Phthalates and breast cancer

Alice Di Pasquale, Hannah Moody

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

1. Summary

Breast cancer is the second most common cancer worldwide, with an estimated 2.3 million new cases in 2022. Exposure to Endocrine Disrupting Chemicals (EDCs) has been proposed to be a risk factor that may contribute to the risk of developing breast cancer. Phthalates are a class of EDCs used in many consumer products, such as polyvinyl chloride (PVC) plastic and cosmetics. They are considered to have strong anti-androgenic activity and weaker oestrogenic effects. Phthalates were observed to induce proliferation of breast cancer cells and affect the mammary gland in animals. In humans, exposure to some phthalates may increase breast cancer risk, thus justifying a precautionary approach. Exposure to phthalates can be reduced by using EDC-free products, eating fresh organic food and avoiding pre-packaged food. The harmful effects of some phthalates have also been recognised by the EU and UK, which has led to some restrictions. However, many phthalates are still unregulated and used in many products. Breast Cancer UK is calling for a progressive phasing out of EDCs in consumer and non-essential products.

2. Introduction

Breast cancer is the second most common cancer worldwide, with an estimated 2.3 million new cases in 2022 [1]. In the UK, around 56,000 women and 400 men are diagnosed with breast cancer each year [2]. High levels of oestrogen or prolonged exposure to this hormone throughout life, caused by early puberty or late menopause, are known to increase breast cancer risk [3]. The important role that hormones play in several types of breast cancer, suggests that other factors that interfere with hormones may also increase risk [4]. Endocrine Disrupting Chemicals (EDCs) are harmful chemicals that can interfere with the endocrine system; the network of hormones that

Glossary box:

Agonist: a chemical that binds to a receptor leading to its activation.

Antagonist: a chemical that binds to a receptor blocking its activation.

(anti-)Androgenic effect: a chemical with androgenic effects can mimic the action of androgens (male sex hormones) or increase their activity, whilst a chemical with anti-androgenic effects reduces their activity.

(anti-)Oestrogenic: a chemical with oestrogenic effects can mimic the action of oestrogens (female sex hormones) or increase their activity, whilst a chemical with anti-oestrogenic effects reduces their activity.

How to cite: Di Pasquale A., Moody H. Phthalates and breast cancer. Breast Cancer UK. 2024. https://www.breastcanceruk.org.uk/resources/phthalates-and-breast-cancer/

control the development and functioning of the human body [5]. EDCs that interfere with any aspect of the oestrogen function may be linked to breast cancer [6]. In this review, we will examine a class of EDCs known as phthalates and their possible link with breast cancer.

3. Properties and uses of phthalates

Chemically, phthalates are diesters of phthalic acid (Figure 1) with different side chains (see Appendix 1 for their chemical structures). They are usually divided into short-chain (< 8 carbon atoms) and long-chain (≥ 8 carbon atoms) phthalates, based on the size of the side chains (Table 1) [7].

The chemical structure of phthalates also roughly determines their uses. Long-chain phthalates are used as plasticisers in polyvinyl chloride (PVC) plastic to give flexibility, transparency, durability and longevity to products [20,21]. However, phthalates are not chemically bound to the plastic and can leach from it and be released into the

Glossary box (cont.):

Biomonitoring studies: studies that measure the levels of certain chemicals in human body fluids (e.g., blood, urine) or tissues (e.g., breast tissue).

Epidemiological studies: studies on human populations to assess if exposure to a certain factor is linked to a disease.

Epigenetic changes: are heritable changes affecting the way genes are expressed, but without altering the DNA sequence.

In vitro studies: experiments conducted with cells grown in the laboratory or biological molecules. Also known as "test-tube experiments" and do not involve a whole living organism.

Meta-analysis: statistical analysis of multiple published scientific studies.

Steroidogenesis: the biochemical process that produces sex hormones from cholesterol.

Transcription: the process that copies DNA into RNA, ultimately resulting in the production of proteins.

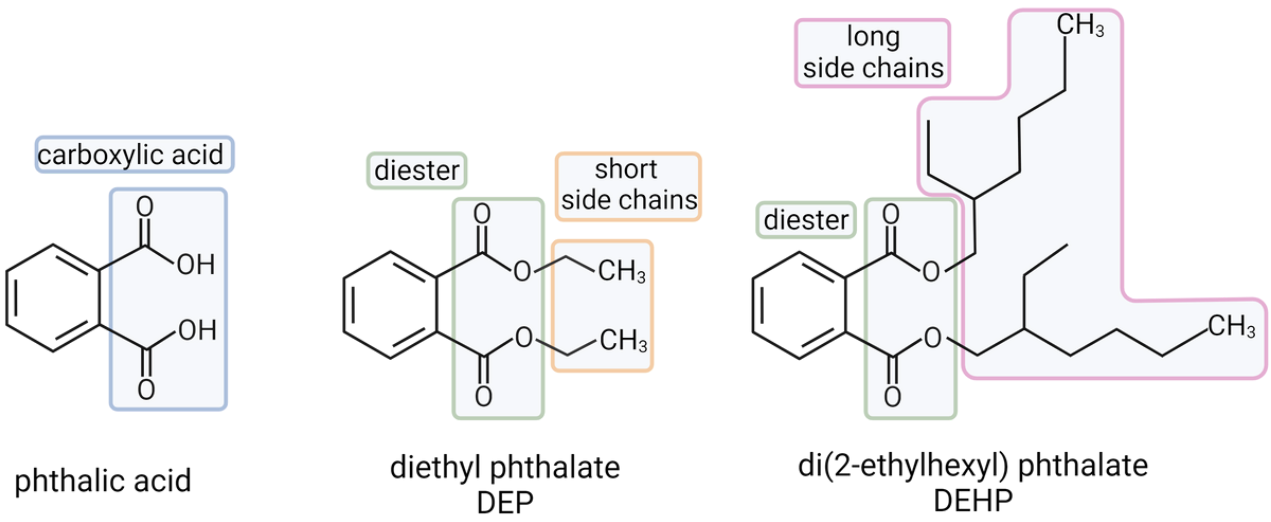


Figure 1.Chemical structures of phthalic acid, DEP (a short-chain phthalate) and DEHP (a long-chain phthalate). Created with BioRender.com

Table 1. List of phthalates discussed in this review, including full names, acronyms, common metabolites (breakdown products) and uses. This is not a comprehensive list of all phthalates that may exist. The acronyms in bold are used throughout this review; other acronyms used in the literature are reported for clarity.

	Full name	Acronym	Metabolites	Uses* [8]
Short chain phthalates	Dimethyl phthalate	**DMP**	MMP	Personal care and cleaning products, cosmetics, toys, building materials, pharmaceuticals [9]
	Diethyl phthalate	**DEP**	MEP	Personal care products, pharmaceuticals, cosmetics, cleaning products
	Di(2-methoxyethyl) phthalate	**DMEP**	MMEP	Plasticiser [10]
	Dibutyl phthalate	**DBP**, DNBP, DnBP	MCPP, MBP	Building materials, personal care products, cosmetics, medications
	Diisobutyl phthalate	**DIBP**	MIBP	Cosmetics, building materials [11]
	Benzyl butyl phthalate	**BBP**, BBzP	MBzP, MBP	PVC plastic, building materials, toys, food packaging, personal care products
	Di-n-pentyl phthalate	**DPP**, DPNP, DPENP	MNPEP	Building materials
	Diisopentyl phthalate	**DIPP**, DiPeP	-	-
	n-Pentyl-isopentylphthalate	**DNPP**, DnPP	-	-
	Dihexyl phthalate	**DNHP**	-	PVC plastic [12]
	Diisohexyl phthalate	**DIHP**	-	Lubricant [13]
	Dicyclohexyl phthalate	**DCHP**, DCP	MCHP	Cleaning products, building materials [14]
	Bis(2-butoxyethyl) phthalate	**BBOP**	-	Plasticiser [15]
	Diheptyl phthalate	**DHP**	-	PVC plastic, lubricants
Long chain phthalates	Di-n-octyl phthalate	**DNOP**, DINOP, DOP	MCPP, MNOP	Plasticiser, medical devices, flooring, packaging, cosmetics, building materials [16]
	Diisooctyl phthalate	**DIOP**	-	Plasticiser [17]
	Di(2-ethylhexyl) phthalate	**DEHP**	MEHP,MEHHP, MEOHP, MECPP [18]	PVC plastic, medical devices, flooring, toys, food packaging
	Diisononyl phthalate	**DINP**, DiNP	MINP, MCOP	PVC plastic, electric cables, building materials, toys
	Diisodecyl phthalate	**DIDP**, DiDP	MCNP	PVC plastic, medications, food packaging, flooring
	Di(2-propylheptyl) phthalate	**DPHP**	-	Plasticiser [19]

*This is not a comprehensive list of all the uses and products where phthalates may be present. In addition, some of these phthalates may be subject to regulations (Table 2).

environment [5]. Phthalates may be found in many PVC products, such as food packaging, toys, cables, vinyl flooring, medical devices, building materials and furniture [22]. Examples of phthalates that are used as plasticisers include DEHP, DINP and DIDP [7], and some short-chain phthalates, such as BBP [23].

Alternative short-chain phthalates (e.g., DEP and DIBP) are mainly used in personal care products, cosmetics, paint, adhesives, and slow-release tablets [22]. In cosmetics and cleaning products, phthalates are often used to allow fragrances to last longer and may be labelled under the terms “fragrance”, “parfum” or “perfume” [24]. Phthalates can also be used as moisturisers and skin penetration enhancers in cosmetics [25].

4. Exposure routes

Humans are mainly exposed to phthalates through ingestion of contaminated food, or inhalation and skin absorption from cosmetics.

Long-chain phthalates may enter food from manufacturing plastic equipment [22], or from packaging and plastic films, especially when these are heated in a microwave [26]. To a lesser extent, they may also enter food through the contaminated external environment [27]. Whilst some contamination has been found in all types of food; fatty, processed and packaged food (e.g., ready meals, fast food) can contain high levels of phthalates [27–29]. A higher intake of DEHP and DINP was associated with the consumption of fast food [29].

Phthalates can also be found in polyethylene terephthalate (PET) plastic bottles. PET plastic does not require plasticisers, but these can enter the plastic due to cross-contamination during plastic production and recycling [30,31]. Migration of phthalates from the bottle into the liquid may result in drinks containing high levels of phthalates, especially if they are acidic liquids (e.g., soft drinks, vinegar and alcohol) [28,31,32].

Phthalates may also be used as plasticisers in medical devices made of PVC plastic, such as tubing, blood bags and dialysis equipment [33]. Whilst this may not affect the wider population, exposure from medical devices can be a significant source of phthalates for people receiving transfusions, intensive care or dialysis [24]. People using medications with delayed or extended-release properties may also be exposed to higher levels of short-chain phthalates [34]. However, for the wider population, the main source of short-chain phthalates (e.g., DEP and DIBP) comes from cosmetic products, from which phthalates can be inhaled or absorbed through the skin [35,36]. Exposure to short-chain phthalates was found to be significantly higher in individuals using cosmetics, perfumes, deodorants and creams [25,37].

In addition to direct exposure, many products may release these chemicals into the home environment where they may accumulate in dust [36,38]. Higher accumulation was seen in homes with recently replaced floors, painted walls and plywood furniture [38]. Exposure to dust, combined with the use of soft-

plastic toys and hand-to-mouth behaviour, may result in children having higher levels of phthalates than adults [24,39].

5. Metabolism and biomonitoring

After entering the body, phthalates are rapidly metabolised and eliminated in the urine within 24 hours from exposure. All phthalates undergo a first transformation from the diester form (e.g., DEHP) to the monoester (e.g., MEHP) [22], as shown in Figure 2. In addition, long-chain phthalates are subject to further processing generating multiple metabolites (e.g., MEOHP, MECPP, MEHHP) [7,40]. The conversion of phthalates into their metabolites (Table 1) may not eliminate their toxicity and the metabolites may still display harmful effects [41].

Biomonitoring studies usually measure metabolite urinary levels to evaluate phthalate exposure in a population [22]. Urinary metabolites of DEHP and DINP were detected in 98% of the US population [42]. In Europe, exposure to DEHP, DBP and BBP has been decreasing in the last 2 decades, due to regulations limiting their uses. However, exposure to their substitutes (e.g., DINP, DIDP and DPHP) has increased [43]. It is worth noting that due to quick elimination, urinary levels are only representative of the exposure that occurred within the last 24 hours [22]. To better estimate the overall human exposure, multiple urine samples should be collected [36].

In addition to urine, phthalates have also been found in other body fluids and tissues, including saliva, amniotic fluid, peritoneal fluid, milk, serum, semen and breast tissues [4,8]. However, in breast milk their concentration may be lower than in other fluids [8].

6. Phthalates and breast cancer

6.1 In vitro

The endocrine-disrupting properties of phthalates have been investigated in vitro using cellular models. Phthalates may interfere with hormones via direct mechanisms, such as binding to hormone receptors and alterations to hormone synthesis, or via indirect mechanisms through other cellular pathways or epigenetic changes [25,44].

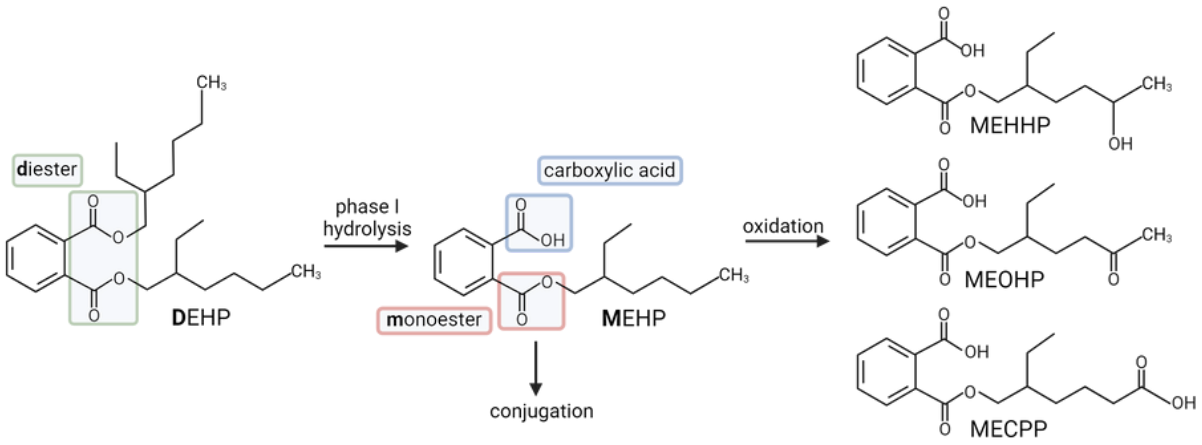


Figure 2. DEHP metabolic transformation to commonly measured metabolites: MEHP, MEHHP, MEHOP, MECPP [39]. The metabolism of DEHP also includes conjugation (not shown). Created with BioRender.com

6.1.1 Hormone receptors

Phthalates may interfere with hormones by binding to their receptors, in particular androgen (AR) and oestrogen receptors (ER). These receptors are proteins that regulate the expression of genes, a process known as transcription. The gene is then "translated" into a protein which mediates a cellular response [45]. Based on their chemical structure, phthalates may bind to hormone receptors as agonists (i.e., activating transcription) or as antagonists (i.e., blocking transcription) [46]. Some phthalates may bind to multiple receptors, whilst others may only bind to a single type [47].

The phthalates DEHP and DBP are known to have strong anti-androgenic activity acting as AR antagonists, thus reducing testosterone activity [45,46]. Phthalates (e.g., BBP, DBP, DEP) can also mimic oestrogen and display oestrogenic activity, with some binding directly to the ER [47–56]. There are two isoforms of the oestrogen receptor: ERα which promotes cancer initiation and progression, and ERβ which inhibits cell proliferation [57]. Most studies have reported BBP and DBP to be ERα agonists and increase proliferation of human breast cancer cells [47,49–52,54]. DEHP is also largely reported to be oestrogenically active [47,49,53–55], however in some studies it displayed anti-oestrogenic properties or no activity [46,50]. This may be due to the concentrations used in the experiments, as different effects may be observed at different concentrations. For instance, BBP and DBP, despite being ER agonists, have anti-oestrogenic effects at high concentrations [51]. It is unclear whether this is due to a genuine anti-oestrogenic effect or caused by cytotoxicity† [51].

Other phthalates have very weak oestrogenic activity (i.e., DIBP and DINP), no oestrogenic effects (i.e., DIDP and DNOP) [50,55] or may be ER antagonists (i.e., DCHP and DPP) [58]. Many metabolites were also found to be oestrogenically inactive, or to have anti-oestrogenic properties at high concentrations [49,50].

Phthalates may also act independently from ERs promoting various aspects of breast cancer development. DEHP has been shown to promote the process of "invasion" of ER-negative breast cancer cells suggesting that it may promote breast cancer metastasis (i.e., spread around the body) [59]. Similarly, BBP and DBP also promote growth, migration and invasion of ER-negative breast cancer cells [60]. DEHP may also induce progesterone receptor (PR)-dependent proliferation and angiogenesis (i.e., new blood vessel growth) in triple-negative breast cancer cells [4,61]. Thus, the effect of phthalates on breast cancer progression is complex.

6.1.2 Steroidogenesis

Phthalates may also display endocrine-disrupting properties and alter hormone levels by interfering with the synthesis of steroid hormones, a process also known as steroidogenesis [46]. Phthalates can directly block enzymes involved in steroidogenesis or affect

†Cytotoxicity. A chemical displaying cytotoxicity can lead to the death of cells.

their expression [62].

DBP and DPP may reduce progesterone and testosterone levels by blocking a key enzyme involved in their production [63]. BBOP and DCHP were found to inhibit different enzymes which are involved in the synthesis of oestrogen, testosterone and progesterone [63,64]. Whilst some metabolites of phthalates (e.g., MEHP and MBP) were not found to significantly block enzymes, MEHP was found to decrease oestradiol (a type of oestrogen) synthesis potentially through reducing enzyme expression [65]. High levels of oestradiol have been linked to an increased risk of breast cancer [66].

6.1.3 Peroxisome Proliferator-Activated Receptors (PPARs)

Phthalates may also interfere with other cancer-relevant transcription factors that regulate gene expression, such as the Peroxisome Proliferator-Activated Receptors (PPARs). There are 3 different variants of PPARs: PPARα and PPARβ, which both promote the growth of human breast cancer cells, and PPARγ, which inhibits cell proliferation [67]. A high concentration of MEHP may activate PPARα inducing cell proliferation, whilst a low concentration may reduce the growth rate of breast cancer cells via PPARγ activation [67]. DEHP, DIBP and DBP may also stimulate the activity of PPARs, but their role needs to be further elucidated [46]. Through PPARs, phthalates may also activate the BRCA1 gene‡ [40] and suppress oestradiol synthesis [7].

6.1.4 Epigenetic changes

Phthalates may also cause epigenetic changes that can affect the endocrine system. Epigenetic changes are heritable alterations to the way genes are expressed, but not to the DNA sequence [8]. A key epigenetic molecular structure is DNA methylation, where methyl groups§ are added to some DNA residues [8]. Methylation (addition of methyl groups) of a gene can switch off its expression, thus preventing protein production. Conversely, demethylation (removal of methyl groups) may switch on gene expression allowing the protein to be produced. Any intervention that alters the epigenetic state can have effects on gene expression patterns and impact cell function. [68]. Some phthalates (e.g., BBP and DBP) have been observed to cause a reduction of DNA methylation at the ERα gene in human breast cells, thus increasing ERα expression [45,69]. In addition, the growth of oestrogen-dependent breast cancer cells was stimulated by exposure to DEHP via changes in DNA methylation [70].

6.1.5 Non-monotonic dose-response curves and cocktail effects

Some studies have shown that phthalates may have non-monotonic dose-response curves [71,72]. This means that they may display different harmful effects based on their concentration. For instance, exposure to mixtures of phthalates inhibits testosterone synthesis at low doses,

‡The BRCA1 gene is responsible for tumour suppression facilitating DNA repair. Certain genetic mutations of the BRCA1 and BRCA2 genes increase the risk of breast and ovarian cancer [143].
§Chemical group with a carbon atom (C) bound to 3 hydrogen atoms (H), with structure CH3.

which are relevant to human exposure, but at higher doses, no effects are observed [71]. Thus, the effects observed at high doses, usually used for regulatory testing purposes, do not correctly predict low-dose toxicity [73]. Chemicals with non-monotonic dose-response curves may appear safe when tested but may not be safe at doses relevant to human exposure [73].

In addition, some mixtures of phthalates have displayed dose-additive and synergistic effects [51,74]. Dose additivity is present when the overall effect of a mixture is given by adding together the effect of each component. If the overall effect is higher than the sum, this is known as synergism [74]. These effects, also called "cocktail effects", can be observed for chemicals displaying similar toxicity, for example through endocrine disruptive activity, and may result in mixtures being harmful even if each component is present at concentrations considered safe [75]. It is important to note that phthalates may be part of mixtures of EDCs of different classes which collectively pose a greater health risk [76].

6.2 Animal studies

In utero exposure to EDCs may alter normal development of the mammary gland and potentially increase breast cancer risk later in life. Read more about this in our review "Critical Windows of Exposure for Breast Development".

In animals, exposure to phthalates during gestation and lactation has been shown to alter the mammary gland of the offspring [77–80]. Pre-pubertal and pubertal exposure to BBP also alters the development of the mammary gland and the gene expression profile [81,82]. Phthalate exposure during gestation or lactation can also affect the maternal mammary gland, with alteration of the morphology, immune system and gene expression being observed in mice [79,83]. Changes to the mammary gland morphology were also observed in adult female rats exposed to DEHP [84].

Phthalates may also increase the susceptibility of the mammary gland to other carcinogens. In utero exposure to phthalates can lead to a higher incidence of mammary tumours in offspring exposed to carcinogens [78]. Adult female rats exposed to a combination of DEHP, bisphenol A (an oestrogenic EDC) and a carcinogen have a higher incidence of mammary tumours compared to rats exposed only to the carcinogen [84].

6.3 Epidemiological studies

In addition to in vitro and animal studies, epidemiological studies on humans have explored the link between phthalate exposure and breast cancer. These studies have been conducted exclusively on female participants, with the majority taking place in North America [85–92], and a few across European and Asian populations [34,93,94]. Exposure to phthalates has usually been evaluated by measuring participants' urinary levels of phthalates or their metabolites [85–94]. However, to better estimate cumulative exposure and to access a large cohort of participants, other studies have used water monitoring data or prescription records for medications containing phthalates [34,95].

These epidemiological studies have evaluated whether an association between individual phthalates and breast cancer exists or not. For instance, a positive association between DBP and breast cancer was seen across different studies, meaning that exposure to DBP may increase breast cancer risk [34,91,93]. The highest cumulative exposure to DBP, assessed via prescription records, was positively associated with ER-positive (ER+) breast cancer [34]. In postmenopausal individuals, a positive association was observed for high urinary levels of DBP and ER+ and PR+ breast cancer diagnosed within 3 years of sample collection, but no association was observed within 5 years [91].

Urinary levels of DEHP and its metabolites were also found to be associated with increased breast cancer risk in multiple studies [18,87,89,93]. A study on the UK population, that used water monitoring data to estimate DEHP exposure, found that DEHP may increase breast cancer risk, especially in premenopausal women [95]. However, the association between DEHP and breast cancer was not confirmed by others [85,96], and MEHOP was linked to a decreased risk of breast cancer reoccurrence [94]. Evidence of a possible link between DEP exposure and breast cancer is also inconclusive [34,85,96].

On the other hand, BBP and its metabolites (i.e., MBP and MBzP), were negatively associated with breast cancer across multiple studies and meta-analyses [18,85,86,89,92,93,96–98]. This suggests that the oestrogenic effects of BBP observed in vitro may not be relevant in vivo [89]. The metabolites MCOP and MIBP were also found to be negatively associated with breast cancer, whilst no link was found for DNOP and MCPP [85,86,93,96].

In addition to considering individual phthalates, some studies have also evaluated the risk associated with total phthalate levels. Most of these have found no significant association between total phthalate levels and breast cancer [18,85,88,91,98]. This may be explained by the fact that phthalates may contribute to breast cancer risk in opposing ways; some may be positively associated (e.g., DBP, DEHP), whilst others (e.g., BBP) may reduce risk. This may result in a null overall effect when considering total phthalate levels [18].

7. Other effects on human health

Phthalates have also been found to have other harmful effects on human health. Research on phthalates has been predominantly focused on studying their effects on the male reproductive system [99]. Exposure to phthalates is associated with reduced testosterone levels and low sperm quality [20,36,100]. In utero exposure is particularly harmful, as this may impair testicular and genital development and spermatogenesis, a condition known as Testicular Dysgenesis Syndrome [46,101].

Phthalates may also affect female reproduction and may be linked to anovulation (when ovaries do not release eggs during the menstrual cycle),

infertility and early menopause by blocking the production of oestradiol from the ovary [46,102]. Phthalates may also be linked to other female cancers, such as cervical and ovarian cancers [46]. Several studies have indicated that phthalate exposure during pregnancy may be implicated in miscarriage, pre-term birth, low birth weight, and issues with the neuro-endocrine development of the newborn [36,40,103].

Phthalates have also been linked to other health issues, including asthma [104,105], ADHD [106] and diabetes [107,108]. They may also affect puberty, obesity and the nervous, gastrointestinal and cardiovascular systems [7,20,27].

8. Interventions to reduce exposure

Although more research is needed to fully understand the link between phthalates and breast cancer, some of their harmful effects are well established. Therefore, a precautionary approach aimed at reducing exposure would be beneficial. One of the best ways to reduce phthalate exposure is through raising awareness, providing advice and support and encouraging lifestyle changes [38,109,110]. Effective lifestyle changes include swapping products, changing food habits and intervening in the home environment.

Studies providing female participants with EDC-free personal care products have observed a marked reduction of MEP urinary levels [111,112]. However, levels of other phthalates were unchanged, perhaps due to longer half-life or alternative exposure routes [112]. Furthermore, exposure to other EDCs was also reduced and cancer-related pathways in the participants' breast tissues were reversed [111].

Food, especially when processed, is also a significant source of phthalates. Eating fresh organic food, cooked and stored without plastic or non-stick cookware, was found to be effective in reducing DEHP exposure [113]. Avoiding plastic cups when drinking can also reduce DEHP and DBP levels [114]. However, low motivation can be a significant barrier preventing individuals from changing food habits [115]. Thus, a better approach would require the removal of phthalates from manufacturing equipment and food packaging [115].

Phthalates may also be released from a variety of products and accumulate in the home. The home is believed to be the main source of exposure to harmful chemicals for children and pregnant people [38]. Interventions aimed at limiting the release of phthalates from materials and their accumulation in dust were effective in reducing DEHP exposure [116]. Handwashing may also reduce phthalate levels by reducing the ingestion of dust [114].

9. Regulations

Some of the harmful effects associated with phthalates have been recognised by governmental bodies, resulting in regulations on some of these chemicals. In the EU and the UK, chemicals are regulated within the Registration,

Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. The UK followed EU regulations (EU REACH) until 2021, when it established its own independent framework (UK REACH).

Table 2: Regulatory status of phthalates in EU and UK, including properties of concerns officially recognised at EU level, listing as SVCH, inclusion in EU and UK REACH Annex XIV (also known as Authorisation List) and in Annex II of the EU and UK Cosmetics regulations.

			REACH Annex XIV		Cosmetics Annex II		
Acronym	Properties of concern ¶	SVCH	EU	UK [119]	EU [120]	UK [121]	Refs
DMP	-	No	No	No	No	No	[122]
DEP	Under assessment as endocrine disruptor	No	No	No	No	No	[123]
DMEP	Toxic to reproduction	Yes	Yes	Yes	Yes	Yes	[124]
DBP	Toxic to reproduction, Endocrine disrupting, Under assessment as persistent, bioaccumulative and toxic	Yes	Yes	Yes	Yes	Yes	[125]
DIBP	Toxic to reproduction, Endocrine disrupting	Yes	Yes	Yes	Yes	Yes	[126]
BBP	Toxic to reproduction, Endocrine disrupting	Yes	Yes	Yes	Yes	Yes	[127]
DPP	Toxic to reproduction	Yes	Yes	Yes	Yes	Yes	[128]
DIPP	Toxic to reproduction	Yes	Yes	Yes	Yes	Yes	[129]
DNPP	Toxic to reproduction	Yes	Yes	Yes	Yes	Yes	[130]
DNHP	Toxic to reproduction	Yes	Yes	Yes	Yes	Yes	[131]
DIHP	Toxic to reproduction	Yes	No	No	Yes	Yes	[132]
DCHP	Toxic to reproduction, Endocrine disrupting	Yes	No	No	Yes	Yes	[133]
BBOP	-	No	No	No	No	No	[134]
DHP	-	No	No	No	No	No	[135]
DNOP	-	No	No	No	No	No	[136]
DIOP	Toxic to reproduction	No	No	No	Yes	Yes	[137]
DEHP	Toxic to reproduction, Endocrine disrupting	Yes	Yes	Yes	Yes	Yes	[138]
DINP	-	No	No	No	No	No	[139]
DIDP	-	No	No	No	No	No	[140]
DPHP	Under assessment as endocrine disrupting	No	No	No	No	No	[141]

¶Other properties of concern, which are not relevant to the scope of this review, may be found on the European Chemical Agency (ECHA) website.

Within the REACH framework, harmful chemicals can be initially defined as Substances of Very High Concern (SVCH), to encourage their replacement. These are then added to the REACH Authorisation List, also known as Annex XIV (Table 2) [117]. Chemicals in this list cannot be manufactured or imported in large quantities unless authorisation is obtained [118].

Phthalates that are officially recognised as toxic for reproduction (Table 2) have been banned from toys [21]. Unfortunately, a recent EU project found that 16% of analysed toys are not compliant with restrictions [142].

In addition to being toxic for reproduction, 5 phthalates have also been recognised to be endocrine disruptors (Table 2) and banned from food contact material and medical devices [21]. In addition to these, DINP and DIDP are also banned from single-use material dedicated to infants [142].

Whilst the REACH regulation only covers chemicals, the Cosmetic Regulation regulates ingredients used in cosmetic and personal care products. A total of 12 phthalates are included in Annex II of the Cosmetics Regulation (Table 2) and are banned from being used as cosmetic ingredients [120,121].

10. Conclusions

Phthalates are chemicals ubiquitously present in our everyday lives and we are chronically exposed to them. They have been shown to be harmful and display endocrine-disrupting properties, promote proliferation of human breast cells, and affect the mammary gland in animals. Studies in humans have shown that some phthalates may be linked to breast cancer, whilst others may not be associated with it. Nonetheless, the negative impact that phthalates have on human health has been, at least partially, recognised by regulatory bodies in the EU and UK. Despite this, some phthalates are still unregulated and are being used in many everyday products. Individuals can reduce their exposure by avoiding packaged food, using EDC-free cosmetics and following dedicated advice. At the same time, regulatory bodies need to do more to protect human health and must acknowledge non-monotonic and cocktail effects when considering EDC safety. At Breast Cancer UK we advocate for a progressive phasing out of EDCs in consumer and non-essential products.

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229–63. https://doi.org/10.3322/caac.21834.
[2] Cancer Research UK. Breast cancer in men. 2023. https://www.cancerresearchuk.org/about-cancer/breast-cancer/types/male-breast-cancer (accessed March 5, 2024).
[3] Travis RC, Key TJ. Oestrogen exposure and breast cancer risk. Breast Cancer Res 2003;5:239–47. https://doi.org/10.1186/BCR628.
[4] Crobeddu B, Ferraris E, Kolasa E, Plante I. Di(2-ethylhexyl) phthalate (DEHP) increases proliferation of epithelial breast cancer cells through progesterone receptor dysregulation. Environ Res 2019;173:165–73. https://doi.org/10.1016/j.envres.2019.03.037.
[5] Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev 2015;36:E1–150. https://doi.org/10.1210/er.2015-1010.
[6] Kay JE, Cardona B, Rudel RA, Vandenberg LN, Soto AM, Christiansen S, et al. Chemical Effects on Breast Development, Function, and Cancer Risk: Existing Knowledge and New Opportunities. Current Environmental Health Reports 2022 9:4 2022;9:535–62. https://doi.org/10.1007/S40572-022-00376-2.
[7] Sree CG, Buddolla V, Lakshmi BA, Kim Y-J. Phthalate toxicity mechanisms: An update. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology 2023;263:109498. https://doi.org/10.1016/j.cbpc.2022.109498.
[8] Benjamin S, Masai E, Kamimura N, Takahashi K, Anderson RC, Faisal PA. Phthalates impact human health: Epidemiological evidences and plausible mechanism of action. J Hazard Mater 2017;340:360–83. https://doi.org/10.1016/j.jhazmat.2017.06.036.
[9] European Chemicals Agency. Dimethyl phthalate. 2023. https://www.echa.europa.eu/web/guest/substance-nformation/-/substanceinfo/100.004.557 (accessed March 5, 2024).
[10] Australian Government Department of Health and Ageing. Bis(2-methoxyethyl) phthalate. 2008. https://www.industrialchemicals.gov.au/sites/default/files/Bis%202-methoxyethyl%20phthalate%20DMEP.pdf (accessed March 5, 2024).
[11] European Chemicals Agency. Diisobutyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.001.412 (accessed March 5, 2024).
[12] Australian Government Department of Health and Ageing. Di-n-hexyl phthalate. 2008. https://www.industrialchemicals.gov.au/sites/default/files/Di-n-hexyl%20phthalate%20DnHP.pdf (accessed March 5, 2024).
[13] Australian Government Department of Health and Ageing. Diisohexyl phthalate. 2008. https://www.industrialchemicals.gov.au/sites/default/files/Diisohexyl%20phthalate%20DIHP.pdf (accessed March 5, 2024).
[14] European Chemicals Agency. Dicyclohexyl phthalate. 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.405 (accessed March 5, 2024).
[15] PubChem. Bis(2-butoxyethyl) phthalate. https://pubchem.ncbi.nlm.nih.gov/compound/Bis_2-butoxyethyl_-phthalate (accessed March 5, 2024).
[16] U.S. Department of Health and Human Services. Toxicological Profile for Di-n-octylphthalate. 1997. https://www.atsdr.cdc.gov/toxprofiles/tp95.pdf (accessed March 5, 2024).
[17] PubChem. Diisooctyl phthalate. https://pubchem.ncbi.nlm.nih.gov/compound/Diisooctyl-phthalate (accessed March 5, 2024).
[18] Fu Z, Zhao F, Chen K, Xu J, Li P, Xia D, et al. Association between urinary phthalate metabolites and risk of breast cancer and uterine leiomyoma. Reproductive Toxicology 2017;74:134–42. https://doi.org/10.1016/j.reprotox.2017.09.009.

[19] PubChem. Bis(2-propylheptyl) phthalate. https://pubchem.ncbi.nlm.nih.gov/compound/Bis_2-propylheptyl_-phthalate (accessed March 5, 2024).
[20] Maffini M V, Geueke B, Groh K, Carney Almroth B, Muncke J. Role of epidemiology in risk assessment: a case study of five ortho-phthalates. Environmental Health 2021;20:114. https://doi.org/10.1186/s12940-021-00799-8.
[21] European Chemicals Agency. Phthalates. https://echa.europa.eu/hot-topics/phthalates (accessed March 5, 2024).
[22] Wittassek M, Koch HM, Angerer J, Brüning T. Assessing exposure to phthalates – The human biomonitoring approach. Mol Nutr Food Res 2011;55:7–31. https://doi.org/10.1002/mnfr.201000121.
[23] World Health Organisation. Butyl Benzyl Phthalate Concise International Chemical Assessment Document 17 1999. https://chemview.epa.gov/chemview/proxy?filename=09022526804d2b59_BBP%20Concise%20International%20Chemical%20Assessment%20Document%2017.pdf (accessed March 5, 2024).
[24] Martínez-Ibarra A, Martínez-Razo LD, MacDonald-Ramos K, Morales-Pacheco M, Vázquez-Martínez ER, López-López M, et al. Multisystemic alterations in humans induced by bisphenol A and phthalates: Experimental, epidemiological and clinical studies reveal the need to change health policies. Environmental Pollution 2021;271:116380. https://doi.org/10.1016/j.envpol.2020.116380.
[25] Li Y, Zheng N, Li Y, Li P, Sun S, Wang S, et al. Exposure of childbearing-aged female to phthalates through the use of personal care products in China: An assessment of absorption via dermal and its risk characterization. Science of The Total Environment 2022;807:150980. https://doi.org/10.1016/j.scitotenv.2021.150980.
[26] Chen M-L, Chen J-S, Tang C-L, Mao I-F. The internal exposure of Taiwanese to phthalate—An evidence of intensive use of plastic materials. Environ Int 2008;34:79–85. https://doi.org/10.1016/j.envint.2007.07.004.
[27] Giulivo M, Lopez de Alda M, Capri E, Barceló D. Human exposure to endocrine disrupting compounds: Their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ Res 2016;151:251–64. https://doi.org/10.1016/j.envres.2016.07.011.
[28] Peivasteh-roudsari L, Barzegar-bafrouei R, Sharifi KA, Azimisalim S, Karami M, Abedinzadeh S, et al. Origin, dietary exposure, and toxicity of endocrine-disrupting food chemical contaminants: A comprehensive review. Heliyon 2023;9:e18140. https://doi.org/10.1016/j.heliyon.2023.e18140.
[29] Zota AR, Phillips CA, Mitro SD. Recent Fast Food Consumption and Bisphenol A and Phthalates Exposures among the U.S. Population in NHANES, 2003–2010. Environ Health Perspect 2016;124:1521–8. https://doi.org/10.1289/ehp.1510803.
[30] Geueke B, Groh K, Muncke J. Food packaging in the circular economy: Overview of chemical safety aspects for commonly used materials. J Clean Prod 2018;193:491–505. https://doi.org/10.1016/j.jclepro.2018.05.005.
[31] Sax L. Polyethylene Terephthalate May Yield Endocrine Disruptors. Environ Health Perspect 2010;118:445–8. https://doi.org/10.1289/ehp.0901253.
[32] Luo Q, Liu Z, Yin H, Dang Z, Wu P, Zhu N, et al. Migration and potential risk of trace phthalates in bottled water: A global situation. Water Res 2018;147:362–72. https://doi.org/10.1016/j.watres.2018.10.002.
[33] Wang W, Kannan K. Leaching of Phthalates from Medical Supplies and Their Implications for Exposure. Environ Sci Technol 2023;57:7675–83. https://doi.org/10.1021/acs.est.2c09182.
[34] Ahern TP, Broe A, Lash TL, Cronin-Fenton DP, Pilgaard Ulrichsen S, Christiansen PM, et al. Phthalate Exposure and Breast Cancer Incidence: A Danish Nationwide Cohort Study. Journal of Clinical Oncology 2019;37:1800–9. https://doi.org/10.1200/JCO.18.02202.
[35] Koch HM, Lorber M, Christensen KLY, Pälmke C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: Results of a 48h fasting study with urine collection and personal activity patterns. Int J Hyg Environ Health 2013;216:672–81. https://doi.org/10.1016/j.ijheh.2012.12.002.
[36] Eales J, Bethel A, Galloway T, Hopkinson P, Morrissey K, Short RE, et al. Human health impacts of exposure to phthalate plasticizers: An overview of reviews. Environ Int 2022;158:106903. https://doi.org/10.1016/j.envint.2021.106903.

[37] Romero-Franco M, Hernández-Ramírez RU, Calafat AM, Cebrián ME, Needham LL, Teitelbaum S, et al. Personal care product use and urinary levels of phthalate metabolites in Mexican women. Environ Int 2011;37:867–71. https://doi.org/10.1016/j.envint.2011.02.014.
[38] Rutkowska A, Olsson A, Piotrowska-Szypryt M, Namieśnik J. Changes in daily life reduce indoor exposure to selected endocrine disruptors in the home environment: a pilot intervention study. Acta Biochim Pol 2020;67:237–76. https://doi.org/10.18388/abp.2020_5369.
[39] Koch HM, Preuss R, Angerer J. Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure – an update and latest results1. Int J Androl 2006;29:155–65. https://doi.org/10.1111/j.1365-2605.2005.00607.x.
[40] Dutta S, Haggerty DK, Rappolee DA, Ruden DM. Phthalate Exposure and Long-Term Epigenomic Consequences: A Review. Front Genet 2020;11. https://doi.org/10.3389/fgene.2020.00405.
[41] Zhang Y-J, Guo J-L, Xue J, Bai C-L, Guo Y. Phthalate metabolites: Characterization, toxicities, global distribution, and exposure assessment. Environmental Pollution 2021;291:118106. https://doi.org/10.1016/j.envpol.2021.118106.
[42] Zota AR, Calafat AM, Woodruff TJ. Temporal Trends in Phthalate Exposures: Findings from the National Health and Nutrition Examination Survey, 2001–2010. Environ Health Perspect 2014;122:235–41. https://doi.org/10.1289/ehp.1306681.
[43] Lange R, Apel P, Rousselle C, Charles S, Sissoko F, Kolossa-Gehring M, et al. The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer. Int J Hyg Environ Health 2021;234:113722. https://doi.org/10.1016/j.ijheh.2021.113722.
[44] Fiocchetti M, Bastari G, Cipolletti M, Leone S, Acconcia F, Marino M. The Peculiar Estrogenicity of Diethyl Phthalate: Modulation of Estrogen Receptor α Activities in the Proliferation of Breast Cancer Cells. Toxics 2021;9:237. https://doi.org/10.3390/toxics9100237.
[45] Kang SC, Lee BM. DNA Methylation of Estrogen Receptor α Gene by Phthalates. J Toxicol Environ Health A 2005;68:1995–2003. https://doi.org/10.1080/15287390491008913.
[46] Hlisníková H, Petrovičová I, Kolena B, Šidlovská M, Sirotkin A. Effects and Mechanisms of Phthalates' Action on Reproductive Processes and Reproductive Health: A Literature Review. Int J Environ Res Public Health 2020;17. https://doi.org/10.3390/ijerph17186811.
[47] Takeuchi S, Iida M, Kobayashi S, Jin K, Matsuda T, Kojima H. Differential effects of phthalate esters on transcriptional activities via human estrogen receptors α and β, and androgen receptor. Toxicology 2005;210:223–33. https://doi.org/10.1016/j.tox.2005.02.002.
[48] Kay VR, Chambers C, Foster WG. Reproductive and developmental effects of phthalate diesters in females. Crit Rev Toxicol 2013;43:200–19. https://doi.org/10.3109/10408444.2013.766149.
[49] Okubo T, Suzuki T, Yokoyama Y, Kano K, Kano I. Estimation of Estrogenic and Anti-estrogenic Activities of Some Phthalate Diesters and Monoesters by MCF-7 Cell Proliferation Assay in Vitro. Biol Pharm Bull 2003;26:1219–24. https://doi.org/10.1248/bpb.26.1219.
[50] Harris CA, Henttu P, Parker MG, Sumpter JP. The estrogenic activity of phthalate esters in vitro. Environ Health Perspect 1997;105:802–11. https://doi.org/10.1289/ehp.97105802.
[51] Ghisari M, Bonefeld-Jorgensen EC. Effects of plasticizers and their mixtures on estrogen receptor and thyroid hormone functions. Toxicol Lett 2009;189:67–77. https://doi.org/10.1016/j.toxlet.2009.05.004.
[52] Fujita T, Kobayashi Y, Wada O, Tateishi Y, Kitada L, Yamamoto Y, et al. Full Activation of Estrogen Receptor Activation Function-1 Induces Proliferation of Breast Cancer Cells. Journal of Biological Chemistry 2003;278:26704–14. https://doi.org/10.1074/jbc.M301031200.
[53] Blom A, Ekman E, Johannisson A, Norrgren L, Pesonen M. Effects of Xenoestrogenic Environmental Pollutants on the Proliferation of a Human Breast Cancer Cell Line (MCF-7). Arch Environ Contam Toxicol 1998;34:306–10. https://doi.org/10.1007/s002449900322.
[54] Chen F-P, Chien M-H, Chen H-Y, Ng Y-T. Effects of phthalates on normal human breast cells co-cultured with different fibroblasts. PLoS One 2018;13:e0199596-. https://doi.org/10.1371/journal.pone.0199596.
[55] Chen X, Xu S, Tan T, Lee ST, Cheng SH, Lee FWF, et al. Toxicity and Estrogenic Endocrine Disrupting Activity of Phthalates and Their Mixtures. Int J Environ Res Public Health 2014;11:3156–68. https://doi.org/10.3390/ijerph110303156.

[56] Jobling S, Reynolds T, White R, Parker MG, Sumpter JP. A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. Environ Health Perspect 1995;103:582–7. https://doi.org/10.1289/ehp.95103582.
[57] Jia M, Dahlman-Wright K, Gustafsson J-Å. Estrogen receptor alpha and beta in health and disease. Best Pract Res Clin Endocrinol Metab 2015;29:557–68. https://doi.org/10.1016/j.beem.2015.04.008.
[58] Okazaki H, Takeda S, Matsuo S, Matsumoto M, Furuta E, Kohro-Ikeda E, et al. Inhibitory modulation of human estrogen receptor α and β activities by dicyclohexyl phthalate in human breast cancer cell lines. J Toxicol Sci 2017;42:417–25. https://doi.org/10.2131/jts.42.417.
[59] Zhang S, Ma J, Fu Z, Zhang Z, Cao J, Huang L, et al. Promotion of breast cancer cells MDA-MB-231 invasion by di(2-ethylhexyl)phthalate through matrix metalloproteinase-2/-9 overexpression. Environmental Science and Pollution Research 2016;23:9742–9. https://doi.org/10.1007/s11356-016-6158-7.
[60] Hsieh T-H, Tsai C-F, Hsu C-Y, Kuo P-L, Lee J-N, Chai C-Y, et al. Phthalates induce proliferation and invasiveness of estrogen receptor-negative breast cancer through the AhR/HDAC6/c-Myc signaling pathway. The FASEB Journal 2012;26:778–87. https://doi.org/10.1096/fj.11-191742.
[61] Jadhao M, Chen C-L, Liu W, Deshmukh D, Liao W-T, Chen JY-F, et al. Endoglin Modulates TGFβR2 Induced VEGF and Proinflammatory Cytokine Axis Mediated Angiogenesis in Prolonged DEHP-Exposed Breast Cancer Cells. Biomedicines 2022;10:417. https://doi.org/10.3390/biomedicines10020417.
[62] Walker C, Garza S, Papadopoulos V, Culty M. Impact of endocrine-disrupting chemicals on steroidogenesis and consequences on testicular function. Mol Cell Endocrinol 2021;527:111215. https://doi.org/10.1016/j.mce.2021.111215.
[63] Yuan K, Zhao B, Li X-W, Hu G-X, Su Y, Chu Y, et al. Effects of phthalates on 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase 3 activities in human and rat testes. Chem Biol Interact 2012;195:180–8. https://doi.org/10.1016/j.cbi.2011.12.008.
[64] Xu R, Mao B, Li S, Liu J, Li X, Li H, et al. Structure-activity relationships of phthalates in inhibition of human placental 3β-hydroxysteroid dehydrogenase 1 and aromatase. Reproductive Toxicology 2016;61:151–61. https://doi.org/10.1016/j.reprotox.2016.04.004.
[65] Lovekamp TN, Davis BJ. Mono-(2-ethylhexyl) Phthalate Suppresses Aromatase Transcript Levels and Estradiol Production in Cultured Rat Granulosa Cells. Toxicol Appl Pharmacol 2001;172:217–24. https://doi.org/10.1006/taap.2001.9156.
[66] Nounu A, Kar SP, Relton CL, Richmond RC. Sex steroid hormones and risk of breast cancer: a two-sample Mendelian randomization study. Breast Cancer Research 2022;24:66. https://doi.org/10.1186/s13058-022-01553-9.
[67] Venkata NG, Robinson JA, Cabot PJ, Davis B, Monteith GR, Roberts-Thomson SJ. Mono(2-ethylhexyl)phthalate and mono-n-butyl phthalate activation of peroxisome proliferator activated-receptors α and γ in breast. Toxicol Lett 2006;163:224–34. https://doi.org/10.1016/j.toxlet.2005.11.001.
[68] La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 2020;16:45–57. https://doi.org/10.1038/s41574-019-0273-8.
[69] Singh S, Shoei-Lung Li S. Epigenetic Effects of Environmental Chemicals Bisphenol A and Phthalates. Int J Mol Sci 2012;13:10143–53. https://doi.org/10.3390/ijms130810143.
[70] Ghosh K, Chatterjee B, Nalla K, Behera B, Mukherjee A, Kanade SR. Di-(2-ethylhexyl) phthalate triggers DNA methyltransferase 1 expression resulting in elevated CpG-methylation and enrichment of MECP2 in the p21 promoter in vitro. Chemosphere 2022;293:133569. https://doi.org/10.1016/j.chemosphere.2022.133569.
[71] Tian M, Wu S, Wang Y-X, Liu L, Zhang J, Shen H, et al. Associations of environmental phthalate exposure with male steroid hormone synthesis and metabolism: An integrated epidemiology and toxicology study. J Hazard Mater 2022;436:129213. https://doi.org/10.1016/j.jhazmat.2022.129213.

[72] Andrade AJM, Grande SW, Talsness CE, Grote K, Chahoud I. A dose–response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic dose–response and low dose effects on rat brain aromatase activity. Toxicology 2006;227:185–92. https://doi.org/10.1016/j.tox.2006.07.022.
[73] Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs Jr. DR, Lee D-H, et al. Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. Endocr Rev 2012;33:378–455. https://doi.org/10.1210/er.2011-1050.
[74] Christen V, Crettaz P, Oberli-Schrämmli A, Fent K. Antiandrogenic activity of phthalate mixtures: Validity of concentration addition. Toxicol Appl Pharmacol 2012;259:169–76. https://doi.org/10.1016/j.taap.2011.12.021.
[75] Howdeshell KL, Hotchkiss AK, Gray LE. Cumulative effects of antiandrogenic chemical mixtures and their relevance to human health risk assessment. Int J Hyg Environ Health 2017;220:179–88. https://doi.org/10.1016/j.ijheh.2016.11.007.
[76] Darbre PD. Chapter Thirteen - Endocrine disrupting chemicals and breast cancer cells. In: Vandenberg LN, Turgeon JL, editors. Adv Pharmacol, vol. 92, Academic Press; 2021, p. 485–520. https://doi.org/10.1016/bs.apha.2021.04.006.
[77] Moral R, Santucci-Pereira J, Wang R, Russo IH, Lamartiniere CA, Russo J. In utero exposure to butyl benzyl phthalate induces modifications in the morphology and the gene expression profile of the mammary gland: an experimental study in rats. Environmental Health 2011;10:5. https://doi.org/10.1186/1476-069X-10-5.
[78] de Freitas T, Zapaterini JR, Moreira CM, de Aquino AM, Alonso-Costa LG, Bidinotto LT, et al. Prenatal exposure to a mixture of different phthalates increases the risk of mammary carcinogenesis in F1 female offspring. Food and Chemical Toxicology 2021;156:112519. https://doi.org/10.1016/j.fct.2021.112519.
[79] Mogus JP, Matouskova K, Clark ZW, Jerry DJ, Vandenberg LN. Effects of butyl benzyl phthalate exposure during pregnancy and lactation on the post-involution mammary gland. Reproductive Toxicology 2023;122:108470. https://doi.org/10.1016/j.reprotox.2023.108470.
[80] Moyer B, Hixon ML. Reproductive effects in F1 adult females exposed in utero to moderate to high doses of mono-2-ethylhexylphthalate (MEHP). Reproductive Toxicology 2012;34:43–50. https://doi.org/10.1016/j.reprotox.2012.02.006.
[81] Moral R, Wang R, Russo IH, Mailo DA, Lamartiniere CA, Russo J. The plasticizer butyl benzyl phthalate induces genomic changes in rat mammary gland after neonatal/prepubertal exposure. BMC Genomics 2007;8:453. https://doi.org/10.1186/1471-2164-8-453.
[82] Su Y, Santucci-Pereira J, Dang NM, Kanefsky J, Rahulkannan V, Hillegass M, et al. Effects of Pubertal Exposure to Butyl Benzyl Phthalate, Perfluorooctanoic Acid, and Zeranol on Mammary Gland Development and Tumorigenesis in Rats. Int J Mol Sci 2022;23:1398. https://doi.org/10.3390/ijms23031398.
[83] Li L, Liu J-C, Zhao Y, Lai F-N, Yang F, Ge W, et al. Impact of diethylhexyl phthalate on gene expression and development of mammary glands of pregnant mouse. Histochem Cell Biol 2015;144:389–402. https://doi.org/10.1007/s00418-015-1348-9.
[84] Zhang X, Cheng C, Zhang G, Xiao M, Li L, Wu S, et al. Co-exposure to BPA and DEHP enhances susceptibility of mammary tumors via up-regulating Esr1/HDAC6 pathway in female rats. Ecotoxicol Environ Saf 2021;221:112453. https://doi.org/10.1016/j.ecoenv.2021.112453.
[85] López-Carrillo L, Hernández-Ramírez RU, Calafat AM, Torres-Sánchez L, Galván-Portillo M, Needham LL, et al. Exposure to Phthalates and Breast Cancer Risk in Northern Mexico. Environ Health Perspect 2010;118:539–44. https://doi.org/10.1289/ehp.0901091.
[86] Humberto P, D GM, Jia C, M CA, I NA, M SR, et al. Urinary Phthalate Metabolite Concentrations and Breast Cancer Incidence and Survival following Breast Cancer: The Long Island Breast Cancer Study Project. Environ Health Perspect 2018;126:047013. https://doi.org/10.1289/EHP2083.
[87] Holmes AK, Koller KR, Kieszak SM, Sjodin A, Calafat AM, Sacco FD, et al. Case–control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women. Int J Circumpolar Health 2014;73:25760. https://doi.org/10.3402/ijch.v73.25760.

[88] Morgan M, Deoraj A, Felty Q, Roy D. Environmental estrogen-like endocrine disrupting chemicals and breast cancer. Mol Cell Endocrinol 2017;457:89–102. https://doi.org/10.1016/j.mce.2016.10.003.
[89] Wu AH, Franke AA, Wilkens LR, Tseng C, Conroy SM, Li Y, et al. Urinary phthalate exposures and risk of breast cancer: the Multiethnic Cohort study. Breast Cancer Research 2021;23:44. https://doi.org/10.1186/s13058-021-01419-6.[90] Segovia-Mendoza M, Palacios-Arreola MI, Monroy-Escamilla LM, Soto-Piña AE, Nava-Castro KE, Becerril-Alarcón Y, et al. Association of Serum Levels of Plasticizers Compounds, Phthalates and Bisphenols, in Patients and Survivors of Breast Cancer: A Real Connection? Int J Environ Res Public Health 2022;19:8040. https://doi.org/10.3390/ijerph19138040.
[91] Reeves KW, Díaz Santana M, Manson JE, Hankinson SE, Zoeller RT, Bigelow C, et al. Urinary Phthalate Biomarker Concentrations and Postmenopausal Breast Cancer Risk. JNCI: Journal of the National Cancer Institute 2019;111:1059–67. https://doi.org/10.1093/jnci/djz002.
[92] Mérida-Ortega Á, Hernández-Alcaraz C, Hernández-Ramírez RU, García-Martínez A, Trejo-Valdivia B, Salinas-Rodríguez A, et al. Phthalate exposure, flavonoid consumption and breast cancer risk among Mexican women. Environ Int 2016;96:167–72. https://doi.org/10.1016/j.envint.2016.08.023.
[93] Mukherjee Das A, Gogia A, Garg M, Elaiyaraja A, Arambam P, Mathur S, et al. Urinary concentration of endocrine-disrupting phthalates and breast cancer risk in Indian women: A case-control study with a focus on mutations in phthalate-responsive genes. Cancer Epidemiol 2022;79:102188. https://doi.org/10.1016/j.canep.2022.102188.
[94] Yang P-J, Hou M-F, Ou-Yang F, Hsieh T-H, Lee Y-J, Tsai E-M, et al. Association between recurrent breast cancer and phthalate exposure modified by hormone receptors and body mass index. Sci Rep 2022;12:2858. https://doi.org/10.1038/s41598-022-06709-3.
[95] Tang L, Wang Y, Yan W, Zhang Z, Luo S, Wen Q, et al. Exposure to di-2-ethylhexyl phthalate and breast neoplasm incidence: A cohort study. Science of The Total Environment 2024;926:171819. https://doi.org/10.1016/j.scitotenv.2024.171819.
[96] Liu G, Cai W, Liu H, Jiang H, Bi Y, Wang H. The Association of Bisphenol A and Phthalates with Risk of Breast Cancer: A Meta-Analysis. Int J Environ Res Public Health 2021;18:2375. https://doi.org/10.3390/ijerph18052375.
[97] Liu H, Sun Y, Ran L, Li J, Shi Y, Mu C, et al. Endocrine-disrupting chemicals and breast cancer: a meta-analysis. Front Oncol 2023;13. https://doi.org/10.3389/fonc.2023.1282651.
[98] Meng M, Yang Y, Song L, Peng J, Li S, Gao Z, et al. Association between urinary phthalates and phthalate metabolites and cancer risk: A systematic review and meta-analysis. Heliyon 2024;10. https://doi.org/10.1016/j.heliyon.2024.e29684.
[99] Radke EG, Galizia A, Thayer KA, Cooper GS. Phthalate exposure and metabolic effects: a systematic review of the human epidemiological evidence. Environ Int 2019;132:104768. https://doi.org/10.1016/j.envint.2019.04.040.
[100] Zhu Y, Han X, Wang X, Ge T, Liu H, Fan L, et al. Effect of the phthalates exposure on sex steroid hormones in the US population. Ecotoxicol Environ Saf 2022;231:113203. https://doi.org/10.1016/j.ecoenv.2022.113203.
[101] Skakkebaek N-E, De Meyts ER, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. APMIS 2001;109:S22–30. https://doi.org/10.1111/j.1600-0463.2001.tb05770.x.
[102] Fletcher EJ, Santacruz-Márquez R, Mourikes VE, Neff AM, Laws MJ, Flaws JA. Effects of Phthalate Mixtures on Ovarian Folliculogenesis and Steroidogenesis. Toxics 2022;10:251. https://doi.org/10.3390/toxics10050251.
[103] Trasande L, Nelson ME, Alshawabkeh A, Barrett ES, Buckley JP, Dabelea D, et al. Prenatal phthalate exposure and adverse birth outcomes in the USA: a prospective analysis of births and estimates of attributable burden and costs. Lancet Planet Health 2024;8:e74–85. https://doi.org/10.1016/S2542-5196(23)00270-X.
[104] Wu W, Wu C, Ji C, Diao F, Peng J, Luo D, et al. Association between phthalate exposure and asthma risk: A meta-analysis of observational studies. Int J Hyg Environ Health 2020;228:113539. https://doi.org/10.1016/j.ijheh.2020.113539.

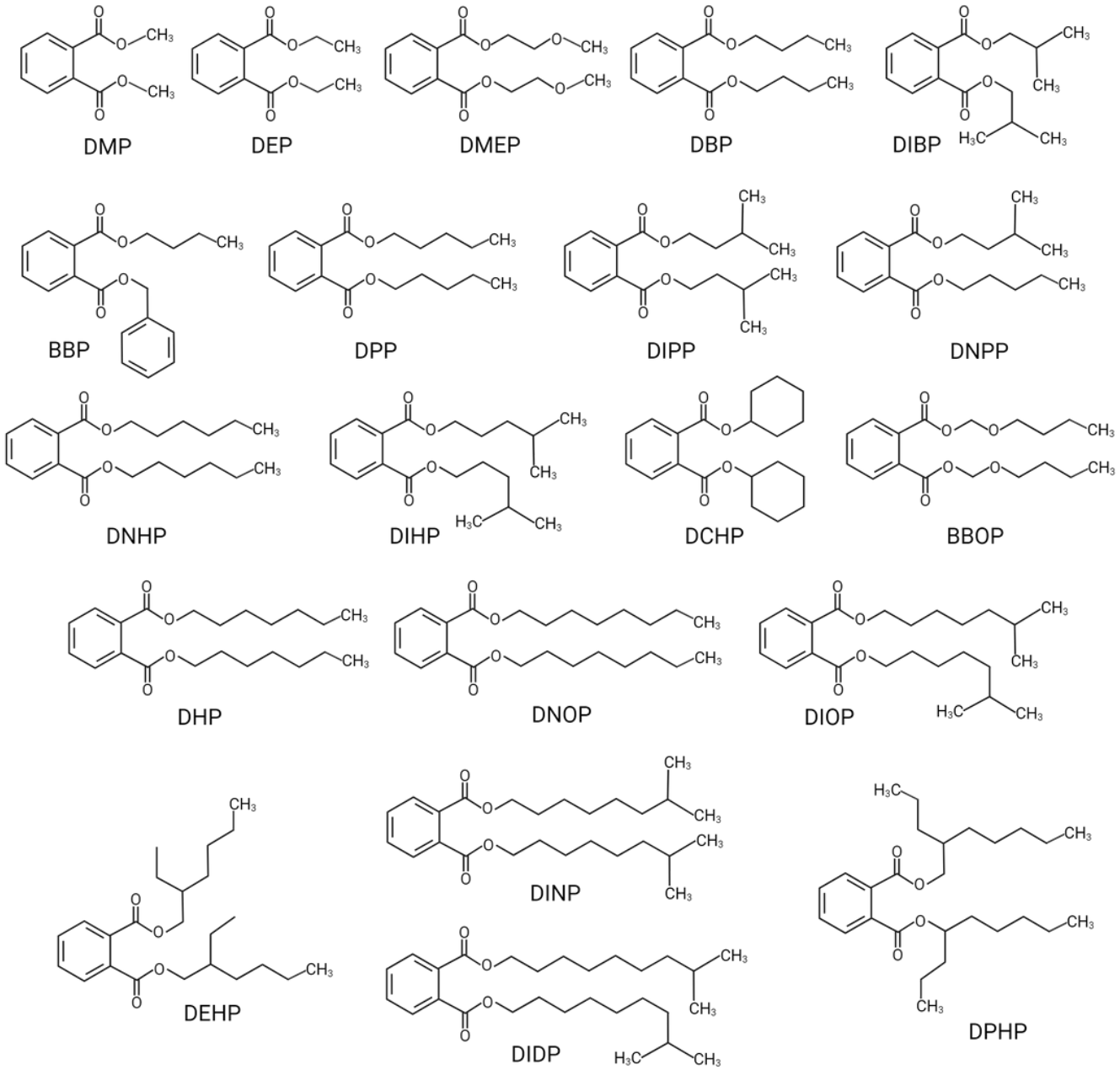
[105] Li M-C, Chen C-H, Guo YL. Phthalate esters and childhood asthma: A systematic review and congener-specific meta-analysis. Environmental Pollution 2017;229:655–60. https://doi.org/10.1016/j.envpol.2017.06.083.
[106] Praveena SM, Munisvaradass R, Masiran R, Rajendran RK, Lin C-C, Kumar S. Phthalates exposure and attention-deficit/hyperactivity disorder in children: a systematic review of epidemiological literature. Environmental Science and Pollution Research 2020;27:44757–70. https://doi.org/10.1007/s11356-020-10652-z.
[107] Zhang H, Ben Y, Han Y, Zhang Y, Li Y, Chen X. Phthalate exposure and risk of diabetes mellitus: Implications from a systematic review and meta-analysis. Environ Res 2022;204:112109. https://doi.org/10.1016/j.envres.2021.112109.
[108] Mariana M, Cairrao E. The Relationship between Phthalates and Diabetes: A Review. Metabolites 2023;13:746. https://doi.org/10.3390/metabo13060746.
[109] Kim JH, Kwak JM, Kang H. Web-based behavioral intervention to reduce exposure to phthalate metabolites, bisphenol A, triclosan, and parabens in mothers with young children: A randomized controlled trial. Int J Hyg Environ Health 2021;236:113798. https://doi.org/10.1016/j.ijheh.2021.113798.
[110] Martin L, Zhang Y, First O, Mustieles V, Dodson R, Rosa G, et al. Lifestyle interventions to reduce endocrine-disrupting phthalate and phenol exposures among reproductive age men and women: A review and future steps. Environ Int 2022;170:107576. https://doi.org/10.1016/j.envint.2022.107576.
[111] Dairkee SH, Moore DH, Luciani MG, Anderle N, Gerona R, Ky K, et al. Reduction of daily-use parabens and phthalates reverses accumulation of cancer-associated phenotypes within disease-free breast tissue of study subjects. Chemosphere 2023;322:138014. https://doi.org/10.1016/j.chemosphere.2023.138014.
[112] Harley KG, Kogut K, Madrigal DS, Cardenas M, Vera IA, Meza-Alfaro G, et al. Reducing Phthalate, Paraben, and Phenol Exposure from Personal Care Products in Adolescent Girls: Findings from the HERMOSA Intervention Study. Environ Health Perspect 2016;124:1600–7. https://doi.org/10.1289/ehp.1510514.
[113] Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, et al. Food Packaging and Bisphenol A and Bis(2-Ethyhexyl) Phthalate Exposure: Findings from a Dietary Intervention. Environ Health Perspect 2011;119:914–20. https://doi.org/10.1289/ehp.1003170.
[114] Chen C-Y, Chou Y-Y, Lin S-J, Lee C-C. Developing an intervention strategy to reduce phthalate exposure in Taiwanese girls. Science of The Total Environment 2015;517:125–31. https://doi.org/10.1016/j.scitotenv.2015.02.021.
[115] Barrett ES, Velez M, Qiu X, Chen S-R. Reducing Prenatal Phthalate Exposure Through Maternal Dietary Changes: Results from a Pilot Study. Matern Child Health J 2015;19:1936–42. https://doi.org/10.1007/s10995-015-1707-0.
[116] Sears CG, Lanphear BP, Calafat AM, Chen A, Skarha J, Xu Y, et al. Lowering Urinary Phthalate Metabolite Concentrations among Children by Reducing Contaminated Dust in Housing Units: A Randomized Controlled Trial and Observational Study. Environ Sci Technol 2020;54:4327–35. https://doi.org/10.1021/acs.est.9b04898.
[117] European Chemicals Agency. Authorisation. Substances of very high concern identification. https://echa.europa.eu/substances-of-very-high-concern-identification-explained (accessed March 5, 2024).
[118] European Chemicals Agency. Authorisation List. https://www.echa.europa.eu/authorisation-list (accessed March 5, 2024).
[119] Health and Safety Executive. UK REACH Authorisation List (Annex 14). https://www.hse.gov.uk/reach/authorisation-list.htm (accessed March 5, 2024).
[120] European Commision. Annex II List Of Substances Prohibited In Cosmetic Products. https://ec.europa.eu/growth/tools-databases/cosing/reference/annexes/list/II (accessed March 5, 2024).
[121] UK Government Legislation. Annex II List Of Substances Prohibited In Cosmetic Products 2022. https://www.legislation.gov.uk/eur/2009/1223/annex/II (accessed March 5, 2024).

[122] European Chemicals Agency. Dimethyl Phthalate Brief Profile. 2024. https://echa.europa.eu/pl/brief-profile/-/briefprofile/100.004.557 (accessed March 5, 2024).
[123] European Chemicals Agency. Diethyl Phthalate Brief Profile. 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.409 (accessed March 5, 2024).
[124] European Chemicals Agency. Bis(2-methoxyethyl) phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.003.830 (accessed March 5, 2024)
[125] European Chemicals Agency. Dibutyl Phthalate Brief Profile. 2024. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.416 (accessed March 5, 2024).
[126] European Chemicals Agency. Diisobutyl Phthalate Brief Profile. 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.412 (accessed March 5, 2024).
[127] European Chemicals Agency. Benzyl butyl Phthalate Brief Profile. 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.475 (accessed March 5, 2024).
[128] European Chemicals Agency. Dipentyl phthalate.. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.004.563 (accessed March 5, 2024).
[129] European Chemicals Agency. Diisopentyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.009.172 (accessed March 5, 2024).
[130] European Chemicals Agency. n-Pentyl-isopentyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.149.209
[131] European Chemicals Agency. Dihexyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.001.417 (accessed March 5, 2024).
[132] European Chemicals Agency. Diisohexyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.069.152 (accessed March 5, 2024).
[133] European Chemicals Agency. Dicyclohexyl Phthalate Brief Profile 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.001.405 (accessed March 5, 2024).
[134] European Chemicals Agency. Bis(2-butoxyethyl) phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.003.831 (accessed March 5, 2024).
[135] European Chemicals Agency. Diheptyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.020.806 (accessed March 5, 2024).
[136] European Chemicals Agency. Dioctyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.003.832 (accessed March 5, 2024).
[137] European Chemicals Agency. Diisooctyl phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.044.097 (accessed March 5, 2024).
[138] European Chemicals Agency. Bis(2-ethylhexyl) Phthalate Brief Profile. 2024. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.003.829 (accessed March 5, 2024).
[139] European Chemicals Agency. Di-''isononyl'' Phthalate Brief Profile. 2024. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.044.602 (accessed March 5, 2024).

[140] European Chemicals Agency. Di-''isodecyl'' phthalate. https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.043.601 (accessed March 5, 2024).
[141] European Chemicals Agency. Bis(2-propylheptyl) Phthalate Brief Profile. 2023. https://www.echa.europa.eu/web/guest/brief-profile/-/briefprofile/100.053.137 (accessed March 5, 2024).
[142] European Chemicals Agency. Hazardous chemicals found in many consumer products 2023. https://echa.europa.eu/-/hazardous-chemicals-found-in-many-consumer-products (accessed March 5, 2023).
[143] Krais JJ, Johnson N. BRCA1 Mutations in Cancer: Coordinating Deficiencies in Homologous Recombination with Tumorigenesis. Cancer Res 2020;80:4601–9. https://doi.org/10.1158/0008-5472.CAN-20-1830.

Appendix

Appendix 1. Chemical structure of the phthalates discussed in this review. Created with BioRender.com



About Breast Cancer UK

Who we are?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk

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

This review is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

Date: 28/06/2024
Next update: 28/06/2027

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

www.breastcanceruk.org.uk

@BreastCancer_UK
@breastcanceruk
@breastcanceruk
@Breast Cancer UK