Cancer Association of South Africa (CANSA)

Fact Sheet and
Position Statement
on
Phthalates

Introduction

Phthalates (pronounced as 'thah-lates') are a group of chemicals used to make plastics more flexible and harder to break. They are often called plasticisers. Some phthalates are used as solvents (dissolving agents) for other materials. They are used in hundreds of products, such as vinyl flooring, adhesives, detergents, lubricating oils, automotive plastics, plastic clothes (raincoats), and personal-care products (examples include: soaps, shampoos, hair sprays, and nail polishes).

[Picture Credit: Phthalates]

Phthalates are used widely in polyvinyl chloride plastics, which are used to make products such as plastic packaging film and sheets, garden hoses, inflatable toys, blood-storage containers, medical tubing, and some children's toys.

Sears, C.G. & Braun, J.M. 2020.

"Phthalates, a class of endocrine-disrupting chemicals, are used widely in many consumer products, and exposure can interfere with a range of hormonal functions during early life. These disruptions may alter development during late childhood and adolescence. This article discusses the potential effects of phthalate exposure on adiposity, puberty, and neurodevelopment during late childhood and adolescence. It also highlights studies of behavioral interventions to reduce phthalate exposures and the roles of health care professionals and policy makers in preventing phthalate exposure."

Qian, Y., Shao, H., Ying, X., Huang, W. & Hua, Y. 2020.
"Phthalates are a group of ubiquitous synthetic endocrine-disrupting chemicals. Fetal and neonatal periods are particularly susceptible to endocrine disorders, which prenatal exposure to phthalates causes. There is increasing evidence concerning the potential endocrine disrupting for phthalate exposure during pregnancy. This article aims to review the endocrine impairment and potential outcomes of prenatal phthalate exposure. Prenatal exposure phthalates would disrupt the levels of thyroid, sex hormone, and 25-hydroxyvitamin D in pregnant women or offspring, which results in preterm birth, preeclampsia, maternal glucose disorders, infant cryptorchidism, infant hypospadias, and shorter anogenital distance in newborns, as well as growth restriction not only in infants but also in early adolescence and childhood. The relationship of prenatal phthalate exposure with maternal and neonatal outcomes in human beings was often sex-specific associations. Because of the potentially harmful influence of prenatal phthalate exposure, steps should be taken to prevent or reduce phthalate exposure during pregnancy."

South Africa a Producer of Phthalates
South Africa is the only producer of phthalates in Africa and approximately 40 000 metric tons are produced and consumed, mostly in the flexible PVC industry.

Phthalates are divided into two distinct groups, with differing applications, properties and toxicological classifications namely 'low phthalates' and 'high phthalates'.

Low Phthalates such as DMP, DEP, DIBP, DEHP and BBP are low molecular weight phthalates which contain 8 or less carbon atoms on the alcohol part of the ester. These phthalates represent about 15% of phthalates consumed in Europe, however, this percentage rises significantly in global terms. Risk assessments have led to the classification and labelling as Category 1B with restrictions on their use imposed in many developed countries and economic blocks such as Europe. Certain restrictions have been placed on their use in toys, child care articles, medical devices, food contact materials and cosmetics.

DEHP (Di-2-ethylhexyl phthalate) is one of the most prolific plasticisers globally and is one of the most cost effective and efficient PVC plasticisers in use. It is listed by the EU hazard classification as a substance of very high concern (SVHC) and REACH authorisation is required. During the last 10 years DEHP has progressively been replaced by high phthalates such as DINP and DIDP, regarded as safer plasticisers.

High Phthalates, such as DINP (Di-isonyl phthalate), DIDP (Di-isodecyl phthalate) and DTDP, are high molecular weight phthalates and have grown in use in Europe and North America to nearly 75% of phthalates consumed. Risk assessments have shown positive results regarding the safe use of the products. They do not require any classification for health and environmental effects. They are safely used in numerous everyday consumer and industrial applications.

The South African Vinyls Association claims that the European Commission has confirmed that products such as DINP and DIDP pose no risk to human health or environment. This has been after many decades of exhaustive scientific evaluation and testing. These products are not regarded as endocrine disrupters, nor human carcinogens and have not been classified.

Common Phthalates and Examples of their Use

The following table provides information regarding the most common phthalates and their use:

Phthalate	Use
DMP	Insect repellent, plastic
DEP	Shampoo, scents, soap, lotion, cosmetics, industrial solvent, medication
DBP	Adhesives, caulk, cosmetics, industrial solvent, medications
DIBP	Adhesives, caulk, cosmetics, industrial solvent
BBP	Vinyl flooring, adhesives, sealants, industrial solvent
DCHP	Stabiliser in rubber, polymers
DEHO	Soft plastic including tubing, toys, home products, food containers, food packaging
DOP	Soft plastic

Table of the Most Common Phthalates

The following is a list of the most common phthalates:

Name	Abbreviation	Structural formula	Molecular weight (g/mol)	CAS No.
Dimethyl phthalate	DMP	$C_6H_4(COOCH_3)_2$	194.18	131-11-3
Diethyl phthalate	DEP	$C_6H_4(COOC_2H_5)_2$	222.24	84-66-2
Diallyl phthalate	DAP	$C_6H_4(COOCH_2CH{=}CH_2)_2$	246.26	131-17-9
Di-n-propyl phthalate	DPP	$C_6H_4[COO(CH_2)_2CH_3]_2$	250.29	131-16-8
Di-n-butyl phthalate	DBP	$C_6H_4[COO(CH_2)_3CH_3]_2$	278.34	84-74-2
Diisobutyl phthalate	DIBP	$C_6H_4[COOCH_2CH(CH_3)_2]_2$	278.34	84-69-5
Butyl cyclohexyl phthalate	BCP	$CH_3(CH_2)_3OOCC_6H_4COOC_6H_{11}$	304.38	84-64-0
Di-n-pentyl phthalate	DNPP	$C_6H_4[COO(CH_2)_4CH_3]_2$	306.40	131-18-0
Dicyclohexyl phthalate	DCP	$C_6H_4[COOC_6H_{11}]_2$	330.42	84-61-7
Butyl benzyl phthalate	BBP	$CH_3(CH_2)_3OOCC_6H_4COOCH_2C_6H_5$	312.36	85-68-7
Di-n-hexyl phthalate	DNHP	$C_6H_4[COO(CH_2)_5CH_3]_2$	334.45	84-75-3
Diisohexyl phthalate	DIHxP	$C_6H_4[COO(CH_2)_3CH(CH_3)_2]_2$	334.45	146-50-9
Diisoheptyl phthalate	DIHpP	$C_6H_4[COO(CH_2)_4CH(CH_3)_2]_2$	362.50	41451-28-9
Butyl decyl phthalate	BDP	$CH_3(CH_2)_3OOCC_6H_4COO(CH_2)_9CH_3$	362.50	89-19-0
Di(2-ethylhexyl) phthalate	DEHP, DOP	$C_6H_4[COOCH_2CH(C_2H_5)(CH_2)_3CH_3]_2$	390.56	117-81-7
Di(n-octyl) phthalate	DNOP	$C_6H_4[COO(CH_2)_7CH_3]_2$	390.56	117-84-0
Diisooctyl phthalate	DIOP	$C_6H_4[COO(CH_2)_5CH(CH_3)_2]_2$	390.56	27554-26-3

Name	Abbreviation	Structural formula	Molecular weight (g/mol)	CAS No.
n-Octyl n-decyl phthalate	ODP	$CH_3(CH_2)_7OOCC_6H_4COO(CH_2)_9CH_3$	418.61	119-07-3
Diisononyl phthalate	DINP	$C_6H_4[COO(CH_2)_6CH(CH_3)_2]_2$	418.61	28553-12-0
Di(2-propylheptyl) phthalate	DPHP	$C_6H_4[COOCH_2CH(CH_2CH_2CH_3)(CH_2)_4CH_3]_2$	446.66	53306-54-0
Diisodecyl phthalate	DIDP	$C_6H_4[COO(CH_2)_7CH(CH_3)_2]_2$	446.66	26761-40-0
Diundecyl phthalate	DUP	$C_6H_4[COO(CH_2)_{10}CH_3]_2$	474.72	3648-20-2
Diisoundecyl phthalate	DIUP	$C_6H_4[COO(CH_2)_8CH(CH_3)_2]_2$	474.72	85507-79-5
Ditridecyl phthalate	DTDP	$C_6H_4[COO(CH_2)_{12}CH_3]_2$	530.82	119-06-2
Diisotridecyl phthalate	DIUP	$C_6H_4[COO(CH_2)_{10}CH(CH_3)_2]_2$	530.82	68515-47-9

Products That Contain the Three Most Potent Phthalates

The three most potent phthalates are diethyl phthalate (DEHP), dibutyl phthalate (DBP), and benzylbutyl phthalate (BBP). Not only do they adversely affect health by themselves, but even in small doses they interact with one another in ways we do not understand. The dominant phthalate, DEHP, which is in, among other things, shower curtains, cable sheathing, garden hoses, and some toys, has been used so widely that it can now be found literally all over the world: in subsurface snow in Antarctica and in jellyfish more than a hundred metres below the surface of the Atlantic.

The following products contain the ‘Big Three’ phthalates:

- DEHP: vinyl products, floor tiles, upholstery, shower curtains, cables, garden hoses, rainwear, car parts and interiors, packaging film, sheathing for wire and cable, some food containers, toys, and medical devices
- DBP: nail polish, cosmetics, and insecticides
- BBP: adhesives, paints, sealants, car-care products, vinyl flooring, and some personal-care products

Sources of Phthalate Exposure

The following are the main sources of exposure to phthalates by humans:

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. Phthalates may also enter food by environmental uptake during crop cultivation or by migration from processing equipment or packaging materials.

- Water - phthalates are found in ground water and drinking water.

- Infant formula and milk - some phthalates occur as contaminants in consumer milk and ready-to-use baby formulas based on cow's milk.

- 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 plasticiser phthalates such as DBP and DEP. Other pharmaceutical products may also have phthalate plasticisers in their coatings, including some antibiotics, antihistamines and laxatives. Patented herbal preparations and nutritional supplements may also contain phthalates.

[Picture Credit: Soft Toys]

- Toys - Polymer toys softened with phthalates are a source of potential oral exposure in children. 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.

Inhalation

- Indoor air and house dust - vapours emitted from building materials, furniture and household fragrances are potential indoor sources of phthalate exposures. Phthalates have been found in house dust in different countries, including the US, Germany, Japan and Norway. inhalation of house dust may be an important source of exposure for the lower molecular weight phthalates, but not the higher weight phthalates.

[Picture Credit: Ventilator]

- Medical devices - some phthalate esters, such as DEHP, may be transferred into respiratory gases passing through PVC tubing.

- Baking modelling clay - polymer modelling 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.

<u>Intravenous</u>

- 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. DEHP has been found in newborns treated in neonatal intensive care units with medical devices made with polyvinyl chloride plastic containing DEHP.

[Picture Credit: IV Therapy]

<u>Skin Absorption</u>

- 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 moisturisers and shampoos. In one study, the levels of selected phthalates were measured in 102 branded hair sprays, perfumes, deodorants, and nail polishes. 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.

[Picture Credit: Nail Polish]

- Modelling clay - skin absorption may occur through direct contact with polymer modelling clay containing phthalates.
- Denture materials - phthalates can be found in temporary denture soft lining materials.

Craig, J.A., Ceballos, D.M., Fruh, V., Petropoulos, Z.E., Allen, J.G., Calafat, A.M., Ospina, M., Stapleton, H.M., Hammel, S., Gray, R. & Webster, T.F. 2019.
"Relatively little is known about the exposure of nail technicians to semivolatile organic compounds (SVOCs) in nail salons. We collected preshift and postshift urine samples and silicone wrist bands (SWBs) worn on lapels and wrists from 10 female nail technicians in the Boston area in 2016-17. We analyzed samples for phthalates, phthalate alternatives, and organophosphate esters (OPEs) or their metabolites. Postshift urine concentrations were generally higher than preshift concentrations for SVOC metabolites; the greatest change was for a metabolite of the phthalate alternative di(2-ethylhexyl) terephthalate (DEHTP): mono(2-ethyl-5-carboxypentyl) terephthalate (MECPTP) more than tripled from 11.7 to 36.6 μg/g creatinine. DEHTP biomarkers were higher in our study participants' postshift urine compared to 2015-2016 National Health and Nutrition Examination Survey females. Urinary MECPTP and another DEHTP metabolite were moderately correlated (r = 0.37-0.60) with DEHTP on the SWBs, suggesting occupation as a source of exposure. Our results suggest that nail technicians are occupationally exposed to certain phthalates, phthalate alternatives, and OPEs, with metabolites of DEHTP showing the largest increase across a work day. The detection of several of these SVOCs on SWBs suggests that they can be used as a tool for examining potential occupational exposures to SVOCs among nail salon workers."

Giuliani, A., Zuccarini, M., Cichelli, A., Khan, H, & Reale, M. 2020.
"Phthalates are a huge class of chemicals with a wide spectrum of industrial uses, from the manufacture of plastics to food contact applications, children's toys, and medical devices. People and animals can be exposed through different routes (i.e., ingestion, inhalation, dermal, or iatrogenic exposure), as these compounds can be easily released from plastics to water, food, soil, air, making them ubiquitous environmental contaminants. In the last decades, phthalates and their metabolites have proven to be of concern, particularly in products for pregnant women or children. Moreover, many authors reported high concentrations of phthalates in soft drinks, mineral waters, wine, oil, ready-to-eat meals, and other products, as a possible consequence of their accumulation along the food production chain and their accidental release from packaging materials. However, due to their different physical and chemical properties, phthalates do not have the same human and environmental impacts and their association to several human diseases is still under debate. In this review we provide an overview of phthalate toxicity, pointing out the health and legal issues related to their occurrence in several types of food and beverage."
Various edible oils were found to contain phthalates of sufficient concentration to warrant further investigation.

Luo, Q., Liu, Z.H., Yin, H., Dang, Z., Wu, P.X., Zhu, N.W., Lin, Z. & Liu, Y. 2020.
"This work investigated the presence of seven major phthalates in nine different kinds of edible oils (i.e. olive, rapeseed, peanut, sesame, tea seed, corn, soybean, sunflower, and blended oil) and their

potential impacts on human. The respective total average phthalates concentrations in the oils studied were found to be 6.01, 2.79, 2.63, 2.03, 1.73, 1.66, 1.57, 1.26, and 0.72 mg/kg. On the other hand, the seven main phthalates in the edible oils with the average concentration ranked from high to low were in order of DiNP, DEHP, DiDP, DBP, DiBP, DEP, and BBP, with 0.90, 0.81, 0.79, 0.71, 0.22, 0.17, and 0.10 mg/kg, respectively. The estimated maximum human daily intakes (EDI) of DEHP, DBP, DiBP, DiNP, BBP, DEP, and DiDP via edible oils were determined to be 552, 2996, 121, 356, 268, 66, and 563 µg/p/d, respectively. It was further revealed that the maximum human EDI of DEHP, DBP, BBP, and DiBP through consumption of edible oils were 2.92, 6.79, 1.24, and 1.06 times higher than those via bottled water. The calculated average estrogenic equivalence (EEQ) values of the seven major phthalates in edible oils fell into the range of 2.7-958.1 ng E_2/L, which were 45-396 times of those in bottled water. With published works, the complete distributions of 15 phthalates in nine kinds of edible oils were established and assessed for the health risks based on EDI and EEQ. This work provided the first evidence that edible oil is a potential source of phthalates, thus the potential adverse estrogenic effects on human health should need to be assessed in a holistic manner."

Health Effects of Phthalates

There are many types of phthalates. The most commonly used and studied is DEHP (diethylhexyl phthalate). The International Agency for Research on Cancer (IARC) classifies DEPH as a possible cause of cancer (Group 2B). The US National Toxicology Program (NTP) says that DEHP "is reasonably anticipated to be a human carcinogen". This means that it is probably something that could cause cancer in humans.

The phthalate DEHP (found in vinyl products and in many medical plastics such as IV bags and tubes) causes tumours and other abnormalities (related to fertility) in the livers of rats and mice. Studies have shown that in pregnant rats and mice, high doses of DBP (dibutyl phthalate, most commonly used in cosmetics) causes a decrease in the number of live babies born.

To cause these abnormalities in laboratory animals, exposure to the substances needs to be relatively high. These substances also seem to have greater effects on young and developing animals.

There is also evidence that certain phthalates act as endocrine disruptors. This means they may mimic or behave like hormones and can interfere with the normal hormonal activity in human bodies. This can lead to physical abnormalities, fertility problems and certain types of cancer.

More research is needed to know for sure whether phthalates affect people in the same way that they affect animals.

Some other health effects include evidence from a recent study of adult males in Sweden which found significantly fewer motile sperm for men with higher urine concentrations of the phthalate metabolite MEP. Reduced sperm motility (motion) was significantly associated with blood concentrations of some polychlorinated biphenyls (PCBs) and urine concentrations of some phthalate metabolites (e.g., MBeP and PCB 153).

Phthalates have been shown to cause a variety of effects in laboratory animals, however, their adverse effects on development of the reproductive system of male animals have led to particular concern.

Those effects include infertility, decreased sperm count, cryptorchidism (undescended testes), hypospadias (malformation of the penis) and other reproductive tract defects and are referred to as the phthalate syndrome. Given these common effects of phthalate exposure that have been observed in laboratory animals, the second question has been answered affirmatively. In addition, the phthalate syndrome in animals has many similarities to a hypothesised syndrome in humans – testicular dysgenesis syndrome – although there ae no human data that directly link the hypothesised syndrome in humans with phthalate exposure.

A 2012 study found that women working in the automotive and food-canning industries have nearly a fivefold increase in risk for pre-menopausal breast cancer, likely because of their exposure to phthalates.

According to the Bureau of Standards, Metrology & Inspection phthalates are endocrine disruptors that can interfere with the hormonal system in mammals and cause early onset of puberty in girls and feminisation in boys.

A recent case-control study examined phthalate levels in apparently healthy girls who went through thelarche (breast development) before the age of 8, as compared with girls who underwent precocious puberty because of abnormalities in their neuroendocrine systems and with girls who were progressing through puberty at normal ages. Increased levels of monomethyl phthalate were associated with early thelarche group, but not with either of the comparison groups (Chou, 2009). Early breast development in otherwise healthy girls is associated with an increased risk for breast cancer (Steingraber, 2007).

A 2012 study examined whether or not there is a relationship between urinary levels of nine different phthalates and the incidence of breast cancer. In this study, urinary phthalate metabolites were detected in 82 percent of the women, whether or not they had been diagnosed with breast cancer. Monoethyl phthalate (MEP), a urinary metabolite of the parent compound diethyl phthalate (DEP; often used in fragrance), was elevated in women with breast cancer. This association was most profound in pre-menopausal women. Metabolites of two other common phthalates (butyl benzyl phthalate, BBP; and di-n-octyl phthalate, DOP) were negatively associated with breast cancer risk in this study (Lopez-Carrillo, 2010). Higher levels of urinary MEHP, a marker of DEHP body burden, has also been associated with increased pregnancy loss in a study of Danish women (Toft, 2012).

Not all phthalates are equivalent in the severity of their effect; some phthalates exhibit less severe or no effects. The age at the time of exposure is also critical with respect to the severity of the effects. The foetus is the most sensitive life stage.

Hormones can increase the risk of some cancers, whether those hormones are natural or synthetic. Too much or too little of a hormone can be harmful. Is a child who is exposed to phthalates more likely to develop cancer as an adult? No one knows for sure but animals exposed to phthalates are more likely to develop liver cancer, kidney cancer, and male reproductive organ damage (Vastag).

Phthalates are believed to also affect girls' hormones, but the health impact is not yet known. Studies also show associations between children's exposure to phthalates and the risk of asthma, allergies and bronchial obstruction (Hsu, et al., 2012; Jaakola & Knight, 2008; Kanazawa & Kishi, 2009).

Researchers at Mount Sinai also found a link between obesity and phthalates (Teitelbaum, *et al*., 2012). They found that among overweight girls ages 6 to 8, the higher the concentration of certain phthalates (including low molecular weight phthalates) in their urine, the higher their body mass index (BMI). BMI takes height and weight into account when determining if someone is overweight. A study among Danish children ages 4 to 9 found that the higher the concentration of phthalates (all of them), the shorter the child. This was true for girls and boys (Boas, et al., 2010). More research is needed to determine the impact of phthalates on height and BMI.

Peer-Reviewed Research on Phthalates

Zhang, Q., Chen, X.Z., Huang, X., Wang, M. & Wu.P. 2019.
BACKGROUND: Phthalate have been detected widely in the environment; while several studies have indicated that prenatal phthalate exposure has adverse effects on neurodevelopment, the results were inconsistent.
OBJECTIVE: We aimed to determine the current research status of the relationship between prenatal exposure to different types of phthalate and cognition and behavioral development in children. We conducted a systematic review to evaluate the current state of knowledge.
METHODS: We systematically searched PubMed, Web of Science, and EMBASE electronic databases up to May 2018 with manual searches of the references of retrieved publications and relevant reviews. Only birth cohort studies that reported on the association between phthalate exposure and cognitive or behavioral development were included in this review. We evaluated the risk of bias for each of the included studies using a modified instrument based on the Cochrane Collaboration's "Risk of Bias" tool.
RESULT: Twenty-six birth cohort studies met our inclusion criteria, nine of which investigated the impact of phthalate exposure during pregnancy on cognition, 13 on neurobehavior, and 4 on both cognition and neurobehavior. However, ten articles reported that the effect of prenatal exposure to phthalates on cognitive development was statistically significant, 15 articles reported that the effect of prenatal exposure to phthalates on neurobehavior was statistically significant. The effect of prenatal phthalate exposure on neurodevelopment differed according to sex, but the results are inconsistent, for instance, among the five studies investigating the association between mental development index (MDI) and Mono-n-butyl phthalate (MnBP), two of them showed a significantly decreasing MDI scores with increasing concentrations of MnBP among girls, but among boys one study showed the inverse association, another showed the positive association.
CONCLUSION: Di(2-ethylhexyl) phthalate, dibutyl phthalate, butyl-benzyl phthalate and di-ethyl phthalate exposure during pregnancy was associated with lower cognitive scores and worse behavior in offspring, and sex-specific effects on cognitive, psychomotor, and behavioral development were identified, especially the impact of phthalate exposure on neurobehavior in boys.

Brehm, E. & Flaws, J.A. 2019.
"Endocrine-disrupting chemicals are known to interfere with normal reproductive function and hormone signaling. Phthalates, bisphenol A, pesticides, and environmental contaminants such as polychlorinated biphenyls and dioxins are known endocrine-disrupting chemicals that have been shown to negatively affect both male and female reproduction. Exposure to these chemicals occurs on a daily basis owing to these compounds being found in plastics, personal care products, and pesticides. Recently, studies have shown that these chemicals may cause transgenerational effects on

reproduction in both males and females. This is of concern because exposure to these chemicals prenatally or during adult life can negatively impact the reproductive health of future generations. This mini-review summarizes the endocrine-disrupting chemicals that humans are exposed to on a daily basis and what is known about the transgenerational effects that these chemicals may have on male and female reproduction."

Ahern, T.P., Broe, A., Lash, T.L., Cronin-Fenton, D.P., Ulrichsen, S.P., Christiansen, P.M., Cole, B.F., Tamimi, R.M., Sørensen, H.T. & Damkier, P. 2019.

PURPOSE: Phthalate exposure is ubiquitous and especially high among users of drug products formulated with phthalates. Some phthalatesmimic estradiol and may promote breast cancer. Existing epidemiologic studies on this topic are small, mostly not prospective, and have given inconsistent results. We estimated associations between longitudinal phthalate exposures and breast cancer risk in a Danish nationwide cohort, using redeemed prescriptions for phthalate-containing drug products to measure exposure.

METHODS: We ascertained the phthalate content of drugs marketed in Denmark using an internal Danish Medicines Agency ingredient database. We enrolled a Danish nationwide cohort of 1.12 million women at risk for a first cancer diagnosis on January 1, 2005. By combining drug ingredient data with the Danish National Prescription registry, we characterized annual, cumulative phthalate exposure through redeemed prescriptions. We then fit multivariable Cox regression models to estimate associations between phthalate exposures and incident invasive breast carcinoma according to tumor estrogen receptor status.

RESULTS: Over 9.99 million woman-years of follow-up, most phthalate exposures were not associated with breast cancer incidence. High-level dibutyl phthalate exposure (≥ 10,000 cumulative mg) was associated with an approximately two-fold increase in the rate of estrogen receptor-positive breast cancer (hazard ratio, 1.9; 95% CI, 1.1 to 3.5), consistent with in vitro evidence for an estrogenic effect of this compound. Lower levels of dibutyl phthalate exposure were not associated with breast cancer incidence.

CONCLUSION: Our results suggest that women should avoid high-level exposure to dibutyl phthalate, such as through long-term treatment with pharmaceuticals formulated with dibutyl phthalate.

Wang, Y., Zhu, H. & Kannan, K. 2019.

"Phthalates (diesters of phthalic acid) are widely used as plasticizers and additives in many consumer products. Laboratory animal studies have reported the endocrine-disrupting and reproductive effects of phthalates, and human exposure to this class of chemicals is a concern. Several phthalates have been recognized as substances of high concern. Human exposure to phthalates occurs mainly via dietary sources, dermal absorption, and air inhalation. Phthalates are excreted as conjugated monoesters in urine, and some phthalates, such as di-2-ethylhexyl phthalate (DEHP), undergo secondary metabolism, including oxidative transformation, prior to urinary excretion. The occurrence of phthalates and their metabolites in urine, serum, breast milk, and semen has been widely reported. Urine has been the preferred matrix in human biomonitoring studies, and concentrations on the order of several tens to hundreds of nanograms per milliliter have been reported for several phthalate metabolites. Metabolites of diethyl phthalate (DEP), dibutyl- (DBP) and diisobutyl- (DiBP) phthalates, and DEHP were the most abundant compounds measured in urine. Temporal trends in phthalate exposures varied among countries. In the United States (US), DEHP exposure has declined since 2005, whereas DiNP exposure has increased. In China, DEHP exposure has increased since 2000. For many phthalates, exposures in children are higher than those in adults. Human epidemiological studies have shown a significant association between phthalate exposures and adverse reproductive outcomes in women and men, type II diabetes and insulin resistance, overweight/obesity, allergy, and asthma. This review compiles biomonitoring studies of phthalates and exposure doses to assess health risks from phthalate exposures in populations across the globe."

Dong, R., Wu, Y., Chen, J., Wu, M., Li, S. & Chen, B. 2019.
"Phthalates are widespread endocrine-disrupting chemicals (EDCs) that have been suggested to affect neurodevelopment. However, association between lactational exposure to phthalates and neurodevelopmental effects has rarely been reported in epidemiological studies. We conducted a pilot prospective study of 138 mother-infant pairs to evaluate whether lactational exposure to phthalates was associated with neurodevelopmental effects in infants. At baseline survey, the spot urine samples from both mothers and infants were collected for measuring ten metabolites of phthalates, and the food intake information of infants was assessed by the food-frequency questionnaire (FFQ). At the follow-up survey in 9 months of age, the neurodevelopmental Function of infants was assessed using the Ages and Stages Questionnaire Edition 3 (ASQ-3). Multivariate logistic regression models were used to calculate the odds ratio (OR) for delayed development according to the level of exposure to phthalates. Our results indicated that MnBP and MiBP were high in lactating infants and mothers. In the overall study population, most metabolites showed positive associations with delayed development of most ASQ-3 domains. In male, MMP, MEP, MiBP and MnBP but not DEHP metabolites were significantly associated with increased odds of delayed development of all domains. In female, most LMWP metabolites and the four oxidative metabolites of DEHP were significantly associated with increased odds of delayed development of most domains. In conclusion, we found a significant negative association between lactational exposure to phthalates and ASQ-3 domains. Some of the sex-specific observations warrant further investigation. The dietary source of lactational phthalates exposure may not the breast milk or infant formula but the complementary food."

CANSA's Position on Hormone Disruptive Phthalates in Children's Soft Toys
CANSA shares the concern expressed over the presence of plasticisers in children's plastic soft toys that may contain hormone disruptive phthalates. It is known that some phthalates are potent endocrine disrupting chemicals that may harm human health. Knowing the harmful effects of certain phthalates, CANSA makes the following recommendations:

- Knowing that children will invariably put toys in their mouths and even chew on them, CANSA advocates that children should not be provided with soft plastic toys as they may contain hormone disruptive phthalates
- Infants and toddlers should not be given soft plastic toys to chew during teething
- Children should not play and/or sleep with soft plastic objects such as bracelets in direct contact with their skins
- Parents and guardians should only provide soft plastic toys to their children if there is clear evidence that the plasticisers used in the manufacture of the toys are free from any of the known hormone disruptive phthalates

CANSA will continue its watchdog role into children's plastic soft toys and will keep the public informed of developments.

Medical Disclaimer

This Fact Sheet and Position Statement is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet and Position Statement. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet and Position Statement.

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