BODY OF EVIDENCE

An overview of the low dose effects
of Bisphenol A in relation to breast cancer

BODY OF EVIDENCE: BREAST CANCER AND BPA

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Foreword by Dr. Philippa Darbre

In the modern world, the human population is exposed on a daily basis to hundreds of pollutant chemicals, many of which are now known to enter human breast tissue and which can mimic or interfere in the actions of the female hormone, oestrogen. Bisphenol A (BPA) is one such chemical.

This is of concern for breast cancer because exposure to oestrogen is the major known risk factor. It remains unknown as to whether, or how, such chemical loading of the human breast might play a causal role in breast cancer development. However, it seems likely to relate to long-term, low dose exposure to mixtures of chemicals, of which some may have oestrogenic properties whilst others may have other adverse effects on breast biology. BPA seems to fit into both of these categories.

Assessment of the impact of oestrogenic compounds challenges classical concepts of toxicology because these chemicals can act at extremely low concentrations. Furthermore, their ability to act through specific receptors in the cell means they can have an adverse impact at lower concentrations and in a very targeted way in the breast. They can also act additively, which challenges the assumption that, if a chemical is involved in breast cancer causation, it must be at higher levels in breasts of women with breast cancer than in those without. When considering hundreds of chemicals with a common mode of action, it is possible for one breast to have high levels of one chemical but another breast to have high levels of another chemical. However, if both chemicals act by a common mechanism of action (such as oestrogenicity), then the cellular response can be the same, even though the same chemicals are not at high levels in both breasts.

With this type of complexity, the only way forward towards breast cancer prevention is to start reducing exposure, based on the precautionary principle. This review demonstrates that reducing exposure to BPA would be an evidence-based starting point. Removal of one chemical alone will probably not solve the problems of breast cancer but it may serve as a springboard for reducing the chemical burdens of the human breast. Every day women are dying of breast cancer, so it is undoubtedly better to start somewhere than to be paralysed by the complexity into inactivity.

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Executive summary

Breast cancer rates in the UK have reached epidemic proportions. In England alone, nearly 42,000 new cases are diagnosed every year. Incidence rates have increased by 90% since 1971 (ONS 2010). Only around 26.8% of breast cancer cases can be attributed to known causes such as a hereditary link, smoking, alcohol consumption, obesity and exogenous hormones, such as prescribed Hormone Replacement Therapy (HRT) or the contraceptive pill (Parkin 2010).

Increased concentrations of circulating oestrogens (both natural and synthetic) in the body are known to be important in terms of increased risk of breast cancer (Bernstein and Ross 1993; Kelsey, Gammon et al. 1993) and there is now compelling evidence that low dose exposure to the hormone (endocrine) disrupting chemical (EDC), Bisphenol A (BPA), could be contributing to the rise in the disease.

BPA is used in polycarbonate plastic food and drinks packaging and epoxy resins, which are used to line some metal tins of food and drink. Over 3 billion kilogrammes of BPA are produced every year (Melzer 2010). Humans are exposed to BPA through a variety of different sources including till receipts, mobile phones and laptops. However, it is thought that diet is the main route of exposure.

The chemical structure of BPA is similar to that of natural oestrogen and the drug Diethylstilboestrol (DES). Both have been classified as class I, 'known human carcinogens', by the International Association for Research on Cancer (IARC).

In England alone, nearly 42,000 new cases are diagnosed every year. Incidence rates have increased by 90% since 1971 (ONS 2010).

The chemical monomer of BPA is unstable and can leach out of products. Leaching levels increase with time, under high temperatures and in ultraviolet light. As a result, BPA is ubiquitous in the environment and is in 99.5% of the adult population (Shankar 2012). It is found in organs and tissues all over the human body, including: the mammary glands; brain; placenta; and liver.

The European Food Safety Authority (EFSA), the USA's Food and Drug Administration (FDA) and the UK's Food Standards Agency (FSA) claim that BPA is safe, based on their assertion that our exposure to BPA is allegedly low and that humans rapidly eliminate it from the body. In reality, it remains unclear exactly how much BPA we as humans are exposed to on a daily basis. Tests reveal that our daily exposure could be as much as eight times more than the so-called 'safe' limit, known as the Tolerable Daily Intake (TDI)[1] (Tharp, Maffini et al 2012; Taylor, vom Saal et al 2011). Some studies indicate that our

[1] The Tolerable Daily Intake (TDI) is an estimate of the amount of a substance expressed on a body weight basis, which can be ingested daily over a lifetime without appreciable risk.

bodies do not necessarily eliminate BPA rapidly – children and babies in particular have high levels of BPA in their bodies (Nahar et al. 2012).

Studies also show that BPA has effects at low doses (Jenkins, Wang et al. 2011). Therefore, it is wrong to assume that safe levels of exposure to BPA can be determined by a point at which no, or low, effects are observed.

Like DES, BPA is a synthetic oestrogen and is able to bind to oestrogen receptors both within and on the cell surface. BPA is, therefore, able to influence how genes and cells behave. Mammary tissues are primed to respond to the presence of oestrogen in order to develop and grow, and therefore bind easily to BPA.

Laboratory experiments carried out over the last 10-15 years have produced evidence to show that BPA has the ability to transform breast epithelial cells into cells with a more cancerous or malignant nature (Fernandez et al. 2007; Goodson, Luciani et al. 2011). Foetal and pre-pubertal exposure of animals to low levels of BPA changes the architecture and structure of mammary glands, increases the rate of cell proliferation, breast density and predisposes the mammary glands to cancer later in life (Markey, Luque et al. 2001 Durando et al. 2007 and 2011; Soto et al. 2008; Jenkins et al. 2011 and 2012).

BPA has also been found to cause gross chromosomal damage, induce the loss or gain of whole chromosomes, trigger DNA strand breaks (Iso et al.) and to interfere with cell division (Lehmann et al. 2004; George, Bryant et al. 2008). Such damage and genetic instability is a hallmark of cancer cells.

In addition to evidence to suggest that BPA could be a causative factor in breast cancer, studies show that it may also be implicated in other health problems such as infertility, obesity, prostate cancer, brain tumours, diabetes, heart disease and neurological and behavioural disorders. BPA has also been found to interfere with chemotherapeutic drugs, making them less effective against breast cancer cells (LaPensee et al. 2010).

The cost of treating breast cancers has now reached a massive £1.5 billion (Leal 2012). The number of lives it affects is increasing year on year. Identifying all the root causes of breast cancer is becoming a financial and moral imperative. Reducing breast cancer rates by just 5% could not only save the National Health Service more than £7.5 million, but also prevent the trauma and loss of thousands of women and the suffering of their families every year.

In short, Professor Tom Zoellor, one of the co-authors of the World Health Organisation (WHO) and United Nations Environment Programme (UNEP) Report on the State of the Science on Endocrine Disrupting Chemicals (WHO/UNEP 2012) said: *"Frankly, for BPA, the science is done..... We have more than enough information ... to make the reasonable decision to ban, or at least take steps to limit exposure."* (Bienkowski, 2013).

Urgent action is needed to reduce human exposure to BPA. As well as improved identification and elimination of EDCs, Breast Cancer UK is calling for the following:

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• That the EFSA reviews the relevance of having a TDI for BPA.

The body of evidence suggests that BPA is a substance for which there are no safe levels. Therefore, the existence of a TDI for BPA provides a false sense of security, as it is assumed that as long as consumption remains below the TDI, levels of exposure are safe. The EFSA is currently in the process of reviewing the TDI for BPA and is due to report in November 2013.

• That the EU implements the precautionary principle and bans the use of BPA in all packaging and articles that are intended to come in to contact with food and drink.

Diet is a key route of exposure to BPA and, therefore, such a ban would be extremely effective in reducing people's daily intake of BPA. It is important that BPA is replaced with safer alternatives, and not with chemicals of a similar compound such as Bisphenol S and Bisphenol F, which are also oestrogenic and could have similar effects to BPA at low doses.

• That guidance is put in place at both EU and UK level to ensure that equal weight and consideration is given to well conducted, independent studies regardless of whether or not they comply with Organisation for Economic Co-operation and Development (OECD) 'good laboratory practice' (GLP) guidelines.

Current decisions on the safety of chemicals are based on studies which comply with OECD GLP studies, but fail to take into account other good scientific data. Better guidance is the only way in which all recorded adverse effects of BPA can be taken into consideration.

• That the UK Government revises the existing UK Strategy for Cancer and includes EDCs as preventable risk factors for breast cancers.

The Government has yet to acknowledge the links between EDCs and breast cancers, which means that a huge gap exists in UK cancer prevention policy and cancer prevention research. Including EDCs as preventable risk factors for breast cancers would be a good first step to help protect the health of future generations.

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Introduction

Breast cancer rates in the UK have reached epidemic proportions. It has become the most common cancer for women in the UK, with one in eight women developing it at some point in their lives. In England alone, nearly 42,000 new cases are diagnosed every year. There were 126 new cases per 100,000 women in 2010, compared with 125 new cases per 100,000 women in 2009. Incidence rates have increased by 90% since 1971 when records began (ONS 2010). During the same period, incidence rates for male breast cancer have also increased by 60% (ONS 2010). Whilst earlier diagnosis, improved treatment and anti-cancer drugs mean that survival rates are improving, we are moving towards a situation in which people are expected to live with cancer, along with its associated physical, mental and financial costs, rather than taking positive steps to prevent people from getting it in the first place.

Government policy and many cancer research organisations in the UK currently underplay the question of whether chemicals could be increasing our risk of developing breast cancer. Yet, the soaring rates of breast cancer cannot be explained by genes, our lifestyles, or even improved diagnosis; these factors have not changed substantially in recent years. However, our exposure to a cocktail of chemicals has increased exponentially and there is now mounting scientific concern that daily exposure to the Endocrine Disrupting Chemical (EDC), Bisphenol A (BPA) is linked to an increased risk of breast cancer.

However, industry protagonists, the European Food Safety Authority (EFSA), the USA's Food and Drug Administration (FDA) and the UK's Food Standards Agency (FSA) all argue that the routine use of BPA in a range of products, including food and drinks packaging, is safe, despite the fact that over the last decade numerous studies have indicated that BPA has adverse health effects as a result of low dose exposure. Doubts about the chemical's safety, highlighted by Breast Cancer UK's 'No More BPA' campaign led to an EU wide ban on the use of BPA in baby bottles in 2010. Since then, governments in France, Sweden, Belgium and Denmark have all taken further measures to reduce exposure to BPA by limiting its use in food and drink applications[2].

This report provides an overview of the scientific evidence that BPA has a quantifiable, low dose effect on breast cancer cells and the mammary gland in test tube and animal test systems. It suggests that the evidence used by the EFSA and the FSA to insist that BPA is safe, is weak. It argues that BPA should be more heavily regulated and its use severely restricted to help protect people from needless daily exposure and its associated health risks.

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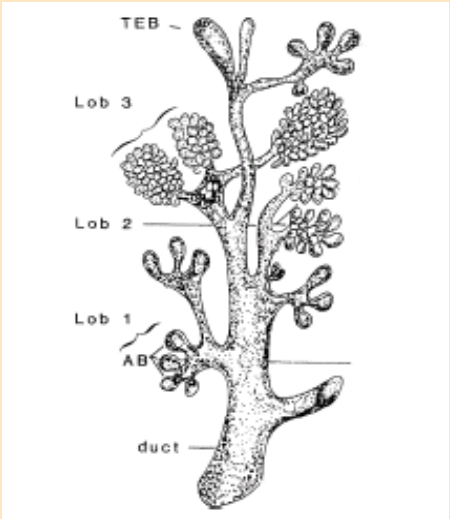
[2] France has now passed legislation that bans BPA from all food packaging and Sweden, Belgium and Denmark have banned the use of BPA in food packaging marketed to children under three. Sweden has since announced its political intention to prohibit the use of BPA in all products.

The human breast

In order to understand the significance of hormone disrupting chemicals on the human breast, it is important to understand how the breast develops and matures over time. Breast development begins not at puberty, but within the womb. In new-borns, the mammary gland consists of between 6-10 straight ducts, lined with a layer or two of epithelial cells that open into the nipple (Russo, Hu et al. 2001). Oestrogen production begins at puberty and leads to the main growth and development of the breast, when these straight ducts become more developed and more branched, only finally becoming fully developed milk ducts once a pregnancy occurs.

Each menstrual, or ovulatory, cycle leads to more differentiation and growth of these ducts (Russo and Russo 2004). Lobule types 1, or terminal ductal lobular units, are the most dominant types present in adult women who have not undergone a pregnancy. They have about 11 ductules and these have the highest proliferative or growth activity (Russo and Russo 2004). The mammary gland is only fully differentiated and completely developed at the end of a full term pregnancy. During pregnancy, further branching and growth occurs, as type 2 and type 3 lobules (with 47 ductules and 80 ductules respectively) are formed and lobules type 4 with secretary cells, mark the completion of mammary gland differentiation and growth (Russo, Moral et al. 2005).

Schematic diagram of the structure of different types of lobules 1, 2 and 3 and terminal end buds (TEB) present in mammary tissue (Russo and Russo 2004).



Most breast cancers originate in the epithelial cells that line the ducts of the lobules (Wellings 1980). Often, the first step is a ductal hyperplasia or an increase in growth of the epithelial cells. Over time, this may develop into a ductal carcinoma in situ (DCIS). DCIS are the most frequently detected types of breast cancer. They originate in the terminal ducts of the lobules type 1, as these lobules have the greatest potential for growth and differentiation (Russo and Russo 1999).

What causes breast cancers?

There are various theories as to what increases a woman's risk of developing breast cancers. In the UK, it is estimated that 26.8% of breast cancers could be attributed to lifestyle factors such as alcohol consumption, smoking, obesity, occupation[3] and exogenous hormones, such as the contraceptive pill and prescribed Hormone Replacement Therapy (HRT) (Parkin 2010).

There is a common belief that those with a familial or hereditary link are most at risk of breast cancers. In fact, only around 5-10% of breast cancer cases are familial or hereditary in origin (Easton, Narod et al. 1994; Miki 1994; Wooster, Bignell et al. 1995).

'Our exposure to exogenous hormones in the last 50 years has increased considerably.'

Statistics show that breast cancer rates are highest in developed countries (Stewart 2003). Immigrants to western countries develop the same breast cancer risk as the residents of the country in which they live, which suggests that environmental and lifestyle factors of developed and industrialised countries are key factors in breast cancer risk (Buell 1973; Pisano 1992; Zeigler, Hoover et al. 1993; Kliewer and Smith 1995; Winter, Cheng et al. 1999).

The hormone, oestrogen is also known to be an important factor in breast cancer development. Raised levels of oestrogens in the body have been linked to an increased risk of breast cancers (Bernstein and Ross 1993; Kelsey, Gammon et al. 1993). Oestrogens are produced naturally, but we are also exposed to other sources of exogenous oestrogen, for example from drugs such as the contraceptive pill and HRT, or synthetic oestrogens used in chemicals and plastics. Our exposure to exogenous hormones in the last 50 years has increased considerably.

Diethylstilboestrol (DES) is a synthetic oestrogen that was given to pregnant women in the 1950's and 1960's to help prevent miscarriage. Women who took DES were found to have a 40% increased risk of developing breast cancer in later life (Greenberg, A.B.Barnes et al. 1984). The first generation of daughters born to women who were exposed to DES, also had an increased risk of developing breast cancer after reaching 40 years of age (Palmer, Lauren A.Wise et al. 2006). It was found that intrauterine exposure to the DES caused an increase in the number of ductal stem cells, and thereby increased the risk of mutations in the cells of the mammary gland, consequently increasing the risk of developing breast cancer later in life. Ironically, men were not permitted to work in factories that synthesised DES,

[3]Women working as hairdressers and beauticians have been associated with having an increased risk of breast cancer (Pollan and Gustavasson 1999).

because those that had developed painful swellings in the chest area. It was these links to breast cancer that led directly to DES being withdrawn from use in the USA in 1971 and the UK in 1975[4].

Ethinyloestradiol is a derivative of oestrogen and is mainly used in oral contraceptives. It has also been found to be carcinogenic in many animals and genotoxic in mammalian cell cultures (Siddique, Tanveer Beg et al. 2005) and to slightly increase the risk of breast cancers in women. In 2005, the International Association for Research on Cancer (IARC) in France, classified oral contraceptives as class 1 human carcinogens (Coliano, Grosse et al. 2005). However, women who stopped taking oral contraceptives after ten years have the same breast cancer risk as if they had not taken it at all (Collaborators 1996). This demonstrates that reducing exposure to synthetic oestrogens can reduce breast cancer risk.

Ten years ago, data published from the 'Million Women Study', which investigates breast cancer risk and various life style factors in women in the UK over the age of 50, found that women who had used prescribed, combined hormone replacement therapy (HRT – artificial oestrogen and artificial progesterone) had an increased risk of invasive breast cancer (Collaborators 2003). As a result, there was a noticeable decline in its use and a corresponding decline in breast cancer incidence. A study published in the British Journal of Cancer in 2010 estimated that 1.1% of all cancers in women were linked to prescribed HRT, with breast cancer accounting for the majority of this total (Parkin 2010).

It is possible that lifestyle factors, such as increased alcohol consumption and obesity, have links to raised levels of oestrogens (and androgens) in the body. One study showed that women who consumed more than two drinks a day had raised levels of oestrogens in their body (Singletary and Gapstur 2001). A lack of physical exercise and associated increased Body Mass Index (BMI) has also been linked to raised oestrogen levels (McTiernan, Wu et al. 2006; Neilson, Friedenreich et al. 2009). Therefore, there is some potential for even the well-known, most publicised risk factors associated with breast cancer to be attributable to mechanisms involving raised levels of oestrogens in the body.

It is likely that the risk factors for breast cancer are multifactorial. However, with only 26.8% of breast cancer cases having a clear attributable cause (Parkin 2010), and many more cases occurring in people who are not considered high risk, it is also likely that there are other risk factors which are being ignored and are a contributing to our risk of developing breast cancer.

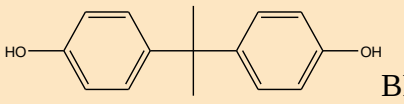
[4] www.federalregister.gov/articles/2012/06/14/2012-14476/notice-of-withdrawal-of-certain-unapproved-abbreviated-new-drug-applications

What is Bisphenol A?

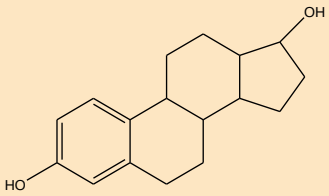
BPA was first synthesised in 1890 and was used to fatten cattle and poultry. It was recognised as being an artificial oestrogen as early as 1930 by the British chemist, Charles Edward Dodds, and preceded the use of DES as a synthetic oestrogen by 30 years. BPA's properties as a plasticiser were not discovered until after World War One, when it was found to react with phosgene and yield a clear, hard plastic polycarbonate. BPA is now used in polycarbonate plastic food and drink packaging and in epoxy resins that line some metal tins of food and drink. BPA is also used as an additive in polyvinyl chloride (PVC) plastics, CDs, mobile phone and computer casings, glasses, dental sealants (NTP 2008), medical devices[5] and thermal till receipts. Chemical production of BPA is big business, with over 3 billion kilogrammes produced per year, and it is estimated to be worth $500,000 (nearly £340,000) an hour to the global economy (Melzer 2010). The production of BPA has increased by 500% in the last three decades.

BPA is able to migrate, rub off on hands, leach into food and drink contents and is dermally absorbed through the skin. This is because the chemical bonds between the monomers, or individual chemicals within articles or products in which BPA is used, are not stable. Exposure to ultra-violet light, high temperatures (such as those used in sterilisation processes), or to acidic conditions (for example, in a can of tinned tomatoes), will lead to higher levels of leaching. Material damage has also been found to increase the rates at which BPA leaches out of the packaging and into the food and drink it contains (Brotons, Olea-Serrano et al. 1995). As a result, BPA is ubiquitous. It is found all over the planet in ecosystems, humans and wildlife (Flint et al. 2012).

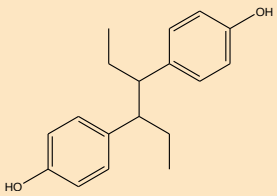
BPA has a similar chemical structure to that of oestrogen and DES both of which are classified as class 1 human carcinogens by the IARC. BPA, DES and oestrogen all have one or two phenolic rings.



BPA



Oestrogen



DES

[5]For example auto-transfusion, apparatus, filters, bypasses, tubing, pumps, instruments, surgical equipment, blood pathway circuits and respiratory tubing circuits. These products are used on all types of patients e.g. adults, children etc.

‘Over exposed?’ Bisphenol A in the human body

Scientific studies indicate that between 93% and 99.5% of adults in the USA have detectable levels of BPA in their urine, indicating that we ingest BPA largely via diet (Shankar & Tempala 2012). Links have been made between the consumption of tinned vegetables (Matsumoto, Kunugita et al. 2003) and tinned coffee and levels of urinary BPA (Braun. 2011). Studies have also found that it can be absorbed through human skin, from sources such as thermal till receipt paper. This could be another route of exposure for humans and one that is able to bypass the direct metabolism routes that occur by oral exposures (Zalko, Jacques et al. 2011). The fact that BPA levels drop after a diet restricted to food with limited packaging (Rudel 2011) suggests that oral consumption via contaminated food is a key route of exposure (Kang, Kondo et al. 2006; Vandenberg, Hauser et al. 2007).

BPA is found all over the human body. It has been found in human urine samples (Calafat, Zsuzsanna Kuklenyik et al. 2005) at levels which equate to approximately one third of the total oestrogen metabolites measured in human urine[6]. It is also present in human serum (Takeuchi and Tsutsumi 2002), sweat (Genuis, Beesoon et al. 2012), placental tissues (Schonfelder, Flick et al. 2002), ovarian follicular fluid and evidence suggests it accumulates over time in human amniotic fluid (Ikezuki, Osamu et al. 2002). It has also been found in human breast milk[7] (Sun, Irie et al. 2004), which confirms its presence in the breast, and at even higher levels in liver, brain and human fat tissue (Fernandez, Arrebola et al. 2007).

‘Scientific studies indicate that between 93% and 99.% of adults in the USA have detectable levels of BPA in their urine.’

Whilst the EFSA, the FDA and the FSA do not deny the presence of BPA in the human body, they claim that the levels at which it is found are harmless. They state that current levels of human exposure to BPA fall well below the recommended Tolerable Daily Intake (TDI), which the EFSA has currently set at 0.05mg per kg of body weight per day. On this basis, they insist that its commercial use in food and drink packaging is safe, arguing that it is metabolised quickly and that the liver quickly de-toxifies it, thus rendering it harmless.

[6] BPA was found in 95% of human urine samples at concentrations of 0.1 µg/L (Calafat, Zsuzsanna Kuklenyik et al. 2005) compared to total oestrogen metabolites which were found to be 0.337 µg/L (Taioli, Im et al. 2010).

[7] It has been found in breast milk at over a mean concentration of 0.61 ng/ml^{-1} (a ng is one billionth of a gram).

There are however, a number of fundamental flaws to this line of argument.

THE EVIDENCE THAT OUR BODY GETS RID OF ALL BPA IS WEAK

Firstly, the argument that BPA passes rapidly through the human body is weak. Two studies by Volkel et al. (2002, 2005) and, more recently, one by Dr. Justin Teeguarden (2011) are used to support this position. The Volkel studies conclude that BPA has a half-life in humans of less than 4-6 hours (Volkel, Bittner et al. 2005; Volkel, Colnot et al. 2002) and suggest that BPA is rapidly eliminated from the body following one exposure. They also assert that it does not remain in any body tissues and, therefore, that humans are not at risk from BPA.

However, whilst the studies by Volkel can provide a snapshot of how one adult might metabolise BPA after a one off dose, they cannot be said to accurately predict how different adults, let alone children, metabolise BPA during a lifetime of exposure.

For example, Volkel's studies only used a single oral dose, whereas humans are exposed to BPA continuously from both oral and non-oral sources over a whole life time. Therefore, neither of these studies therefore can be used to predict what effect daily exposure to BPA can have on our bodies.

Volkel's suggestion that BPA is unlikely to bioaccumulate is also flawed. BPA has been found at higher levels in the liver, brain and fatty tissue (National Health and Nutrition Examination Survey) and is known to be more soluble in fat than in water[8] (Hunt 2003). Therefore, like other fat soluble chemicals, it will possess the ability to bioaccumulate, especially in fat rich tissues, such as the human mammary gland. As we are exposed to BPA on a daily basis, it is likely that BPA will accumulate little by little over time. A little is all that is needed to be carcinogenic in situ.

Volkel's studies only tested between six (Volkel 2005) and ten (Volkel 2002) human subjects, which does not allow for differences in human physiology or different rates of metabolism. Several bio monitoring studies have shown that men and women differ in their metabolism of BPA (Calafat et al. 2005, 2008, Kim et al. 2003). This means that some people will not be able to get rid of BPA as quickly as others, and, therefore bioaccumulation is likely to be greater.

Volkel et al. also failed to consider the potential for BPA to have effects at very low levels (in the nanograms per millilitre range), which is crucial since BPA is known to be non-monotonic (have different effects at different doses), a property which we will explore in more detail below.

One scientific paper concludes that Volkel's studies "*have significant deficiencies, are directly contradicted by hypothesis-driven studies, and are therefore not reliable for risk assessment purposes.*" (Vandenberg et al. 2010)

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[8] BPA has a log kow value of 3.3. It is generally accepted that a chemical with a log kow of greater than 3 has the potential to bioaccumulate (OECD 1995).

More recently, industry protagonists have cited a study by Dr. Justin Teeguarden, published in the Journal of Toxicological studies (2011). This concluded that there were no detectable levels of BPA in the human body, following a high dietary intake of BPA from tinned food and bottled juices. However, the methodology of this study has been criticised for having "major shortcomings" (Vandenberg 2011). For example, all participants drank 3.5 litres of water per day (a far higher amount than most people can normally consume in a day), but no method to account for dilution caused by this amount of water was used in the study. The food and drink consumed by the participants was not tested for BPA; it was just assumed that it contained BPA, whereas the presence of BPA in food can vary from tin to tin and brand to brand. Furthermore, the study relied on industry-funded studies for key citations regarding how the body handles BPA and how much BPA people consume.

CHILDREN HAVE HIGHER LEVELS OF BPA IN THEIR BODIES

Another flaw in the EFSA/FDA position is their failure to take into consideration the differences between children and adults, and the subsequent difference both in the way children metabolise BPA and the effect that it might have on them.

There is evidence that human new-born babies have three times more BPA in their bodies than adults and are unable to metabolise BPA in the same way. Each of the three studies above, used to justify the rapid excretion of BPA in humans, only tested adults. All three failed to assess the levels of BPA in small children or the unborn child.

One recent study found high levels of BPA in foetal liver tissues, suggesting not only that there is risk from exposure during pregnancy but also that foetal excretion of BPA is much slower than in adults (Nahar, M. et al.2012). This is because the detoxification enzyme system that clears toxins from the body is not yet fully active (Mielke and Gundert-Remy 2009).

'BPA is able to accumulate little by little in fatty tissues. A little is all that is needed to be carcinogenic in situ'

The World Health Organisation (WHO), the United Nations Environment Programme (UNEP) and, more recently, the EFSA, acknowledge that children can have higher exposures to chemicals and that there are "sensitive" windows of exposure to EDCs "during critical periods of development such as during foetal development and puberty" (WHO/UNEP 2012). For example, one study found that the adverse effects of BPA were effectively amplified when exposure occurred during foetal development. In this study, BPA had the same effect as DES on the mammary glands of mice when exposed in the womb (Taylor et al. 2010). The Congressionally mandated Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) concluded: *"Timing*

matters: The breast is especially sensitive to environmental exposures during fetal development (when the organ is formed), and during puberty and pregnancy" (IBCERCC 2012).

'The adverse effects of BPA were effectively amplified when exposure occurred during foetal development. In this study, BPA had the same effect as DES on the mammary glands of mice when exposed in the womb'

Therefore, new-borns and the young are not only likely to be at risk of accumulating higher levels of BPA in their bodies compared to adults, but also at an increased risk of adverse effects as a result. Therefore, a TDI based on adult exposure and metabolism of BPA has little or no relevance for children and it would seem dangerous to assume the chemical is safe as a result.

WE DO NOT KNOW HOW MUCH BPA WE ARE EXPOSED TO ON A DAILY BASIS

Another reason the EFSA/FDA argument that current use of BPA is safe is flawed, is, quite simply because there is actually very little data that helps us to identify how much BPA we are exposed to daily. For example, the rate at which BPA leaches into the food or drink, or the rate at which it is absorbed through the skin, can vary enormously. Studies that have tested BPA levels in tinned food found that BPA levels varied from tin to tin; some had up to 200 times the UK Government's recommended safe level (Breast Cancer Fund 2011; Environmental Working Group 2007). The levels of leaching can also vary enormously depending on the conditions. Adding hot water, or microwaving products containing BPA, can increase (and sometimes quadruple) the rate at which BPA leaches into the food or drink. Constant use of plastic products and the damage caused by scrubbing and numerous dishwasher cycles, for example can also increase the rate at which BPA leaches (Brede et al. 2003).

In addition, it is important to consider that humans are exposed to BPA from multiple sources. Our exposure via computers, mobile phones, laptops, Blue Ray DVDs, receipt paper and consoles mean that we are far more exposed to BPA than ever before. This makes it even more difficult to establish exactly what our exposure levels are. For example, a combination of tinned foods over one meal, or exposure from other sources, could mean that some people, and especially children, can have very high levels of exposure.

Therefore, as mentioned above, studies that try to measure exposure to BPA by testing metabolism of BPA following a one-off dose do not offer a realistic reflection of our actual daily, repeated exposure to BPA and may explain why some studies have conflicting results.

For example, studies which test the presence of BPA following repeated exposure via diet are therefore, more comparable to the human experience, find higher concentrations of BPA after longer

periods (Sieli, Jasarevic et al. 2011), compared to those that measure BPA following a one-off dose given intravenously (Doerge, Twaddle et al. 2012).

One study which looked at the metabolism of BPA in non-human primates, found that adult primates fed a diet of 400µg (0.4mg) per kg of body weight per day (eight times the recommended human TDI) led to the detection of BPA in their serum at levels similar to those found in human serum (Tharp, Maffini et al. 2012). Therefore, this suggests that human exposure to BPA via oral intake must be far higher than the current TDI – potentially ***eight*** times that of the EPA's TDI of 0.05mg (50µg) per kg of body weight per day. (Taylor, Vom Saal et al. 2011).

BPA HAS EFFECTS AT LOW DOSES

Another problem with assuming that we are safe as long as we do not ingest or absorb levels of BPA above the TDI is that it fails to take into account the effects which occur below this level. A growing number of scientists now recognise that some chemicals have what is called a 'non – monotonic' effect or can produce a 'U shaped' dose response curve. Usually, the greater the dose, the greater the effect or, as the Renaissance physicist and early toxicologist, Paracelsus said: *"the dose makes the poison".* In such cases, a safe limit is usually based on the point under which adverse effects no longer occur. However, where a chemical has effects at both low and high doses, it is difficult to determine a safe dose. This presents a challenge for both toxicologists and regulators. Usually, effects are investigated at the high dose level and extrapolated down to levels considered not to be harmful, or to induce unwanted effects. However, this is not as simple if a chemical produces a U shaped dose response curve, as there is an effect at both high and low concentrations[9].

'BPA and has been found to cause effects at low doses but not high doses on fertility, reproductive behaviour, embryo development and mammary tumour development.'

This is a well-known phenomenon, or paradox, observed in the clinical setting with hormonally active drugs, such as Tamoxifen (Vandenberg, Colborn et al. 2012). Tamoxifen is used to treat oestrogen positive breast cancers, and, in some countries, it is used as a preventative drug. When Tamoxifen is initially administered, levels are low in the body before they begin to accumulate over time. Therefore, at low doses the observed paradox effect is an initial worsening of breast cancer symptoms, caused by an increase in the growth of the oestrogen dependent breast cancer cells (Howell 2001). However, the overall effect is considered sufficiently

[9] http://ihcp.jrc.ec.europa.eu/our_activities/food-cons-prod/endocrine_disrupters/endocrine-active-chemicals-jrc-and-niehs-workshop

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beneficial by health authorities to be prescribed to breast cancer patients for up to five years.

Research has concluded that oestrogens produce a non-monotonic dose response in mammary tissue. At low to moderate concentrations, oestrogens can enhance ductal elongation and terminal end bud formation (pubertal development) and in higher doses, they inhibit those processes (Vandenburg, Perinaaz R. Wadia et al. 2006).

BPA and DES also have a U shaped dose response curve (Vandenberg, Colborn et al. 2012). Both have been found to cause effects at low doses, but not at high doses, on fertility (Cabaton, Wadia et al. 2011), reproductive behaviour (Jones, Shimell et al. 2011), embryo development (Nishizawa, Morita et al. 2005) and mammary tumour development (Jenkins, Wang et al. 2011).

In 2000, the National Toxicology Programme (NTP) stated that DES was found to have effects at low doses. However, despite its similarity to DES, the NTP did not draw the same conclusions for BPA. The reason given at the time was "lack of evidence". Since 2000 however, there has been a significant amount of research on BPA and numerous studies have found that it does have effects at low doses. In 2006, Frederick vom Saal reviewed the literature on low dose effects of BPA. He found over 100 published studies stating low dose effects of BPA (vom Saal and Welshons 2006), with over 40 of them reporting effects below the recommended safe dose set by the EPA and the FDA. In 2012, one study calculated that there are more than 200 published animal studies, many of which focused on the low dose effects of BPA. (Vandenberg et al. 2012). Today a search for "low dose effects of BPA" within the Pub Med science literature database will yield well over 200 studies. In short, study upon study concludes that low dose exposure to BPA has adverse effects.

We as humans are exposed to significant amounts of BPA on a daily basis, either via diet, dermal absorption or otherwise and it is ubiquitous in our bodies. It is highly likely, and almost certain in the case of children, that we absorb levels of BPA far above the so-called 'safe' limit of the EFSA's TDI of 0.05mg per kg of body weight per day. This is all the more concerning given that, as Vandenberg points out, the TDI was calculated not from a 'No Observed Effect Concentration' but a 'Low Observed Effect Concentration' (Vandenberg, Chahoud et al. 2010). In other words, there was no measurable level at which BPA produced no visible effects. So what does this mean for our health?

Bisphenol A and the human breast

It is known that, like DES, BPA is able to bind to the oestrogen receptors in a cell and this can cause problems, as we have already seen in the case of DES. Oestrogens influence the expression of genes involved in cell division and growth, especially in the breast. Therefore, when a synthetic oestrogen, such as BPA, binds to the oestrogen receptor (ER), it can influence what is called the transcriptional regulation of oestrogen responsive genes. In other words, BPA can influence a variety of genes and the way in which they behave.

The human endocrine system is adapted to be responsive to tiny fluctuations in hormones. Minimal changes in oestrogen levels in female humans can have significant effects. When levels of oestrogens are very low in the body, a 10 fold increase in the levels of oestrogens causes a 9 fold increase (or 90% increase) in oestrogen receptor binding and, therefore, has a much greater effect upon cell growth. However, when oestrogen levels are higher, there are fewer unbound oestrogen receptors and a 10 fold increase in oestrogens will cause as little as a 1.1 fold increase (or 10% increase) in oestrogen receptor binding (Welshons, Nagel et al. 2006; Vandenberg, Colborn et al. 2012). Therefore, when levels of bioavailable oestrogens are low, for example in infants, children and at certain times during menstrual cycles, there are many free receptors which are available to bind easily to BPA, as well as a multitude of other similar chemicals.

Mammary tissues, which are primed to respond to the presence of oestrogens in order to develop and grow, are particularly susceptible to binding to BPA, even when BPA is present at very low levels. This could lead to increases in cellular growth of epithelial cells which would not be expected or wanted, as this is not a signal produced by the body's own intrinsic hormone or signalling mechanisms. Increased cellular growth, or hyperplasia, is one of the first stages of the development of a potential cancer.

We know oestrogen receptors exist inside the cell, but recent research has shown that oestrogen receptors also exist on the cell surface, where it is possible they may bind more easily and could lead to even more rapid changes in cell signalling pathways (Yamakawa and Arita 2004). The impact of these new discoveries and what they mean for human diseases and cancer are still being explored, but it could mean that BPA has even greater potential to influence cell signalling and cell growth pathways than previously thought. Given the similarities between BPA and DES, we have every reason to be concerned about its long-term health effects on the human breast.

Adverse effects of Bisphenol A: *in vitro* data

Numerous *in vitro* tests, which take cells from specific organs, such as breast epithelial cells, and grow them in a laboratory, have revealed clearly the adverse effects of BPA, both its ability to stimulate the growth of cancerous cells and its ability to trigger changes which could lead to cancerous growths.

In 1993, Krishnan et al. found that BPA was released from polycarbonate flasks during a sterilisation process and stimulated the growth of an oestrogen dependent breast cancer cell line (the MCF7 cells). This study also found that BPA enhanced progesterone receptors but the effect could be blocked by the addition of Tamoxifen, the anti-oestrogen drug given to breast cancer patients to help prevent recurrence.

We know that BPA binds to both types of oestrogen receptor (both ERα and ERβ) and can cause similar effects to natural oestrogens such as promoting cell growth (Hiroi, Tsutsumi et al. 1999). BPA is also able to block the effects of oestrogen in certain cell types, which means that BPA may induce unwanted effects in other organs as both receptors are not only present in mammary and endocrine tissues, such as ovaries, prostate and testis, but are also in organs such as the brain, bladder and lungs (Kurosawa 2002).

Research carried out on human breast cells in more recent years has also revealed that BPA can induce specific changes that could lead to breast cancers (Fernandez et al. 2007; Goodson 2011; Tilghman 2012). In 2007, Fernandez et al. found that BPA acts in a similar manner to oestrogens by its ability to transform breast epithelial cells in the laboratory into more aggressive cells with a cancerous nature. BPA induced the ability of breast epithelial cells to grow colonies in suspension medium, instead of growing in flat monolayer on the surface of a Petri dish; this is considered to be representative behaviour of a carcinoma in situ (Fernandez et al. 2007). In 2011, Goodson et al. took non-malignant donor cells from women with a high risk of breast cancer occurrence. After exposure, it was found that BPA induced changes that were frequently found in malignant tissues (Goodson, Luciani et al. 2011).

'It was found that BPA induced changes that were frequently found in malignant tissues.'

In vitro testing provides compelling evidence that BPA effects human breast cells. This is vital given the absence of test data in live humans. In order to understand how BPA effects living organisms, we will look at data from tests carried out on animals to assess the metabolism, routes and toxic effects of BPA in relation to the development of mammary tumours. Here, the evidence is just as compelling.

Adverse effects of Bisphenol A: *in vivo* data

In 1998, toxicologist Dr Patricia Hunt discovered by accident that BPA had adverse low dose effects in animals. During one of her studies, Hunt discovered that the number of congressional failures of mice egg cells (i.e. eggs that did not develop on fertilisation) suddenly increased from 1% to 40%, due to a misalignment of chromosomes during cell division. Further investigations found that an acidic solution normally used for cleaning floors had instead been used to clean the mouse cages and water bottles and this had damaged the plastic, causing it to leach BPA. The effects were replicated to confirm the observation that BPA had a dramatic and disruptive effect on cell division (Hunt 2003). Since 1998, dozens of studies have been carried out which consistently show that BPA can adversely affect the mammary tissues of animals.

As stated above, many scientists agree that there are sensitive windows of exposure to EDCS during critical periods of development, where EDCs have significant effects at low doses (WHO/UNEP 2012; IBCERCC 2012; Barouki 2012). Animal tests reveal that BPA is no exception. Numerous studies carried out on animals show that foetal or pre-pubertal exposure to BPA can alter the structure of mammary glands and lead to increased susceptibility to chemically induced mammary tumours (e.g. Markey, Luque et al. 2001; Durando et al. 2007 & 2011; Soto et al. 2008; Jenkins et al. 2011 & 2012).

In 2001, a study showed that female mice offspring that had been exposed to very low levels of BPA whilst in the womb underwent significant increases in terminal end buds and ductal elongation in the mammary gland. These changes occurred at exposure levels many times lower (1/4000 lower) than the standard tests used to increase the uterine weight of a rodent, compared with an unexposed animal (Markey, Luque et al. 2001.)

In a study carried out by Durando et al. (Durando, Kass et al. 2007), BPA was administered to rats via osmotic pumps, delivering the low dose of 25 µg per kg of body weight per day prenatally (in the womb). This resulted in a change to the structure and architecture of the mammary tissue after puberty and the animals became more susceptible to a carcinogen. Another study by Durando in 2011 concluded that: *"prenatal exposure to BPA alters the endocrine environment of the mammary gland and its angiogenic process.....[which] could explain the higher frequency of pre-neoplastic* [pre-cancerous] *lesions found later in life"* (Durando 2011).

'A number of animal studies have also shown that BPA effects breast density and increases the number of breast epithelial cells.'

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Additional critical exposure periods for BPA appear to be not just during gestation in the womb but also in the pre-pubertal phase. Low dose exposure to BPA in pre-pubertal rats has been found to increase tumours in rat carcinogen models, compared to control or unexposed rats (Lemartine et al. 2011; Betancourt et al. 2012).

Jenkins et al. (2009) exposed juvenile rats to low doses of BPA via the mother's milk. More mammary tumours appeared in a shorter time in the rats fed milk from the BPA treated mothers, compared to the control population. Additionally, the proliferative rate of cells in the mammary tissue increased, as did the cell survival rate, when compared to the control (Jenkins, Raghuraman et al. 2009). This study is important because it demonstrates the impact of low dose exposure to BPA, its ability to pass from mother to baby via breast milk, and the increased sensitivity to carcinogens following pre-pubertal exposure via the diet to BPA. It also shows that BPA has an impact on cell survival. Jenkins concluded in a later study that: "*early life exposure to BPA and DES increases rodent susceptibility to chemically induced mammary carcinogenesis, presumably through retardation of normal mammary gland maturation and/or disrupting the ratio of cell proliferation and apoptosis in the mammary gland*" (Jenkins et al. 2012).

Usually, cells with much damaged DNA or chromosomes undergo programmed cell death or apoptosis, or they remain frozen until the DNA has been repaired. Therefore, increased cell survival of damaged cells is detrimental for any organism.

'Numerous studies carried out on rodents show that foetal or pre-pubertal exposure to BPA can alter the structure of mammary glands and lead to increased susceptibility to chemically induced mammary tumours'

A number of animal (rodent and monkey) studies have also shown that BPA effects breast density and increases the number of breast epithelial cells (Soto 2008; Ayyanan et al. 2011; Weber Lozarder 2011; Tharp, Maffini et al. 2012). Increased breast density and increased cell numbers is an acknowledged risk factor for breast cancer in humans (Boyd 2005). Therefore, if exposure to BPA has this adverse effect in animals, including monkeys, it would suggest a similar effect is probably taking place in humans.

In short, as Vandenberg states in her 2012 review, there is now *"undisputed evidence regarding low dose effects of BPA in mammary tissues"* (Vandenberg, Colborn et al. 2012).

Bisphenol A and chromosomes

BPA may also be causing damage via non-oestrogenic pathways. For example, it has been shown to interfere with chromosomes within cells. As we know, Hunt discovered that BPA could disrupt cell division in the production of female rodents eggs (Hunt 2003; Zhang et al. 2012). Such chemicals are known as 'aneugens' and can induce loss or gain of chromosomes. Loss or gain of whole chromosomes can cause genetic instability in a cell. Genetic instability is the hallmark of cancer cells. This is because DNA repair genes, or genes involved in cell replication control, may be lost. Similarly, there may be a gain or amplification of certain genes involved in cell survival and growth, which could be beneficial for a cancer cell. For example, hyperplasia, when cells start to over grow, is one of the first stages of cancer.

A number of studies indicate that BPA can transform cells (Tsutsui 2000), interfere with the microtubule assembly, (Lehmann et al. 2004; George, Bryant et al. 2008) and induce DNA strand breaks (Iso et al. 2006). Microtubule assembly is the formation of the cellular apparatus upon which the replicated chromosomes align. Studies suggest that BPA can prevent cells from separating properly, which can cause gross chromosomal damage. Similarly, studies also suggest that exposure to BPA can induce gross chromosomal change in cells and microtubule polymerisation in fish erythrocytes and mussels (Metzler 1995; Pfeiffer, Rosenberg et al. 1997; Bolognesi, Perrone et al. 2006; Barsiene, Syvokiene et al. 2006). In another study carried out in 2003, both DES and BPA were found to weaken telomeres (Roy, Palangat et al. 1997), a region of repetitive nucleotide sequences at each end of a chromosome that protects the end of the chromosome from deterioration. Short telomeres are associated with genetic instability and increased risks of cancers (Wu, Amos et al. 2003).

Whilst there have been relatively few studies that have investigated this non oestrogen receptor pathway of BPA action and its relevance for breast cancer, those that have been carried out suggest that there is reason for concern. Any evidence that suggests gross chromosomal damage warrants urgent further investigation on the part of industry, government and regulatory authorities. These worrying sets of data suggest that BPA is not just an oestrogen mimic, but can have other far-reaching and possibly even worse health impacts. Regulatory authorities can no longer rely on the argument that the oestrogenic effects of BPA are weak and, therefore, can be safely ignored.

Just the tip of the iceberg?

Numerous studies reveal that BPA is able to induce visible and unwanted effects of cell growth, chromosome segregation and initiation of tumours in animals, but this is just the tip of the iceberg. The health effects of BPA are wide ranging.

In vivo testing shows that exposure to low doses of BPA in animals during gestation has been found to cause reduced fertility (Cabaton, Wadia et al. 2011; Karavan and Pepling 2012), reproductive tract abnormalities, accelerated puberty and increased body weight (Honma, Suzuki et al. 2002). In male rodents, exposure to low doses of BPA caused increases in prostate size (vom Saal 1998; Gupta. 2000), sperm production and increased levels of infertility (Salian 2011). In vitro experiments also showed that low environmentally relevant doses of BPA decreased the survival capabilities in human eggs cells (Brieno-Enriquez, Robles et al. 2011).

'Exposure to low doses of BPA in animals during gestation has been found to cause reduced fertility, reproductive tract abnormalities, accelerated puberty and increased body weight.'

BPA exposure has been cited as a possible cause of increasing levels of certain reproductive disorders, such as recurrent miscarriage (Mayumi 2005) and male reproductive health issues (Meeker 2010). Some researchers have linked high levels in human urine with high blood pressure, peripheral cardiovascular disease and coronary heart disease (Melzer, Osborne et al. 2012; Shankar 2012; Shankar, Teppala et al. 2012), increased levels of obesity (Shankar, Teppala et al. 2012), and diabetes (Shankar 2011).

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BPA may also interfere with certain chemotherapeutic drugs used in breast cancer, making them less effective. Low doses of BPA and oestrogen were both found to reduce the ability of a chemotherapeutic drug to kill breast cancer cells (LaPensee et al. 2010). This effect was observed even when the oestrogen receptors were knocked out of the cancer cells, which suggests the presence of alternative cell signalling mechanisms. This also infers that there are implications for the interference of chemotherapy with all types of breast cancer, not just oestrogen receptor positive ones. It suggests that the adverse effects of BPA may be far more extensive than initially considered.

The unwanted health effects of BPA are potentially widespread and, therefore, action to reduce exposure to it is in the broader public health interest.

Why is the evidence ignored?

Despite the evidence, that we should be taking a precautionary approach to the use of BPA, the regulatory authorities and industry continue to insist that low dose exposure to the chemical is safe. So why is the evidence being ignored?

Part of the problem is that when assessing EDCs, like BPA, regulatory authorities, such as the EFSA, tend to prioritise studies which comply with OECD (Organisation for Economic Co-operation and Development) 'good laboratory practice' (GLP). However, GLP guidelines are designed to control data collection, animal care and equipment, rather than being a benchmark of more accurate scientific test data. Whilst industry funded studies tend to adhere to OECD GLP guidelines, it does not mean that they are any more accurate and, therefore, should not be given more weight, or more influence in safety assessments. Nor should the fact that they do not always find adverse effects, or appear to contradict other tests that do, be used as a justification for greater influence.

OECD test methods have also been criticised for having gaps and shortfalls when it comes to accurately identifying EDCs (Kortenkamp et al. 2011, CHEM Trust 2013). Instead, regulatory authorities should carefully consider all well conducted, peer reviewed scientific data in order to more accurately assess the adverse effects of EDCs.

The fact is that the vast majority of scientific evidence published points to low dose adverse effect. Two scientists, Vom Saal and Hughes, collated the outcomes of low dose *in vivo* BPA research and found that 90.4% of government funded studies revealed that BPA caused harm at very low doses. This increased to 96% when studies which used Charles River Sprague Dawley (CD-SD) rats, which are insensitive to oestrogens, were excluded. Only eight studies (all industry-funded) have been published which show no effects.

The fact that we have no human studies to prove that BPA causes breast cancer should not be used as an indication that BPA is safe, nor should it distract from key findings that BPA is harmful in hundreds of *in vivo* and *in vitro* tests. Industry has played down the effects of BPA in rodents, but rodents have been used as test systems for the safety and efficiency of pharmaceutical drugs for decades, and were previously used to confirm whether cosmetics were safe for human use. Moreover, tests of DES on rodents successfully predicted the human effects of exposure to DES decades ago. It is difficult to test the effects of BPA on humans, especially when the damage could take place in the womb. Therefore, we must rely on the evidence produced in laboratories and on animals, which suggests that we have every reason to be concerned.

The financial costs of breast cancer

Increasingly, breast cancer is something society is told it should be willing to live with. Headlines and statistics tell us that mortality rates are steadily decreasing, whilst ignoring the fact that incidence rates are increasing rapidly.

According to the ONS (2010), breast cancer rates in England have increased by 90% since 1971 and by 6.3% between 2001 and 2010. Breast cancer rates amongst men in England have also increased by over 60% since 1971. Even more alarming are the recent headlines that breast cancer rates in women under 50 are also increasing and now 1 in 5 women that get breast cancer will be in that age group[10].

A report published by the Health Economics Research Centre at Oxford stated that: "*cancers impact the economy as a whole – and not just the health service. Premature deaths, time off work and unpaid care by friends and family account for 64 per cent of all cancer costs (£10.2bn) in the UK in 2009"*. The cost of breast cancer is calculated to be £1.5 billion, making it the third highest costing cancer after lung and prostate cancer. As such, it is vital that focus is now turned towards helping to ***prevent*** women and men from getting breast cancer in the first place. Based on these financial calculations, even if incident rates were cut by just 5%, this would represent a saving of £7.5 million.

The sheer quantity of evidence which suggests that BPA is a problem indicates that more action is needed to help protect the public and, in particular, vulnerable sectors of society such as infants, children, pregnant and breast feeding women. By cutting our exposure to man-made oestrogens, such as BPA, we could help to slow or even reverse the long term steady increase in breast cancer incidence. There are numerous ways in which this can be done, especially in the case of BPA.

"The cost of inaction could mean lags of a decade or more before today's research investments can be applied to preventing breast cancer" (IBCERCC 2012).

[10] See www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2013-05-02-breast-cancer-in-women-under-50-tops-10,000?rss=true

Conclusions

There is a substantial amount of scientific evidence that paints a worrying picture concerning BPA, due to its ability to act at very low doses. Not only does it appear that the human body is exposed to far more BPA than was once thought, it is also by no means the case that the human body rapidly 'de-toxifies', or wholly eliminates, BPA from the system. Whilst there are still many questions that require answers and further clarification, such as the specific toxicokinetics of BPA in humans, it is unsafe to base decisions regarding the TDI for this chemical on two studies which clearly have limitations.

It is clear that there is much evidence to suggest that BPA has adverse effects at very low levels. Laboratory experiments on breast cells carried out over the last 10-15 years have produced evidence to show that BPA has the ability to transform breast epithelial cells into cells of a more cancerous or overall malignant nature. There is significant evidence from animal studies which shows that exposure to BPA prenatally and during pre-pubescent phases increases mammary density and mammary cell proliferation, increases susceptibility to carcinogens and increases the number of tumours formed. BPA has been found to cause gross chromosomal damage, trigger DNA strand breaks and to interfere with cell division. There is multiple evidence in animal models to suggest that there may not be a safe concentration of BPA to which humans can be exposed and suffer no adverse effects.

Whilst it would be ideal if we had more human studies on which to draw, absence of such data does not prove that BPA is safe. On the contrary, the parallels between BPA and the synthetic oestrogens DES and those used in prescribed HRT, as well as the numerous studies which show adverse effects, clearly points to the need to take action to reduce our everyday exposure to BPA.

Whilst data can appear conflicting, it is significant that it is largely industry-funded studies that show no ill effects of BPA. It is important that such studies are not given greater weight and influence in safety assessments than other well-conducted, independent peer reviewed studies, simply because they do not always conform to OECD GLP guidelines.

Ultimately, lessons from history, as well as decades of studies and new data, have yielded compelling evidence that BPA is ubiquitous, present in the human body, is carcinogenic and is linked with breast cancers. Governments must take action now to reduce exposure to this hazardous and endocrine disrupting chemical in order to prevent further generations of women and, increasingly, men suffering from this devastating disease.

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Summary of recommendations

Urgent action is needed to reduce human exposure to BPA. As well as improved identification and elimination of EDCs, Breast Cancer UK is calling for the following:

• That the EFSA reviews the relevance of having a TDI for BPA.

The body of evidence suggests that BPA is a substance for which there are no safe levels. Therefore, the existence of a TDI for BPA provides a false sense of security, as it is assumed that as long as consumption remains below the TDI, levels of exposure are safe. The EFSA is currently in the process of reviewing the TDI for BPA and is due to report in November 2013.

• That the EU implements the precautionary principle and bans the use of BPA in all packaging and articles that are intended to come in to contact with food and drink.

Diet is a key route of exposure to BPA and, therefore, such a ban would be extremely effective in reducing people's daily intake of BPA. It is important that BPA is replaced with safer alternatives, and not with chemicals of a similar compound such as Bisphenol S and Bisphenol F, which are also oestrogenic and could have similar effects to BPA at low doses.

• That guidance is put in place at both EU and UK level to ensure that equal weight and consideration is given to well conducted, independent studies regardless of whether or not they comply with Organisation for Economic Co-operation and Development (OECD) 'good laboratory practice' (GLP) guidelines.

Current decisions on the safety of chemicals are based on studies which comply with OECD GLP studies, but fail to take into account other good scientific data. Better guidance is the only way in which all recorded adverse effects of BPA can be taken into consideration.

• That the UK Government revises the existing UK Strategy for Cancer and includes EDCs as preventable risk factors for breast cancers.

The Government has yet to acknowledge the links between EDCs and breast cancers, which means that a huge gap exists in UK cancer prevention policy and cancer prevention research. Including EDCs as preventable risk factors for breast cancers would be a good first step to help protect the health of future generations.

Glossary

Apoptosis: The process of programmed cell death.

Aneugenic: Agents that affect cell division, resulting in the loss or gain of whole chromosomes.

Angiogenic: The Angiogenic process is the physiological process through which new blood vessels form from pre-existing vessels.

Diethylstilboestrol (DES): A synthetic oestrogen that was given to pregnant women in the 1950's and 1960's to help prevent miscarriage.

ER: Estrogen (Oestrogen) receptors are a group of proteins found inside cells. There are two different forms of the estrogen receptor, usually referred to as α and β.

Ethinyloestradiol: A chemical mainly used in oral contraceptives.

In vitro: Scientific studies performed outside the body of a person or animal, sometimes called 'test tube' experiments.

In vivo: Scientific studies on living organisms, such as animals or humans.

Neoplastic: An abnormal new growth of tissue in animals or plants; a tumour.

Oocyte: A female egg cell involved in reproduction.

Prepubertal: Before puberty, the period during which secondary sex characteristics start to develop and the capability for sexual reproduction is attained.

mg: A milligram, equivalent to a thousandth of a gram.

µg: A microgram, equivalent to one millionth of a gram.

ng: A nanogram, equivalent to a billionth of a gram.

Non-monotonic dose response curve (NMDRC): In a NMDRC, there is no given order to the shape of the curve. Some NMDRCs are shaped like U's, with high observable effects recorded at low and at high doses. Others are shaped like inverted U's with the highest observer able effects recorded in intermediate ranges.

Serum: Serum is a component of blood. Although serum does not contain white or red blood cells, it includes all proteins not used in blood clotting as well as antibodies, antigens, hormones, and any other substances, such as drugs and microorganisms.

Tolerable Daily Intake (TDI): An estimate of the amount of a substance expressed on a body weight basis, which can be ingested daily over a lifetime without appreciable risk.

Tamoxifen: A hormonal drug used to treat oestrogen positive breast cancers.

Transgenic mice: Mice which are genetically modified as embryos to either carry an oncogene that has the potential to cause cancer, or have tumour suppressing genes removed, thereby increasing their probability of developing cancer over time.

Telomeres: These protect the end of the chromosome from deterioration or from fusion with neighbouring chromosomes.

Tumorigenesis: The process by which normal cells are turned into cancer cells.

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