chemicals and protect the nation’s health.

We look forward to supporting you and officials in any way possible in the coming months as work on the Chemicals Strategy develops.

We look forward to your reply,

Best wishes,

Thalie Martini, CEO, Breast Cancer UK
Roz Bulleid, Deputy policy director, Green Alliance
Dr Anna Watson - Head of Advocacy, CHEM Trust
Kate Metcalf, Co-Director, Women’s Environmental Network
Helen Lynn, Facilitator, Alliance for Cancer Prevention

Notes:

Breast Cancer UK is dedicated to the prevention of breast cancer by investigating and tackling the environmental and lifestyle causes of the disease. It is the only charity in the UK that exclusively funds animal-free research into the effects of EDCs on breast cancer risk. In recognition of the need for greater research investment to improve understanding of the chemical and environmental causes of breast cancer, its research projects focus entirely on
this area and has led to changes in policy and practice. For example, its research on bisphenol substitutes was used to support a bill by the State of New York to prevent children being exposed to these harmful chemicals [i]

**CHEM Trust** has been closely involved in the debate on EDCs over many years and are experts in this field, from both a wildlife and human health perspective. We actively contribute to discussions in EU expert groups, political and stakeholder meetings and public consultations of EU agencies, such as the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA). We are members of the European Commission’s expert group on Endocrine Disrupters.

**Wen (Women's Environmental Network)** supports women to take action on issues that connect gender, health, equality and the environment. Through collective action and campaigning, we work together towards a healthier planet. Wen has a long history of working on issues around gender, health and the environment, particularly on the primary prevention of breast cancer, given that lifestyle risk factors only account for 30-50% of breast cancer cases. Wen is currently working with the Alliance for Cancer Prevention calling for recognition of the environmental and occupational risk-factors for breast and other cancers in all cancer plans.

**The Alliance for Cancer Prevention** campaigns to reduce preventable cancer incidence by calling for recognition of environmental and occupational risk factors for breast and other cancers. The Alliance aims to challenge the existing perception of control and treatment of cancer being the best way forward and get equal recognition for primary prevention. We work to ensure that the cancer establishment acknowledges the environmental and occupational risk factors for preventable cancers.

Formed in 2009, the Alliance is a multi-stakeholder group which includes representatives from; NGOs, environmental and occupational health organisations, trade unions, public health advocates and civil society groups, to work together on cancer prevention.
Table 1:  
Studies linking EDCs found in everyday products and the environment to breast cancer risk

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<th>Publication</th>
<th>Key Findings</th>
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· Endocrine disrupting chemicals (EDCs) may enter human breast tissue from a range of environmental sources  
· Many EDCs possess oestrogenic activity (mimic oestrogen) and exposure to natural oestrogen is a risk factor for breast cancer.  
· EDCs have been shown to enable all the hallmarks of cancer to develop in human breast cancer cells.  
· Many studies report that hallmarks can develop at EDC concentrations within the range of those measured in human breast tissues, especially when added as mixtures.  
· Varied levels of different EDCs measured in individual breast tissue samples together with the overlapping and complementary mechanisms of action, imply that mechanisms will be driven by different types of chemical mixtures.  
· EDCs should be acknowledged as a risk factor for breast cancer in order for preventative strategies to include reduction in EDC exposure |
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<td>• Systematic review which investigated the association between human exposure to EDCs and the risk of breast cancer</td>
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<td>• Most studies reported that exposure to organochlorine pesticides, phthalates, heavy metals, and polycyclic aromatic hydrocarbons was associated with increased breast cancer risk.</td>
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<td>• Qualitative analysis of observational studies indicates that human exposure to EDCs is associated with increased breast cancer risk.</td>
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<td>• Additional studies are needed to determine whether this association is causal.</td>
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<th>Wormsbaecher et al. (2020). In utero estrogenic endocrine disruption alters the stroma to increase extracellular matrix density and mammary gland stiffness. Breast Cancer Research 22(1):41</th>
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<td>• Examined long-term effects of in utero exposure to BPA in rodents</td>
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<td>• Showed BPA increases collagen production and mammary gland stiffness, which are known risk factors for breast cancer</td>
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<td>• Also showed in utero exposure to DES (a compound known to cause breast cancer) also increases gland stiffness in the adult animals</td>
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<td>• Identified long-term reprogramming events within the mammary fibroblast cell population associated with in utero EDC exposures lead to increased collagen production, resulting in a stiffer mammary gland.</td>
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<td>• Data provide a mechanistic link between early life endocrine disruption and adult disease susceptibility.</td>
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| • Reviewed current knowledge about the role of environmental chemicals in breast cancer progression, metastasis formation and resistance to chemotherapy.  
- Strong evidence, mostly at the experimental level, that breast cancer progression is linked to BPA, three phthalates, benzophenone-1, nonylphenol, benzo(a) pyrene and other PAHs, iron, copper, zinc, lead, chromium and nickel.  
- PFOS and PFOA can stimulate breast cancer migration and invasion through the nuclear receptor, PPARα.  
- Epidemiological and experimental studies suggests that several PCBs are linked to breast cancer aggressiveness.  
- Certain EDCs (e.g. benzo(a) pyrene) may be linked to chemoresistance to breast cancer drugs.  
- Low levels of BPA can antagonise the cytotoxicity of multiple chemotherapeutic agents.  
- Organochlorine pesticides (DDT, DDE and dieldrin) were associated epidemiologically and experimentally to breast cancer progression through non-genomic mechanisms of action involving oestrogen receptor. |

|---|
| • Systematic review of epidemiological studies about the association of the levels of environmental exposures of EDCs with breast cancer risk.  
- Synthetic EDCs reviewed included pesticides, dioxin, bisphenol A (BPA), phthalates, PFAS, parabens, PCBs, PBDEs, contraceptive pills.  
- Certain EDC exposures (e.g. PCBs), could potentially elevate the risk of breast cancer.  
- As most EDCs are highly persistent in the environment and bioaccumulative, it is essential to assess the long-term impacts of EDC exposures, especially multi-generational and transgenerational. |
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<th>Reference</th>
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<td>Hiatt &amp; Brody (2018). Environmental determinants of breast cancer. Annual Review of Public Health 39: 113-133.</td>
<td>This review covers known and suspected environmental factors that have been associated with breast cancer and includes epidemiology, toxicology, and mechanistic studies.</td>
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<tr>
<td>Pierozan et al. (2022). Tumorigenic activity of alternative per- and polyfluoroalkyl substances (PFAS): Mechanistic in vitro studies. Science of the Total Environment 808: 151945</td>
<td>Mechanistic study of the effects of PFAS on breast cells. Five out of six PFAS increased cell proliferation and neoplastic transformation. Cell cycle proteins, nuclear receptors affected. Epigenetic changes which lead to malignancy induced by certain PFAS.</td>
</tr>
<tr>
<td>Bleak and Calaf (2021). Breast and prostate glands affected by environmental substances (Review). Oncology Reports 45.</td>
<td>Review of studies that examine the effects of BPA, DDT and PCBs in mammary and prostate tissues. BPA exposure can induce cell proliferation, morphological alterations and alter carcinogenesis in both glands. BPA, DDT and PCBs contribute to the risk of cancer particularly in mammary and prostate glands. Postnatal exposure to DDT induces male infertility.</td>
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- Examines the evidence that in utero exposure to pesticides (which are EDCs) affects mammary gland development and increase susceptibility to breast cancer
- Proliferative and organisational deregulation of mammary epithelial cells can be induced by pesticides.
- Expression and signalling of steroid receptors in the breast can be altered by pesticides
- The body burden of pesticides may increase the risk of developing breast cancer

Table 2: Studies linking exposure to EDCs with an increase in the incidence of other diseases

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- Strong evidence for the following associations:
  - PFAS and child & adult obesity, impaired glucose tolerance, gestational diabetes, reduced birthweight, reduced semen quality, polycystic ovarian syndrome, endometriosis, and breast cancer.
  - Evidence for associations between:
    - bisphenols and adult diabetes, reduced semen quality, polycystic ovarian syndrome;
    - phthalates and prematurity, reduced anogenital distance in boys, childhood obesity, and impaired glucose tolerance;
    - organophosphate pesticides and reduced semen quality;
    - occupational exposure to pesticides and prostate cancer.
    - cognitive deficits and attention-deficit disorder in children following prenatal exposure to BPA, organophosphate pesticides, and polybrominated flame retardants. |
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- Demonstrates links between exposure and manifestation of disease can be substantiated by experimental animal models and are consistent with correlative epidemiological data in humans.  
- Focused on low dose effects, *in utero* exposures and non-monotonic responses (responses typically characterized by a U- or inverted U-shaped relationship between dose and effect).  
- Found most evidence was for associations between EDCs and obesity and diabetes; male and female reproduction, hormone-sensitive cancers including breast cancer, and effects on thyroid; neurodevelopment and neuroendocrine system. |
- BPA decreases insulin synthesis and secretion after prenatal or adult exposure and decreases insulin action after prenatal, perinatal and adult exposure.  
- Good evidence of BPA toxicity on pancreatic cells  
- Evidence that BPA may increase metabolic disturbances leading to type-2 diabetes development through endocrine disruption.  
  Similarities in regulation of insulin production and sensitivity between rodents and humans and *in vitro* experimental data using human cells or tissues suggest effects will be similar in humans. |
| Sifakis et al. (2017). Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems. Environmental Toxicology & Pharmacology, 51: 56 - 70. | - Review of studies examining the harmful effects of EDCs on male and female reproductive systems  
- EDCs included BPA, organochlorine pesticides, phthalates  
- Most studies indicate an association between exposure to EDCs and reproductive disorders such as infertility, endometriosis, breast cancer, testicular cancer, poor sperm quality or function.  
- Based on animal and *in vitro* studies, EDCs affect hormone dependent pathways responsible for male and female gonadal development through direct interaction with hormone receptors or via epigenetic and cell - cycle regulatory modes of action (epigenetic changes are those which affect gene expression but do not directly alter DNA sequences). |
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· Found robust evidence for an association with lower semen quality, neurodevelopment and risk of childhood asthma  
· Moderate to robust evidence for impact on anogenital distance in boys.  
· Moderate evidence for an association between phthalates/metabolites and low birthweight, endometriosis, decreased testosterone, ADHD, Type 2 diabetes and breast/uterine cancer. |
· Evidence suggests that exposure to certain congeners of flame retardants, PCBs, certain phthalates and certain pesticides may potentially be associated with an increased risk of thyroid cancer. |
| Molehin D. et al. (2016). Prenatal exposures to multiple thyroid hormone disruptors: effects on glucose and lipid metabolism. Journal of Thyroid Research 2016:8765049 | · Review of studies of prenatal exposures of thyroid hormone (TH) disruptors on glucose and lipid metabolism  
· Prenatal exposure to TH disrupting EDCs may increase risk of adverse birth outcomes, childhood obesity, intellectual disability and adverse short- or long-term health outcomes due to foetal reprogramming.  
· TH imbalance is linked to many metabolic processes and effects are particularly pronounced in early development. Exposure to either single or mixtures of EDCs results in deleterious effects on metabolism. |
| Garcia J et al. (2017). Association of reproductive disorders and male congenital anomalies with environmental exposure to endocrine active pesticides. Reproductive Toxicology, 71: 95–100. | · A population-based case-control study on pregnant women and male children living in districts with high and low environmental exposure to pesticides (many of which are EDCs)  
· investigated the prevalence and risk of developing gestational disorders and male congenital malformations  
· Prevalence rates and risk of miscarriage, low birth weight, hypospadias, cryptorchidism and micropenis were significantly greater in areas with higher use of pesticides compared to those with lower use |

- Reviewed literature on the association of EDCs and autism spectrum disorder (ASD).
- Prenatal exposure to EDCs has been correlated with ASD and autistic traits in humans
- Due to the importance of sex hormones on brain development prenatal and perinatal exposures to EDCs may by inducing long-lasting neurological and behavioural effects through the disruption or dysregulation of hormone signalling pathways.
- EDCs are likely to exert lasting influences on the development and behaviour of organisms through the induction of epigenetic changes
- Research on EDCs in animal and cellular models have revealed large-scale changes in gene expression, particularly in pathways relevant to the pathogenesis of ASD.

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| **World Health Organisation the Public health impact of chemicals: knowns and unknowns Report (2021)** | - Estimated that 2 million lives and 53 million disability-adjusted life-years were lost in 2019 due to chemical pollution[x].
- Acknowledged that exposure to certain chemicals is associated with reduced neurodevelopment in children and increases the risk of attention deficit disorders. |
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| **Endocrine Society (2020) ‘Plastics, EDCs & Health’** | - Estimated that more than 1000 manufactured chemicals in use today are suspected or confirmed EDCs that leach from plastics and threaten public health; these include **bisphenol A and related chemicals**, organic **flame retardants**, **phthalates**, **per- and polyfluoroalkyl substances (PFAS)**, **dioxins**, **UV-stabilizers**, and **toxic metals**[xi].  
- Called for effective public policy interventions to protect public health from EDCs, given industry’s dramatic growth projections. |
| **United Nations Environment Programme Global Chemicals Outlook Report (2019)** | - Confirmed that the global goal of minimising the adverse impacts of chemicals such as EDCs would not be achieved by 2020.  
- Found that harmful chemicals such as EDCs were now “ubiquitous in humans and the environment” [xii]. |
| **Environmental Audit Committee ‘Toxic Chemicals in Everyday Life Report (2019)’** | - Called on the UK Chemicals Strategy to support a non-toxic environment by setting out an ambitious vision for chemicals in the environment including a plan for remediation of regulated substances with binding targets.  
- Concluded that foetuses, children and pregnant women are the most vulnerable groups to the effects of exposure to harmful chemicals. |
| **European Parliament ‘Endocrine Disruptors from Scientific Evidence to Human Health Protection’ (2019)** | - Found EDCs are linked to disorders including obesity and metabolic disorders, reproductive disorders, reproductive cancers, thyroid disorders and neurodevelopmental disease[xiii].  
- Annual costs related to EDC exposure estimated to be €163 billion. The report advocated for further research on EDC effects and the development of chemical alternatives to those with endocrine-disrupting activity. |
Chief Medical Officer Annual Report Health impacts of all pollution (2017)

- Recognised the body of literature documenting increased incidence of breast cancer in women and accepted the role EDCs play in contributing to increases in hormonal cancers[xiv].
- The report concluded EDCs will remain chemicals of concern for the 21st century with the hazards of some EDCs established the report called for the development of further testing methods.


- Stated that Worldwide, there had been a failure to adequately address the underlying environmental cases of trends in endocrine diseases and disorders... healthcare systems do not have mechanisms to address the contribution of environmental risk factors to endocrine disorders... the benefits that can be reaped by adopting primary prevention measures...remain unrecognised. [xv]

EU Beating Cancer Plan

Europeans rightly expect to live in healthy, sustainable environments. Yet, despite extensive legislation on environmental pollution, environmental causes are thought to be behind over a quarter of a million cancer deaths in Europe every year. Environmental pollution has a particularly harmful effect on young children. Finally, implementing the actions under the Commission’s Chemicals Strategy for Sustainability will make it possible to deal with hazardous chemicals more rapidly, and effectively reduce the exposure of consumers and professionals to carcinogenic substances, or to other hazardous chemicals that interfere with the endocrine and immune systems.