

BREAST CANCER & THE ENVIRONMENT RESEARCH CENTERS
Early Life Exposure to Phthalates and Breast Cancer Risk in Later Years
FACT SHEET on PHTHALATES

Abstract

Phthalates are a family of man-made compounds used in the manufacture of plastics, including polyvinyl chloride plastics (PVC), and solvents. Phthalates can leach from these products into the environment. The ubiquitous use of phthalate esters in plastics, personal care products, medical devices used in patient care, and food packaging materials results in widespread general population exposure. Ingestion, inhalation, intravenous injection tubing and solutions, and skin absorption are all potential pathways of exposure. Phthalates can cross the placenta and have been found in human breast milk. Phthalate metabolites have also been found in the urine of average Americans and people worldwide. In general, females have higher levels of phthalates than males. It is possible that phthalates influence early onset of puberty in girls, but more research needs to be conducted. Phthalates are endocrine disrupters and have been linked to adverse reproductive effects in male rodents. Several studies have shown that phthalate exposure increases the growth of breast cancer cells *in vitro*, however, studies of phthalate exposure *in vivo* are limited. Epidemiological studies are needed to determine the association between phthalate exposure and human breast cancer risk. Phthalates are one of the most intensely studied class of compounds due to their extensive use and high production levels - not necessarily their toxicity. The International Agency for Research on Cancer (IARC) has not determined whether phthalates are carcinogenic to humans.

This fact sheet provides information about the ten phthalate biomarkers being measured and examined by the Breast Cancer and the Environment Research Centers (BCERC) epidemiology studies, sources of exposures, effects on puberty, effects in the body, and research studies looking at phthalates as being associated with breast cancer risk.

What are phthalates?

Phthalates are a family of compounds made from alcohols and phthalic anhydride. They are oily, colorless, odorless liquids that do not evaporate readily. Often called plasticizers, phthalates are used in the manufacture of plastics, including polyvinyl chloride plastics (PVC). Phthalates can prolong the lifespan or durability of plastics and increase the flexibility of some plastics. They can be found in hundreds of products such as toys, vinyl flooring, herbal pill coating, and plastic shower curtains. In addition, phthalates are also used as solvents. Phthalates are used in a variety of cosmetic products, such as nail polishes, perfumes, skin moisturizers and shampoos to enhance penetration and hold scent and/or color (1). Phthalates are ubiquitous in the environment.

Some of the most widely used phthalates and their human metabolites are:

- | | | |
|---------------------------------------|----|---------------------------------------|
| ◆ BBzP: butyl benzyl phthalate | —▶ | MBzP: mono benzyl phthalate |
| ◆ DnBP: di- <i>n</i> -butyl phthalate | —▶ | MnBP: mono- <i>n</i> -butyl phthalate |
| ◆ DEHP: di-(2-ethylhexyl)phthalate | —▶ | MEHP: mono-(2-ethylhexyl) phthalate |
| ◆ DEP: diethyl phthalate | —▶ | MEP: monoethyl phthalate |
| ◆ DiBP: di-isobutyl phthalate | —▶ | |
| ◆ DiDP: di-isodecyl phthalate | —▶ | |
| ◆ DiNP: di-isononyl phthalate | —▶ | |
| ◆ DMP: di-methyl phthalate | —▶ | |
| ◆ DnHP: di- <i>n</i> -hexyl phthalate | —▶ | |
| ◆ DnOP: di- <i>n</i> -octylphthalate | —▶ | |

Uses of the various phthalates depend in part on their molecular weight:

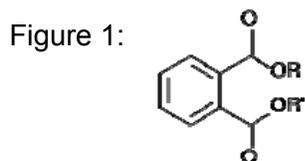
- Higher molecular weight phthalates, DEHP, DiDP, and DiNP, are the phthalates produced in highest volume for use in construction material, clothing, children's toys, and household furnishings.



- Relatively low molecular weight phthalates, DBP, DEP, DMP, tend to be used as solvents and in adhesives, waxes, inks, cosmetics, insecticides, and pharmaceuticals.

The physiochemical characteristics of phthalates vary with the chemical structure and may include a vapor phase, although vapor pressures are generally low. Phthalates are generally lipophilic, which influences their leaching and environmental partitioning characteristics. Phthalates are not chemically bound in the polymers. Therefore, migration or emission of phthalates from the products into the environment is likely to occur (2).

The general chemical structure of phthalates (R and R' = C_nH_{2n+1}) is shown in figure 1.



How are humans exposed to phthalates?

The ubiquitous use of phthalate esters in plastics, personal care products and food packaging materials results in widespread general population exposure. All populations of people, domestic animals, and wildlife regularly encounter opportunities for exposure to phthalates because of their widespread use.

Ingestion, inhalation, intravenous injection tubing and solutions, and skin absorption are potential pathways of exposure. Human exposure to phthalates can occur as a result of direct contact or use of a product containing phthalates, through the leaching of phthalates from one product into another, as may occur with food packaging or intravenous fluids, or by general contamination of the ambient environment.

Ingestion

When ingested, phthalates are often converted to other forms, called metabolites. Human metabolism of di-(2-ethylhexyl) phthalate (DEHP) is complex and yields mono (2-ethylhexyl) phthalate (MEHP) and numerous oxidative metabolites. Diethyl phthalate (DEP) yields phthalate monoester mono-ethyl phthalate (MEP) and di-n-butyl phthalate (DBP) yields monobutyl phthalate (MBP).

- **Food**

Phthalates can be released into aqueous solution foods during microwaving in plastic containers (3). Phthalates may also enter food by environmental uptake during crop cultivation or by migration from processing equipment or packaging materials (4, 5)

- **Water**

Phthalates are found in ground water and drinking water. From 1987 to 1993, according to EPA's Toxic Chemical Release Inventory, DEHP releases to land and water totaled over 500,000 lbs., of which about 5 percent was to water (6).

- **Infant formula and milk**

Some phthalates occur as contaminants in consumer milk and ready-to-use baby formulas based on cow's milk (7-8). One study analyzed seven samples of consumer milk and ten samples of infant formula (7). Only MBP and MEHP were detected in these samples, in the ranges 0.6–3.9 ug L⁻¹ (MBP) and 5.6–9.9 ug L⁻¹ (MEHP).

- **Medications and nutritional supplements**

Pharmaceutical preparations intended to treat diseases of the gastrointestinal tract, such as ulcerative colitis and colorectal cancer, are often coated with a polymer that allows the drug to be delivered directly to the colon or small intestine. This polymer may contain plasticizer phthalates such as DBP and DEP (9, 10). Other pharmaceutical products may also have phthalate plasticizers in their coatings, including some antibiotics, antihistamines and laxatives. Patented herbal preparations and nutritional supplements may also contain phthalates (2).

- **Toys**
Polymer toys softened with phthalates are a source of potential oral exposure in children (2). In 1999, the European Union temporarily banned marketing of all children's toys and child-care articles containing DEHP, DBP, and BBP as well as toys containing DiNP, DnOP, and DiDP intended for children <3 years old. DiNP is the primary phthalate used in toys in the US. The estimated mean DiNP exposure resulting from children's mouthing activities range from 5.7 to 44 ug/kg/day depending on the assumptions and statistical techniques used in several different studies (11).

Inhalation

- **Indoor air and house dust**
Vapors emitted from building materials, furniture and household fragrances are potential indoor sources of phthalate exposures (12, 13). Phthalates have been found in house dust in different countries, including the US, Germany, Japan and Norway (14-18). One study in Norway found a mean of 960 µg total phthalates/g dust in 38 homes (range 130–2920 µg/g dust) (14). Of the individual phthalates tested, DEHP was present in the highest levels (mean 640µg/g dust; range 100–1610 µg/g dust). The researchers estimated mean adult inhalation exposure to DEHP from this source to be 0.76 µg/day. A German study of 254 children, found that the levels of DEHP in house dust were not correlated with urinary levels of DEHP metabolites (15). However, another study found a significant correlation between urinary levels and house dust levels of DEP, DBP and BBP (16). This suggests that inhalation of house dust may be an important source of exposure for the lower molecular weight phthalates, but not the higher weight phthalates (2).
- **Medical devices**
Some phthalate esters, such as DEHP, may be transferred into respiratory gases passing through PVC tubing (2, 19).
- **Baking modeling clay**
Polymer modeling clay contains a complex mixture of phthalates that give the clay a soft consistency at room temperature. When the clay is baked, phthalates are released into the air and can be inhaled (20).

Intravenous

- **Medical devices**
A variety of medical devices used to deliver medical care such as bags and tubing for intravenous fluids, nutritional formulas, blood transfusions, and dialysis are made of PVC plastics softened with phthalates, usually DEHP. DEHP can leach out from these products (20). DEHP has been found in newborns treated in neonatal intensive care units with medical devices made with polyvinyl chloride plastic containing DEHP (22-24).

Estimated Upper-Bound Dose of Intravenous Exposure to DEHP from Select Medical Procedures		
Procedure	DEHP dose (mg/kg/day)	
	Adult (70 kg)	Neonate (4kg)
Infusion of crystalloid IV solutions	0.005	0.03
Total parenteral nutrition with added lipid	0.13	2.5
Blood transfusion in a trauma patient	8.5	
Exchange transfusion in a neonate		22.6
Coronary artery bypass graft	1.0	
Artificial heart transplant	2.4	
Hemodialysis	0.36	
Enteral nutrition	0.14	0.14
Extracorporeal membrane oxygenation (ECMO)		14.0

Source: Adapted from <http://www.fda.gov/cdrh/ost/dehp-pvc.pdf> (20).

Skin Absorption

- **Clothing**

Skin absorption can occur through direct contact with phthalate-containing clothing products, such as DEHP-containing gloves (artificial leather) and waterproof clothing.

- **Cosmetics and personal care products**

Phthalates are used in a variety of cosmetic and personal care products, such as nail polishes, perfumes, hairsprays, skin moisturizers and shampoos. In one study, the levels of selected phthalates were measured in 102 branded hair sprays, perfumes, deodorants, and nail polishes (25). The median exposure levels to phthalates in cosmetics by skin absorption were estimated to be 0.0006 g/kg body weight /d for DEHP, 0.6 g/kg body weight /d for DEP, and 0.103 g/kg body weight/d for DBP. Skin absorption of chemicals from the face may be up to 10-fold higher than the arm (2).

- **Modeling clay**

Skin absorption may occur through direct contact with polymer modeling clay containing phthalates (20).

- **Denture materials**

Phthalates can be found in temporary denture soft lining materials. One study tested four brands of plasticizer-based soft lining materials (26). For two of the brands, the average amount of leached DBP within the first day exceeded the proposed tolerable daily intake for an average adult person by about 11 and 32 times, respectively. The cumulative amount leached over 30 days for each of the four materials was 128-253 mg plasticizer /g(-1).

How do phthalates work in the human body?

Diester phthalates are hydrolyzed into monoester phthalates in the intestine and parenchyma, i.e., phthalates are converted in the body to a metabolite, a break-down substance produced by metabolism (27). For example, metabolism of the phthalate diester DEP yields the phthalate monoester MEP. Short-branched phthalates (e.g. DEP and DMP) are mainly excreted in urine as monoester phthalates, while the more long-branched phthalates (e.g. DEHP) undergo several biotransformations, including further hydroxylation and oxidation before they are excreted in urine and feces (27). Metabolism of DEHP is complex and yields MEHP and numerous oxidative metabolites, such as diacids and ketoacids.

In vitro and in vivo studies have shown that diester phthalates have a greater effect when they are hydrolyzed to monoester phthalates (28).

Phthalate metabolites are routinely found in the urine of average Americans and people worldwide (1, 29-32). Phthalate metabolites can activate a nuclear receptor PPAR-alpha (peroxisome proliferator-activated receptor) in the liver, which may be linked to the development of liver cancer in animals (33). In addition, *in vitro* phthalate treatment of breast cancer cells leads to increased cell proliferation and PPAR-alpha activation (34, 35).

Are phthalates endocrine disruptors?

Yes. According to EPA, an endocrine disrupter is an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of *homeostasis* (biological stability), reproduction, development and/or behavior ().

Phthalates are capable of binding to the estrogen receptor. In breast cancer cells, some phthalates have weak estrogenic effects and some have weak anti-estrogenic effects in the presence of 17beta-estradiol (35, 37, 38). In animal studies, several phthalates show antiandrogenic activity (39). Phthalates have been linked to adverse reproductive effects in male pubertal and adult rodents exposed in utero and during lactation, such as reduction in the weights of reproductive organs and a reduction in sperm count (40-42). There is also some evidence of

reproductive toxicity in adult female rodents exposed to DEHP, such as prolonged estrous cycles and lowered circulating estradiol levels (43).

In one human study, infant boys born to mothers with high phthalate urine levels were more likely to have smaller penises and scrotums and incomplete testicular descent (44). Boys born to mothers with the highest levels of phthalates were four to ten times more likely to have reduced genital development. The odds ratios for MBP, MEP, MBzP, and MiBP were 10.2, 4.7, 3.8, and 9.1, respectively (all p-values < 0.05).

Does phthalate exposure influence onset of puberty in girls?

Unknown. BCERC's biology and epidemiology studies are investigating this question.

Some evidence indicates that *in utero* and prepubertal exposure to DEHP, including dose levels relevant for human exposure, delays the onset of puberty in rats (45, 46).

Human studies on pubertal female development and phthalate exposures are limited. One study in Puerto Rico found that girls with premature breast development (younger than 8 years) had higher blood levels of several phthalates than a control group of girls without premature breast development (47).

The BCERC epidemiology study entitled "Environmental and Genetic Determinants of Puberty" completed a small pilot study in November 2006 and measured phthalates in young girls urine. The pilot study examined urinary biomarkers in ninety peripubertal Asian, Black, Hispanic and White girls to determine exposures to three chemical families known or likely to possess hormonal activity that may be estrogen agnostic or antagonistic (phytoestrogens, phthalate acids, and phenolic compounds). Phytoestrogens as a group had the highest concentrations (48). The study found detectable and variable amounts of three phthalate metabolites (MBP, MBzP, MEP). The exposures varied by characteristics that may be relevant to hormonal activity during developmental years. The highest median concentrations for individual analytes in each chemical family were for the phytoestrogen enterolactone (298 µg/L), phthalate acid monoethylphthalate (MEP; 83.2 µg/L), and phenolic compound benzophenone-3 (BP3; 14.7 µg/L) (48). This small pilot data set will guide future expanded cohort studies.

Do phthalates cross the placenta?

Yes.

Phthalates are found in young children and in human amniotic fluid (49-51). There is evidence in rodents and humans that *in utero* exposure to phthalates adversely affects reproductive development (40-42, 44).

Are phthalates found to be present in breast milk?

Yes.

Results from several studies have shown significant levels of phthalates in breast milk (7, 52, 53). In a study of Danish and Finnish women, phthalate monoesters were found in breast milk with large variations [medians (minimum-maximum)]: MMP 0.10 (< 0.01-5.53 µg/L), MEP 0.95 (0.07-41.4 µg/L), MBP 9.6 (0.6-10,900 µg/L), mBzP 1.2 (0.2-26 µg/L), mEHP 11 (1.5-1,410 µg/L), miNP 95 (27-469 µg/L) (51). Interestingly, levels of some phthalate esters in German women were higher than in Canadian mothers, indicating a regional exposure to specific phthalates (53). Despite the potential for phthalate exposure, breast milk remains the best and most complete nutritional source for young infants.

Are concentration levels of phthalates the same in men and women?

No. In the National Health and Nutrition Examination Survey (NHANES) 2001-2002, females had higher urine levels of several phthalate metabolites than males (39). The table below shows the urine concentrations of MIBP, MnBP, MBP, and MEHP, adjusted for creatinine, for males and females in NHANES 2001-2002.

Phthalate Metabolite	Mean Concentration in µg/g of creatinine	
	Males	Females
MnBP	14.4(13.5-15.4)	21.7(19.6-23.9)
MiBP	2.21(2.08-2.35)	2.87(2.59-3.17)
MBP	12.7(11.4-14.2)	15.7(14.2-17.3)
MEHP	3.49(3.06-3.98)	4.53(4.01-5.11)

Source: Adapted from <http://www.cdc.gov/exposurereport/> (39).

Are there medical tests for phthalate exposure?

Yes.

There are no routine medical tests for phthalate exposure currently offered to patients by physicians. However, phthalates can be measured in both urine and blood. Because phthalates are metabolized before being excreted, urine and blood tests typically measure the monoester phthalate metabolites instead of the diester phthalates. In addition, because the diester phthalates are ubiquitous, they often contaminate samples and cause high background levels. This problem is eliminated by measuring the monoester phthalates as a biomarker for exposure (27).

Short-branched phthalates (e.g. DEP and DMP) are mainly excreted in urine as monoester phthalates, while the more long-branched phthalates (e.g. DEHP) undergo several biotransformations before they are excreted (27). Recent metabolism studies of DEHP indicate that the secondary metabolites such as MECPP in urine and MCMHP in serum are much stronger biomarkers for DEHP exposure than the previously used biomarker MEHP (54-56).

One study showed that the content of phthalate metabolites in serum is generally lower compared with the excretion of metabolites in urine (57). Phthalates are excreted in even lower amounts in semen, meconium and saliva (27).

In vitro studies, what is the association between phthalate exposure and breast cancer risk? [An experiment in a test tube or cell culture system is an *in vitro* experiment.]

Several studies have shown that phthalate exposure increases the growth of breast cancer cells *in vitro* (35, 37, 38, 65). This effect may be mediated through phthalate activation of the estrogen receptor as well as activation of the PPARalpha receptor (34). In addition, phthalates have low binding affinity for the estrogen receptor (ER), thus possibly affecting breast cancer cell growth in the absence of estrogen, such as under hormone therapy conditions (58). In rodents, however, levels of phthalate exposure required to elicit an effect is at a high dose level (~ 1g/kg/day) which is significantly greater than levels humans are normally exposed to (~ 113 ug/kg bodyweight/day).

In vivo studies, what is the association between phthalate exposure and breast cancer risk? [An experiment in an animal model is referred to as an *in vivo* experiment.]

BCERC's laboratory-based biology research project entitled, "Environmental Effects on the Molecular Architecture and Function of the Mammary Gland across the Lifespan," is investigating this question.

To date, only one published study has been conducted on phthalate exposure and mammary tumors in animals (59). This study only examined BBP, and it found that phthalate exposure actually decreased the incidence of mammary tumors in rats exposed to the polycyclic aromatic hydrocarbon DMBA. More studies are needed to determine the association between phthalates and breast cancer *in vivo*.

In epidemiological studies, what is the association between phthalate exposure and breast cancer risk? [Studies of diseases in populations of humans or other animals.]

To date, only one epidemiological study on the association between phthalate exposure and breast cancer risk has been published (60). This small, limited occupational study examined one phthalate (BBP) and did not find an association with breast cancer risk. More epidemiological studies are needed to determine the association between phthalate exposure and human breast cancer risk.



Were phthalates included in biomonitoring measurements from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) Third Report?

Yes.

Urinary levels of phthalate metabolites were measured in a subsample of NHANES participants aged 6 years and older (39). Participants were randomly selected with the specified age range to be a representative sample of the U.S. population. For most of the phthalate metabolites tested, levels were higher in children aged 6 to 11 than they were in teens and adults. Eleven out of 12 phthalate metabolites measured higher in children aged 6 years and older than adults. The CDC study did not test children under 6.

What has the IARC determined about phthalates and carcinogenesis?

There are no phthalates classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC). The IARC in January 2000 downgraded its former classification of the phthalate di(2-ethylhexyl) phthalate (DEHP) to a Group 3 agent – meaning the substance cannot be classified as causing cancer in humans. DEHP was initially classified as a potential carcinogen following rodent studies, in which it was found to cause liver tumors through a mechanism called peroxisome proliferation when administered at high doses. IARC has now ruled that the mechanism by which DEHP increases the incidence of liver tumors in rats and mice is not relevant to humans. The IARC is part of the World Health Organization.

Has the federal government made recommendations to protect human health?

Yes.

NIEHS

In 2000, the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel selected seven phthalate chemicals to evaluate because of high production volume, extent of human exposures, use in children's products, and/or published evidence of reproductive or developmental toxicity. The seven phthalates selected were:

- Butyl Benzyl Phthalate
- Di-n-Butyl Phthalate
- Di-(2-Ethylhexyl) Phthalate
- Diisodecyl Phthalate
- Diisononyl Phthalate
- Di-n-Hexyl Phthalate
- Di-n-Octyl Phthalate

Expert panel reports were published on all seven phthalates and links to the reports can be found at <http://cerhr.niehs.nih.gov/reports/index.html>. Many of the reports cite lack of data on the reproductive and developmental effects of phthalates in human. After reviewing the expert panel report on DEHP, the NTP concluded that there is serious concern that human development or reproduction might be adversely affected by exposure to DEHP in critically ill male infants (60). There is also concern for male infants younger than one year, and male offspring of women undergoing certain medical treatments during pregnancy. There is some concern for male offspring exposed during pregnancy and male children older than one year.

EPA

The US Environmental Protection Agency (EPA) reference doses (RfDs) for phthalates (DBP, DEP, and DEHP) were formulated in the early 1990s using older animal studies. The RfDs, as defined by the US EPA, are intended to be a dose for which daily oral exposure to the human population is likely to be without an appreciable risk of deleterious effects during a lifetime. According to the US EPA, the lowest tested dose of a substance (LOEAL) that has been reported to cause harmful (adverse) health effects on people or animals for DEHP is 19 mg/kg/day (61). However, adverse effects have been seen in male newborns of mothers treated with DEHP at much lower levels (i.e. 1.32 to 9.32 ug/kg/day) (44). The EPA has set the Maximum Contaminant

Level (MCL) for DEHP in drinking water at 6 parts per billion (ppb). (6)

FDA

The FDA allows the use of phthalates in food contact items, and in the past has found that exposures are very low. Food contact items include packaging materials (adhesives and compounds of coatings, paper, and paperboard products, polymers, adjuvants, and production aids) as well as a wide array of other materials. However, there has not been a recent review of their toxicities and the potential for exposures via this use (63).

In September 2001, the Food and Drug Administration (FDA) completed its safety assessment of DEHP released from medical devices made with PVC (21). It found that, for several medical procedures, the dose of DEHP that patients might receive exceeds the "Tolerable Intake" (TI) value for DEHP. However, the FDA advises that "the risk of not doing a needed procedure is far greater than the risk associated with exposure to DEHP (64)." In addition, it recommends considering "alternatives when these high-risk procedures are to be performed on male neonates, pregnant women who are carrying male fetuses, and peripubertal males. One source for identifying alternative devices that do not contain DEHP-plasticized PVC is <http://www.sustainablehospitals.org>, associated with the University of Massachusetts Lowell."



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For more information on the Breast Cancer and the Environment Research Centers, go to <http://www.bcerc.org>.

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