Breast Cancer UK
Prevent the preventable

BCUK Background Briefing | Parabens

What are parabens?

Parabens and para-hydroxybenzoic acid are synthetically produced preservatives used in cosmetics and food. They are also produced naturally. Para-hydroxybenzoic acid is produced by all flowering plants[1], and parabens are produced by some plants and bacteria, possibly for their anti-microbial properties[2 - 5]. Parabens are known by various names (see Appendix Table 1) and are also referred to collectively as esters of para-hydroxybenzoic acid (see Appendix Figure 1 for chemical structures).

Where are they used?

The most common use for parabens is as a preservative in cosmetics and personal care products (which include shampoos, conditioners, deodorants, moisturizers, makeup, creams, lotions, skin cleansing products and mouth wash)[6]. They are usually listed as the ingredients ethyl-, methyl-, propyl-, and butyl parabens. Parabens are also used in pharmaceuticals, medicines, and some food products where they may be listed as E numbers (see Appendix Table 1). Their use as food additives, which include E214, E215, E218 and E219, is uncommon in the UK. It is estimated the UK uses around 150 tonnes of parabens annually[7].

How are we exposed?

Many people are exposed to parabens and para-hydroxybenzoic acid on a daily basis, particularly through use of personal care products. Parabens are readily absorbed through the skin, so leave-on skin products containing parabens, such as lotions and make-up, provide continuous exposure[8].

Parabens absorbed through the skin or ingested in food are eventually metabolised and excreted in urine. Parabens from food are usually excreted more quickly than those absorbed through the skin[6, 9, 10]. Parabens have been measured in blood and urine, including that of pregnant women, placental tissue, amniotic fluid, cord blood after crossing the placenta, in breast milk and in breast tissue[11-16].

> Many of us are exposed to **parabens** on a regular basis. These compounds have been measured in breast tissue, breast milk and placental tissue. In laboratory tests, high concentrations of parabens have been found to mimic oestrogen. Oestrogen is associated with increased breast cancer risk, and compounds which mimic this hormone may also be linked to breast cancer. When breast tissue is developing, it is particularly sensitive to the effects of oestrogen and oestrogen mimics. Although more research is needed to better understand the risks from exposure to oestrogen mimics, Breast Cancer UK believes it is important to take precautionary measures to protect ourselves and our families.

Parabens have become widespread in the environment. They have been measured in drinking water[17], river water[18], groundwater[19], soil and sediments[20], aquatic organisms[21, 22] including farmed fish and shrimp[23], as well as in house dust, and indoor and outdoor urban air[24, 25, 26].

Is there a link between parabens and breast cancer?

There is growing evidence that parabens and para-hydroxybenzoic acid can act as oestrogenic endocrine disrupting chemicals, interfering with our hormone system, in particular with the hormone oestrogen[9]. At high concentrations, parabens may increase breast cancer risk[27], and may also be implicated in the proliferation of breast cancer[28, 29].

Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs, also called endocrine disruptors) are substances which alter

the functioning of the endocrine system and interfere with hormone action in a way which has a negative impact on health[30], including increasing the risk of some cancers.

The potential negative effects of exposure to endocrine disrupting chemicals *in utero* (in the womb), may not develop until later in life, or in the next generation, which makes it very hard to show definitively the association between exposure to endocrine disruptors and adverse health impacts[31]. For more information on EDCs see Breast Cancer UK's EDC webpage.

The important role of oestrogen and oestrogen mimics

Oestrogen works by binding to oestrogen receptors, which are found in tissues throughout the body. The resulting complex triggers a chain of important biological events including the development of breast tissue[32]. High levels of oestrogen are linked to an increased risk of breast cancer because oestrogen encourages cells to divide more rapidly. A higher rate of cell division increases the possibility of mutations occurring, including those that lead to breast cancer.

Many of the EDCs suspected of increasing breast cancer risk are oestrogenic. Oestrogenic compounds are linked to increased breast cancer risk because they mimic oestrogen's ability to bind to oestrogen receptors, encourage cell division, and trigger oestrogen-sensitive gene expression. Exposure to oestrogenic EDCs is thought to be most potentially damaging if it occurs during periods of breast tissue development when breast cells divide and change; *in utero*, around puberty, and during pregnancy[33 - 36].

How oestrogenic are parabens?

In vitro tests (those carried out in a test tube or culture dish) show that parabens and para-hydroxybenzoic acid are oestrogenic. The order of

Parabens are used as preservatives in many cosmetics products

decreasing oestrogenicity of these compounds is as follows: butyl paraben > propyl paraben > ethyl paraben > methyl paraben > para-hydroxybenzoic acid (see Appendix Table 2). However, the concentration of parabens and para-hydroxybenzoic acid needed to have an oestrogenic effect (effective concentration) is much higher (one hundred thousand to ten million times) than that of natural oestrogen[37, 9, 38] (see Appendix Table 2). These differences in effective concentrations between parabens and natural oestrogen might not mean parabens are safe. Natural oestrogen is a very powerful chemical which is effective at extremely low concentrations, and concentrations of parabens in the products we use are much higher. Research *in vitro* shows that when parabens are tested using high concentrations, individually, or in combination, they can bind to oestrogen receptors, stimulate cell proliferation, and trigger the first stage of oestrogen-receptor-dependent gene expression. Therefore, the concentrations we have of these compounds in our bodies is essential for an

evaluation of whether parabens and para-hydroxybenzoic acid may increase our breast cancer risk.

What concentrations of parabens are we exposed to?

There have been many studies measuring parabens and paraben metabolites (break-down products) in urine (as opposed to human tissue) which demonstrate the almost universal human exposure to parabens. Studies show that relatively high concentrations of parabens are efficiently metabolised and removed from our bodies[39-41]. Research also shows that reducing exposure to parabens results in lower levels in urine after a few days[42]. Generally, methyl paraben, the paraben with the weakest oestrogenicity, is found in the highest concentrations in urine, followed by propyl paraben, and ethyl paraben, with lowest concentrations found of butyl paraben, the most oestrogenic of the permitted parabens[43]. Measurements of parabens in urine show a wide range of concentrations, which may be influenced by individual levels of usage of personal care products, cosmetics and pharmaceuticals[44]. Studies of paraben concentrations in blood generally show very low levels[13, 45].

Information on concentrations of parabens in human tissue is very limited. There is one study which measured paraben concentrations in 160 non-cancerous breast tissue samples from breast cancer patients[11] (see Appendix Table 2). This study found that 99% of breast tissue tested contained parabens. Surprisingly, a very wide range of paraben concentrations was found, even in samples from the same patient. Average concentrations were much lower than the effective concentrations used in the *in vitro* tests (Appendix Table 2), although the highest concentrations found in breast tissue were within the range of effective concentrations used in some of the tests (see Appendix Table 2). However, measurements of *in vitro* test concentrations and breast tissue concentrations are not directly comparable, as the breast tissue originated *in vivo* (as part of a whole biological system) and the *in vitro* tests were carried out in culture media.

Parabens are permitted for use in processed and precooked meat, cereal or potato based snacks, coated nuts & confectionery

Low levels of parabens have also been measured in placental tissue. In one small study parabens were detected in 90% of the placental tissue samples, at concentrations similar to average concentrations measured in breast tissue[11], which were low overall[46]. Other research has estimated that the oestrogenic dose from parabens measured in blood samples from children could be similar to the dose they are exposed to from their natural oestrogen, effectively doubling their oestrogenic burden[47]. Together this research suggests that parabens can occasionally be present in our bodies at concentrations high enough to mimic the effects of naturally occurring oestrogen, and, therefore, potentially have a negative effect on breast cancer risk and outcomes, but more research is needed as this conclusion is based on a single study.

Other studies have found an association with a person's level of use of products containing

parabens, and concentrations found in urine and breast milk[15], and have demonstrated that reducing exposure to parabens rapidly reduces levels in urine[42], suggesting that reducing exposure is effective. However, we do not yet know whether it is high exposure to parabens that leads to high concentrations in tissue including breast tissue, if individuals store parabens in their body tissue in different amounts, or how long parabens remain in our tissues.

Another area of research which is lacking is tests on the effect of mixtures of parabens with other oestrogen compounds. This is important as multiple chemicals could interact to have harmful effects which may not be evident from studies of individual chemicals.

Could parabens play a role in breast cancer progression?

Some research has indicated a possible role of parabens in breast cancer progression. One *in vitro* study showed that parabens at levels lower than the average concentrations found in breast tissue stimulated the expression of female sex hormone receptors (i.e. oestrogen and progesterone receptors)[48]. This suggests that they may be implicated in breast cancer progression, even at low concentrations. Furthermore, results from tests using non-cancerous breast cells suggest that such low concentrations of parabens could play a possible role in breast cancer initiation[48], while results from one experiment suggest that propyl paraben might inhibit programmed cell death in cancer cells, enabling these cells to survive[49]. Another study found that *in vitro* exposure of human breast cancer cells to high concentrations of parabens increased the cells' migratory and invasive properties[50]. A recent study showed that molecules known as human epidermal growth factor receptor ligands (HER ligands), which are found in breast cells, may enhance the cell

Parabens are added to many types of personal care product

proliferation activity induced by butyl paraben[30]. Another study suggests that methyl paraben may increase breast cancer tumour proliferation by enhancing the activity of tumour-initiating cells, making breast cancer resistant to chemotherapy[29]. It has also been shown *in vitro* that parabens can increase active oestrogen in cells by blocking a natural chemical reaction which normally reduces active oestrogen concentrations by converting them to an inactive form of oestrogen. In addition, an additive effect was seen when more than one paraben was present[10].

Recently a study was carried out into the effects of low concentrations of methyl paraben on rodents during critical windows of development[28]. Paraben exposure during puberty resulted in changes in gene expression similar to those seen in human breast cancer, suggesting that the timing of exposure is important and that parabens can play a role in breast cancer proliferation.

Another study of methyl and ethyl paraben found that the paraben dose needed to produce the human-matched level of parabens in rat urine was close to the EU permitted level of parabens in food[51, 52]. The study demonstrated that at these concentrations parabens caused an increase in the expression of oestrogen responsive genes[1].

Conclusion

In the course of our daily lives we are likely to be exposed to parabens and para-hydroxybenzoic acid on a regular basis. We also know that these compounds are removed from our bodies in urine.

Research shows that parabens and para-hydroxybenzoic acid can mimic the effects of oestrogen in three widely accepted *in vitro* oestrogenicity tests, albeit at much higher concentrations than natural oestrogen.

Average concentrations of parabens measured in one study of breast tissue were much lower than the concentrations used in the tests. However, some of the higher concentrations measured in breast tissue are within the range of concentrations used in the oestrogenicity tests. In addition, some research suggests that much lower concentrations of parabens may play a role in breast cancer initiation and progression. Together, this suggests that some of us may have levels of parabens in our bodies which can mimic oestrogen, potentially increasing our risk of breast cancer. This risk is thought to be higher during periods of breast tissue development. However, it is not yet possible to say how small or large the increase in risk might be, or how strong the link with breast cancer is in comparison to other known risks.

Although there is some evidence suggesting that parabens may play a role in breast cancer, studies of the direct effects of parabens on humans are lacking, especially during important stages of development, and long term studies are needed to assess the possible effects of exposure over a life time. Therefore, we must be cautious in interpreting results of a few studies.

Research is also needed to find out if differences in exposure levels account for differences in the amount of parabens in our tissues, and how long these compounds remain in our tissues following any exposure. In addition, it is important to consider interactions between parabens and other compounds in the products we use, which may enhance or counteract any potentially harmful effects.

It may take a long time before we can be sure of the link between parabens and breast cancer risk. Until then, we can take precautions to reduce our parabens exposure, which can do no harm and which may have a beneficial effect.

Regulation of parabens and para-hydroxybenzoic acid

Currently, the regulation of parabens and para-hydroxybenzoic acid falls under EU legislation and each compound has permitted concentration limits. Under this legislation, seventeen different parabens and para-hydroxybenzoic acid are permitted for use in cosmetics and personal care products, the most commonly used being ethyl paraben methyl paraben propyl paraben and butyl paraben[51]. Ethyl paraben, methyl paraben and their sodium salts are permitted for use as preservatives in processed and precooked meat, cereal and potato based snacks, coated nuts, and confectionery[53].

In medicines and pharmaceutical products, methyl paraben, propyl paraben, ethyl paraben and butyl paraben are used as preservatives[54].

In 2014, the EU banned five parabens previously used in cosmetics (phenyl paraben, benzyl paraben, pentyl paraben, isopropyl paraben and isobutyl paraben) because there was insufficient information to evaluate their safety[51]. This legislation also reduced the permitted amounts of ethyl paraben, methyl paraben, propyl paraben and butyl paraben in cosmetics because of their potential endocrine disrupting properties and prohibited use of butyl paraben and propyl

parabens in the nappy area of children under three years of age.

Under the EU Community Rolling Action Plan (CoRAP)[55], parabens are being re-evaluated because of their potential endocrine disrupting properties. Methyl paraben and propyl paraben are currently undergoing re-evaluation, including further safety tests and butyl paraben will be re-evaluated by 2019.

Para-hydroxybenzoic acid has been re-evaluated and concluded to be safe at current permitted levels.

Breast Cancer UK policy position

Breast Cancer UK supports efforts to reduce the amounts of parabens permitted in products designed to be applied to the skin or used in food; the long-term phase out of parabens in products designed to be applied to the skin or used in food; and asks that cosmetics and personal care products no longer be exempt from the EU Regulation on Classification, Labelling and Packaging (EC) No 1272/2008, in order that they display hazard warnings if applicable.

What can you do to reduce your exposure to parabens?

There are many risk factors for breast cancer, and therefore, many actions we can take that can help us to reduce our risk. One of these actions is to reduce exposure to potentially harmful chemicals including oestrogen mimics such as parabens and para hydroxybenzoic acid:

- where possible, choose personal care products and make up that do not contain parabens.
- in particular, if you use leave-on products applied to the skin (such as body creams, tanning lotions and makeup) choose paraben-free products. This is especially important during pregnancy and breastfeeding, for young children, and during puberty.
- check your children's snacks and processed foods for the relevant E numbers (E214, E215, E217, E218); if present find alternative products where possible.
- in general, try to buy fresh food, rather than canned or packaged; minimise intake of processed food and eat freshly cooked food as often as possible.

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Breast Cancer UK works to save lives and reduce breast cancer rates by tackling the environmental and chemical causes of the disease.

For further information on how harmful chemicals may be linked to breast cancer and full references please visit our website www.breastcanceruk.org.uk

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Appendix

Table 1. List of parabens permitted for use in the EU with common alternative names. For a more comprehensive list of alternative names see EWG's skindeep cosmetics database website.

Common name	E number	Alternative name	Alternative name
para-hydroxybenzoic acid		p- hydroxybenzoic acid	4-hydroxybenzoic acid
ethyl paraben	E214	ethyl p-hydroxybenzoate	ethyl 4-hydroxybenzoic acid
sodium ethyl paraben	E215	sodium ethyl p-hydroxybenzoate	sodium ethyl 4-hydroxybenzoic acid
propyl paraben	E216	propyl p-hydroxybenzoate	propyl 4-hydroxybenzoate
sodium propyl paraben	E217	sodium propyl p-hydroxybenzoate	sodium propyl 4-hydroxybenzoate
methyl paraben	E218	methyl p-hydroxybenzoate	methyl 4-hydroxybenzoate
sodium methyl paraben	E219	sodium methyl p-hydroxybenzoate	sodium methyl 4-hydroxybenzoate
potassium ethyl paraben		potassium ethyl p-hydroxybenzoate	potassium ethyl 4-hydroxybenzoate
potassium methyl paraben		potassium methyl p-hydroxybenzoate	potassium methyl 4-hydroxybenzoate
sodium paraben		sodium p-hydroxybenzoate	sodium 4-hydroxybenzoate
potassium paraben		potassium p-hydroxybenzoate	potassium 4-hydroxybenzoate
calcium paraben		calcium p-hydroxybenzoate	calcium 4-hydroxybenzoate
butyl paraben		butyl p-hydroxybenzoate	butyl 4-hydroxybenzoate
sodium butyl paraben		sodium butyl p-hydroxybenzoate	sodium butyl 4-hydroxybenzoate
potassium butyl paraben		potassium butyl p-hydroxybenzoate	potassium butyl 4-hydroxybenzoate
potassium propyl paraben		potassium propyl p-hydroxybenzoate	potassium propyl 4-hydroxybenzoate
hexamidine paraben			
hexamidine diparaben			

Table 2. Results of paraben and para-hydroxybenzoic acid a) oestrogen binding assays, b) cell proliferation assays and c) reporter gene assays, with concentrations of parabens in 160 non-cancerous breast tissue samples from breast cancer patients. Note that 17β-oestradiol is referred to as natural oestrogen throughout the text. References: [a] Byford et al. 2002 R; [b] Pugazhendi et al. 2005 R; [c] Charles & Darbre 2013 R; [d] Barr et al. 2012 R. Cell proliferation assay durations: [a] 12 days; [b] 7 days, [c] 14 days. For example, in a cell proliferation assay, butyl paraben achieved a similar level of cell proliferation to 17β-oestradiol, when a $1x10^{-5}$ Molar concentration of butyl paraben was used. This concentration is 100 000 times stronger that the concentration of 17β-oestradiol used in the test [a].

a) Oestrogen receptor binding assays	
substance name	**relative concentration for maximum observed effect**
	brackets show effect strength as %
17β-oestradiol [a]	x 10 (100%)
butyl paraben [a]	x 1 000 000 (86%)
propyl paraben [a]	x 1 000 000 (77%)
ethyl paraben [a]	x 1 000 000 (55%)
methyl paraben [a]	x 1 000 000 (21%)
17β-oestradiol [b]	x 100 (100%)
methyl paraben [b]	x 10 000 000 (72%)
p-hydroxybenzoic acid [b]	x 10 000 000 (99%)
b) Cell proliferation assays	
substance name	**molar concentration in growth medium for maximum observed effect**
	brackets show concentration relative to that of 17β-oestradiol =E means effect achieved equivalent to that from 17β-oestradiol
17β-oestradiol [a]	$1x\ 10^{-10}$
butyl paraben [a]	$1x10^{-5}$ =E (x 100 000)
propyl paraben [a]	$5x10^{-5}$ =E (x 500 000)
ethyl paraben [a]	$1x10^{-4}$ =E (x 1 000 000)
methyl paraben [a]	$2x\ 10^{-4}$ (x 2 000 000)
p-hydroxybenzoic acid [b]	$1x10^{-4}$ (x 1 000 000)
	brackets show concentration relative to that of 17β-oestradiol
17β-oestradiol [c]	5×10^{-11}
butyl paraben [c]	5×10^{-6} (x 100 000)
propyl paraben [c]	6×10^{-6} (x 120 000)
ethyl paraben [c]	4×10^{-5} (x 800 000)
methyl paraben [c]	2×10^{-4} (x 4 000 000)
c) Reporter gene assays (oestrogen-sensitive gene expression)	
substance name	molar concentration in growth medium 24 hours
	round brackets: concentration relative to 17β-oestradiol; curly brackets: % increase in oestrogen-sensitive gene expression
17β-oestradiol [a]	$1x\ 10^{-8}$ {260%}
butyl paraben [a]	$1x\ 10^{-5}$ (x 1 000) {20%}
propyl paraben [a]	$1x\ 10^{-5}$ (x 1 000) {30%}
ethyl paraben [a]	$1x\ 10^{-4}$ (x 10 000) {40%}
methyl paraben [a]	-
17β-oestradiol [b]	$1x\ 10^{-8}$ {207%}
methyl paraben [b]	$1x\ 10^{-3}$ (x 100 000) {63%}
p-hydroxybenzoic acid [b]	$5x\ 10^{-4}$ (x 10 000) {26%}

Table 2 cont.

Concentrations of parabens in breast tissue	
substance name	maximum concentration in breast tissue (nanograms of compound per gram of tissue)
butyl paraben [d]	95
propyl paraben [d]	2053
ethyl paraben [d]	500
methyl paraben [d]	5103

Figure 1

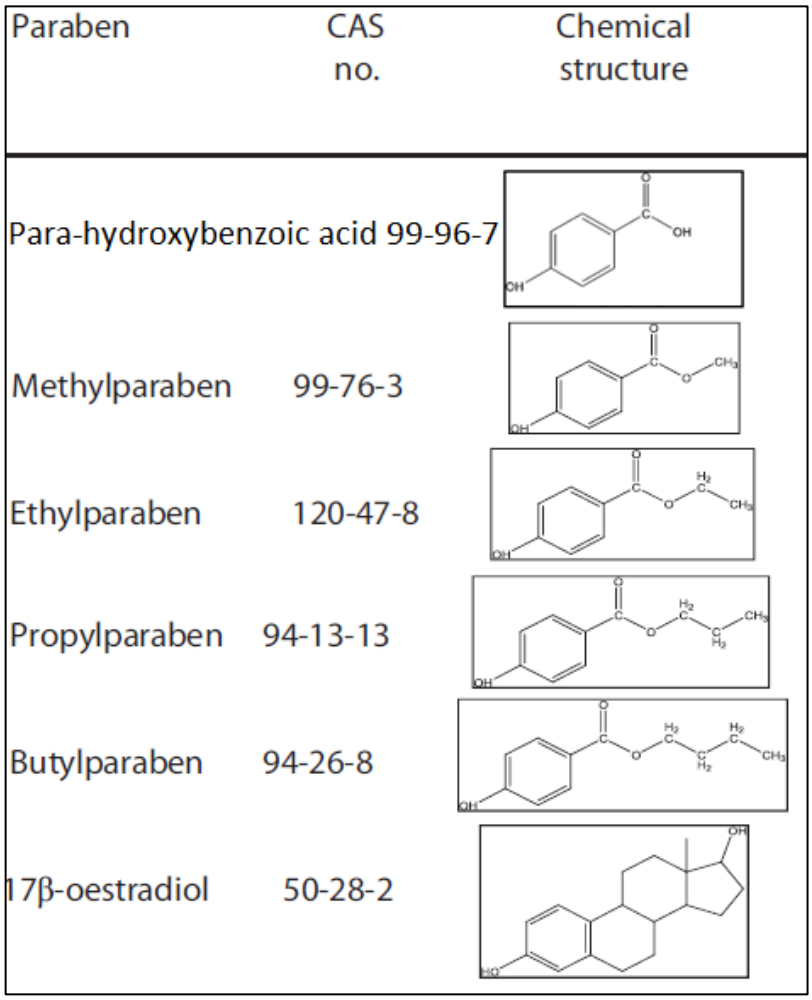

Figure 1. Chemical structure and CAS number of para-hydroxybenzoic acid, parabens and 17β-oestradiol. Adapted from Pugazhendi et al. (2005)[9], and Darbre and Harvey (2014)[27].