

Review Article

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Phthalates - A Serious Concern to Health

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ABSTRACT

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Phthalates are ubiquitous contaminants in food, indoor air, soils and sediments. PVC medical devices contain, on average 20% to 40% Diethylhexyl Phthalate (DEHP) by weight. DEHP imparts important qualities to polyvinylchloride products, such as flexibility, strength, temperature tolerance, stability during sterilization and resistance to kinking. Phthalic acid esters are well-known peroxisome proliferators (PPs). After binding to the peroxisome proliferator receptor they increased the formation of peroxisomal enzymes which participate in metabolism of fats and enhanced β -oxidation of fatty acids. As a result of oxidation of fatty acids, reactive oxygen species (ROS) and large quantities of hydrogen peroxide are generated which aggravate tissue damage and ultimately leads to carcinogenicity and teratogenicity. It has been known that DEHP exposure activates metallothioneins in the liver of pregnant females and prevents it from being carried to foetuses by blood. Many phthalates are hormone-disrupting chemicals that interfere with the production of the male sex hormone, testosterone, which is necessary for proper development and function of the male reproductive organs. Foetal exposure in male animals has been associated with infertility, decreased sperm count, undescended testes and malformations of the penis and urethra. Phthalate exposures in humans have been linked to changes in sex hormone levels, altered development of genitals, low sperm count and quality. Phthalates have also been linked with obesity, reduced female fertility, preterm birth with low birth weight, allergy and asthma.

Introduction

Phthalates or phthalic acid esters are synthetic compounds that are mostly used as plasticisers to improve the softness, flexibility, and extensibility of a variety of plastic products. Phthalates can be added to numerous products for general use such as toys, personal care and household products, car cosmetics, various solvents, adhesives,

glues, pesticides, food packaging, medical devices, electronics, tubing, paints and building materials (Horn *et al.*, 2004).

Phthalates which are used most commonly as plasticizer are inert organic compounds with low molecular weight, high boiling point and low vapour pressures that are used as polymer additives. The main role of the plasticizer is to improve mechanical properties of the

polymers by increasing flexibility, decreasing tensile strength. In plasticised polyvinyl chloride (PVC) products they make up to 40% (w/w). According to International Union of Pure and Applied Chemistry (IUPAC) a plasticizer are “substance or material incorporated in a material (usually a plastic or an elastomer) to increase its flexibility, workability, or distensibility” (Shea, 2003).

Diethylhexyl phthalates (DEHP) and Monoethylhexyl phthalates (MEHP) are infused with blood products and during hemodialysis since the early 1970s. Investigators measured DEHP and MEHP delivered during neonatal exchange transfusions since 1980s. Phthalates are primarily used to enhance plasticity of industrial polymers (Sears and Darby, 1982).

Nearly 11 billion pounds of phthalates were produced worldwide every year (Lowell Center for Sustainable Production, 2011). While these plasticizing agents impart beneficial properties to plastics, they are not bound to the polymer by a covalent linkage which makes them susceptible to leaching from the matrix (Fromme *et al.*, 2012). Phthalates have bioaccumulation activity. Bioaccumulation is the net accumulation of a contaminant in or on an organism from all sources including water, air and diet. Phthalates with lesser molecular weights, such as diethyl phthalate (DEP) have greater bioaccumulation factors (BAFs), while larger phthalates such as di-(2-ethyl hexyl) phthalate (DEHP) tend to have lesser BAFs (Gobas, 2003).

Phthalates have been detected in human matrices such as blood, urine, saliva, amniotic fluid, breast milk and cord blood (Latini *et al.*, 2003). Infants and toddlers are the most vulnerable receptors because they exhibit more hand-to-mouth activity and consume the most food as a percent of their body weight

(Wargo *et al.*, 2008). There are two types of phthalate contamination: contamination with phthalate residues, which are undesired in products (for example, phthalates in beverages and food) and contamination with phthalates intentionally added to products (for example, phthalates in soft Polyvinylchloride products). The situation is exaggerated by the fact that ubiquitous phthalates such as DEHP, which have been classified as endocrine disrupting chemicals (EDCs) (Rhodes *et al.*, 1986). These include effects on reproduction, damage to sperm (Rozati *et al.*, 2002), early onset of puberty in females, anomalies of reproductive tract (Desdoits-Lethimonier *et al.*, 2012), infertility and adverse outcomes of pregnancy (Latini *et al.*, 2003), neurodevelopment, allergies (Bornehag *et al.*, 2004).

Phthalates are not covalently bound to the plastic matrix and leach out of Polyvinylchloride when they come in contact with lipophilic substances. In addition, they are released directly into the environment during production and use and after disposal of PVC and other phthalate-containing products (Silva *et al.*, 2004). Phthalates bioaccumulate in invertebrates and plants but do not biomagnify, because higher animals efficiently metabolize and excrete phthalates (Engel *et al.*, 2010).

Sources of phthalates

Phthalate contamination of food and beverages from packaging materials or processing methods is presumed to be a major route of exposure, but people can also ingest or inhale phthalate-contaminated dust and absorb phthalates across their skin. Phthalates are not chemically bound to the products and easily released from products with use. Widespread use of phthalates in consumer products has resulted in nearly universal contamination of people's bodies with certain

phthalates, which have also been measured in breast milk, umbilical cord blood and amniotic fluid.

Phthalates as industrial chemicals have become ubiquitous environmental pollutants due to their widespread use. The major source of human exposure is food contamination during growth, production, processing or packaging. Food surveys have documented highest levels of phthalate in fatty foods such as dairy (including infant formulas), fish, meat, and oils.

The second highest source of exposure is indoor air, where DEHP adheres strongly to aerosol particles. Because of its low water solubility and low vapour pressure, little DEHP is found in outdoor air or water. It is estimated that exposure to DEHP in the general population (excluding occupational exposure), medical exposures, and non-dietary ingestions in children is in the range of 3 to 30µg/kg of body weight per day. Other sources of contamination with phthalates include tubes, piping systems, and tanks used in wine and spirit production (Barron, 1995).

Phthalates in foods

The intake of phthalates contained in food is the most significant source of exposure for humans. It has been established that the amount of phthalates found in foods or meals depends on the initial contamination of ingredients used in the production of the food, food production technologies, period of storage (the time of contact with packaging materials), storage temperatures, ways of preparing dishes, fat content in foods and type of packaging material used.

Phthalates were distributed primarily to tissues with the high fat contents (subcutaneous fat and muscle tissue of pigs, mesenteric fat and skin of chickens), where

they are also accumulated. The lipophilic character of phthalates was also demonstrated by measurements of phthalate concentrations in water, milk and dairy products. The source of phthalates were disposable Polyvinylchloride gloves worn in the preparation of packed lunches as a protection against the spreading of diarrhoeal diseases caused by *Escherichia coli*. The amount of phthalates released to the dishes further increased if the gloves had been disinfected with ethanol. Because DEHP levels found in foods and dishes repeatedly exceeded the tolerated daily intake (TDI), the Japanese government banned the use of disposable Polyvinylchloride gloves for the handling of foods and dishes (Jaakkola *et al.*, 2000).

Phthalates in medicines

Phthalates are used in medicinal products chiefly as excipients in enteric-coated capsules/tablets where they make sure the medicinal product itself is not released until the capsule has passed through the highly acidic environment of the stomach. Furthermore, phthalates can be used to protect the active substance in medicinal products against humidity, ensure the flexibility of a capsule or tablet (so that it will not break) or cover up the smell or taste of the product. The following phthalates are the most widely used in medicinal products: diethylhexyl phthalate (DEHP), cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose acetate phthalate, dibutyl phthalate (DBP) and polyvinyl acetate phthalate (PVAP).

Ex-Creon®

Inactive ingredients include: cetyl alcohol, dimethicone, hypromellose phthalate, polyethylene glycol, and triethyl citrate. The imprinting ink on the capsule contains dimethicone, 2 ethoxyethanol, shellac, soya lecithin and titanium dioxide.

ULTRESA™

Inactive ingredients include: colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc and triethyl citrate.

Zenpep® -

Inactive ingredients include: colloidal silicon dioxide, croscarmellose sodium, hydrogenated castor oil, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, talc, and triethyl citrate and are contained in hypromellose capsules (Rozati *et al.*, 2002).

Paediatric exposure

Phthalates have been shown in animal studies to cross the placenta and pass into breast milk, so prenatal exposure and exposure from breastfeeding may occur in humans. Infants and young children consume more calories per kilogram of body weight, consume relatively more dairy and other fatty foods, so dietary exposures and exposure from indoor air would be expected to be higher in infants and young children.

In the United States and Canada, the uncertainty in predicting exposure levels, especially in very young children and infants, has led to the removal of all phthalates from infant bottle nipples, pacifiers, teething rings, and infant toys intended for mouthing. 2-DINP has been substituted for the more toxic DEHP in many other toys intended for children (Miodovnik *et al.*, 2011).

Pediatric medical exposures

Neonates can have high exposures to DEHP and its toxic monoester metabolite,

monoethylhexyl phthalate (MEHP), when undergoing replacement of blood products, exchange transfusion, extracorporeal membrane oxygenation (ECMO) and other lifesaving procedures. DEHP is the only phthalate currently used in medical devices (Tranfo *et al.*, 2012).

Physical and chemical property

Diethylhexyl phthalates are oily liquids at room temperature. They have low to moderate vapour pressures and negligible to moderate water solubility. DEHP have moderate volatility from moist soil surfaces and water. They have low to moderate mobility in soil and water systems. DEHP are expected to be readily biodegradable and the rate of abiotic hydrolysis is considered negligible to slow under environmental conditions. Those having short alkyl groups, such as methyl and butyl group [e.g. dimethyl phthalate (DMP) and DBP], are water-soluble, while those with long alkyl or aromatic moieties in the side chains (e.g. BBP and DEHP) are less water-soluble (Rudelet *et al.*, 2003).

Common routes of exposure

For humans, the main route of exposure is ingestion, followed by inhalation, dermal, and intravenous exposure. General population is mainly exposed through food products contaminated with DEHP from plastic containers or wrappers. Exposure from drinking water and ambient air makes a minor contribution to the total daily intake. Phthalates also readily cross the placental barrier. While low-molecular-weight and more volatile phthalates [diethyl phthalate (DEP), DBP, and BBP] present in consumer products as solvents and fixatives are absorbed primarily through skin or inhalation, phthalates used as plasticisers, like DEHP, are mainly ingested. An important source of DEP is unrecorded alcohol (homemade and

illegally produced alcohol) present on market for human consumption. DEHP is used to denature ethyl alcohol. Most studies cover human exposure to DEHP as the most abundant phthalate in consumer products. If

we exclude occupational and medical exposure, estimated adult DEHP intake ranges from 2 to 20 µg kg⁻¹ body weight per day, mostly from food (Adibi *et al.*, 2003).

Types of phthalates

Six common phthalates, their primary functions and products in which they are used

Phthalates	Function(s)	Products
DEHP (Diethyl hexyl phthalate)	Primarily used as a plasticizer for PVC	Dolls, shoes, raincoats, clothing, medical devices (plastic tubing and intravenous storage bags), furniture, automobile upholstery and floor tiles
DINP (Di isononyl phthalate)	Primarily used as a plasticizer for PVC	Teethers, rattles, balls, spoons, toys, gloves, drinking straws, rubber, adhesives, ink, sealant, paints and lacquers, food and food related uses, clothes, shoes, car and public transport interior
DBP (Di butyl phthalate)	Used as a plasticizer for PVC, poly vinyl alcohol (PVA) and rubber. Also used as solvent and fixative in paint and cosmetics	Latex adhesives, sealants, car care products, cosmetics, some inks and dyes, insecticides, food wrapping materials, home furnishing, paint, clothing and pharmaceutical coating. (may sometimes be present in toys as impurity or by-product in trace amounts)
DIDP (Di isodecyl phthalate)	Primarily used as a plasticizer for PVC	Electrical cords, leather for car interiors and PVC flooring
DnOP (Di-n-octyl phthalate)	Primarily used as a plasticizer for PVC	Floorings, tarps, pool liners, bottle cap liners, conveyor belts and garden hoses
BBP (Butyl benzyl phthalate)	Used as a plasticizer for PVC, polyurethane, polysulfide and acrylic-based polymers	Vinyl flooring, sealants, adhesives, car care products, automotive trim, food conveyor belts, food wrapping material, and artificial leather. (low concentrations have been detected in baby equipment and children's toys as by-products and impurities; not intentionally added to those products)

Mode of action

Phthalic acid esters are well-known peroxisome proliferators (PPs). A very potent peroxisome proliferator is di(2-ethylhexyl) phthalate (DEHP), while dibutyl phthalate, butyl benzyl phthalate and diisononyl phthalate (DBP, BBP, DINP) are somewhat

less effective (Valles *et al.*, 2003). It should be stressed that adverse effects of diester phthalates are attributable to their monoesters produced when diesters are hydrolysed in the gastrointestinal tract (Hurst and Waxman 2003). Peroxisome proliferators are bound by PPAR α - PPAR δ , i.e. peroxisome proliferator- activated receptors, which they

activate (Melnick, 2001). Peroxisome enzymes participate in the metabolism of fats by enhancing β -oxidation of fatty acids in tissues. As a result of the oxidation processes of fatty acids, reactive oxygen species (ROS) and large quantities of hydrogen peroxide are generated that might aggravate tissue damage (the so-called oxidative stress) (Seo *et al.*, 2004).

A role in the process of hepatotoxicity and carcinogenesis is played by subtype PPAR α . The activated PPAR α and the retinoid X receptor (RXR) combine to form a heterodimer (Silva *et al.*, 2003). The PPAR α -RXR complex produced is specifically bound to PPREs (peroxisome proliferator response elements) in the promoter region of genes that control peroxisome proliferation. The transcription of these genes is activated by the PPAR α -RXR complex bond. The consequence is an increase in DNA synthesis, hepatocyte proliferation, hepatomegaly, induction of peroxisome and microsomal enzymes, and suppression of hepatocyte apoptosis (Melnick, 2001).

The low sensitivity of humans is probably due to the lower expression of PPAR α in the human liver compared with the liver of mice or rats (Hurst and Waxman 2003). Toxicity of phthalates to the reproductive system of female rats is probably due to the suppression of the aromatase enzyme, which transforms testosterone in the cells of the *stratum granulosum* of the ovary follicles to estradiol. At the same time, an increased activity of enzymes participating in the breakdown of estradiol in the liver of females exposed to DEHP and DBP was confirmed. They also assumed that the female reproductive system may be damaged as a result of processes related to the peroxisome proliferation mediated not only through PPAR α but also through PPAR γ . An impairment of testosterone metabolism in testes of

adolescent male rats has been observed, which is probably due to a number of factors (Lovekamp-Swan and Davis 2003).

Kim *et al.*, (2004) reported that testicular impairment and tubular atrophy were especially aggravated by hormone regulation disturbances that cause a decrease in the production of testosterone in testes, by adverse effects of reactive oxygen species and by testicular cell apoptosis. The impairment of the male reproductive system due to the DEHP is also caused by alterations of the cytosolic phospholipase enzyme A2 (cPLA2) and of enzymes that metabolise the arachidonic acid.

The factor that is probably responsible not only for the reproductive toxicity of phthalates but also for their teratogenicity is the availability of zinc in the period of foetal development. Zinc is an essential element for embryonic and foetal development. It has been demonstrated that DEHP exposure activates metallothioneins in the liver of pregnant females. Metallothioneins in the liver of females retain zinc and prevent it from being carried by blood to foetuses.

Toxico kinetics

Phase-I biotransformation products (metabolites) of phthalates in humans are monoesters, which can further be metabolised to oxidative products. In the phase-II biotransformation, monoesters and oxidative metabolites can conjugate with glucuronide, and free or conjugated forms are eliminated from the body through urine and faeces. Because of rapid metabolism phthalates do not accumulate significantly in tissues. Oxidative metabolites of DEHP are not detected in the environment (river water) or in plastic bags, but have been determined in human urine, which makes them suitable biomarkers for monitoring human exposure to

phthalates and for evaluating toxicological risk to human reproduction (Silva *et al.*, 2003).

In the case of human exposure to phthalates, phthalate diesters are relatively rapidly hydrolysed to their respective monoesters in the intestine by pancreatic or liver hydrolases (the first stage of phthalate biotransformation). The monoesters thus produced are bioactive molecules responsible for the adverse effects of phthalates. Monoesters are absorbed in the blood stream and then metabolised in liver. They are subject in a varying degree to hydroxylation and oxidation reactions that enhance water solubility of the products. Phthalate monoesters with a short side chain are oxidised to a lesser extent. The second stage of phthalate biotransformation is conjugation with glucuronic acid mediated by the enzyme UDP-glucuronyl transferase. The conjugation affects mainly monoesters and their oxidised metabolites with a long side chain because the conjugation facilitates the excretion of relatively lipophilic metabolites. Both the conjugated and the free (non-conjugated) phthalate metabolites are excreted in urine and partly also faeces. On the basis of their measurement assumed that Diethylhexyl phthalates (DEHP) was absorbed unchanged from the intestine and was hydrolysed to monoethylhexyl phthalate (MEHP) in kidneys. Because MEHP is relatively readily soluble in water, it need not be transported to liver for conjugation and is excreted in urine mainly in the non-conjugate form (Kato *et al.*, 2004).

Toxicity of phthalates

General Toxicity (Toxicity in Mature Animals)

In mature animals, each phthalate has a different toxicity profile. The liver, kidneys,

thyroid and testes are common targets for general toxicity from oral exposures. Much of the concern about phthalates arises from reports beginning in the 1980's showing several to be carcinogens in rodents. DEHP causes liver cancers and DINP causes kidney and liver cancers in rodents. Acute toxicity of phthalates is very low. Low molecular phthalates, e.g. diethyl phthalate (DEP), may cause irritation of the skin, conjunctiva, and the mucous membrane of the oral and nasal cavities in animals.

Much more important are subchronic and chronic toxic effects of phthalates. Most important, numerous experiments in rodents have shown adverse effects of phthalates on the reproductive system and on the intrauterine development of foetuses (Ema *et al.*, 1996). Monitored the effects of monobenzyl phthalate (MBzP) and monobutyl phthalate (MBP) administered to female rats during pregnancy. It follows from their studies that the exposure to phthalates at doses of about 500mg/kg during pregnancy may cause in female rats an increase in the number of foetus resorption and dead foetuses, lower weights of the offspring at birth and last but not least, foetus malformation e.g. cleft palate, atresia ani and skeletal deformations.

Female rats exposed to di(2-ethylhexyl) phthalate (DEHP) at a dose of 2000 mg/kg also demonstrated a prolongation in their estrous cycles and anovulation as a result of a decrease in serum estradiol levels. The anovulation was related to the absence of the corpus luteum in the ovary and the occurrence of follicular cysts (Lovekamp-Swan and Davis, 2003).

Testicular lesions, hypospadias, cryptorchidism and other disorders in sexual organs of male rats were also found, which testify to antiandrogenic effects of some

phthalates, particularly of dibutylphthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) (Moore *et al.*, 2016).

Many phthalates are hormone-disrupting chemicals that interfere with the production of the male sex hormone, testosterone, which is necessary for proper development and function of the male reproductive organs. Interference with testosterone activity, especially early in life, can have irreversible effects on male reproduction. Foetal exposure in male animals has been associated with infertility, decreased sperm count, undescended testes, and malformations of the penis and urethra. When combined at low levels, some phthalates can act together to cause similar harm as seen with exposure to just one phthalate at high levels. Phthalate exposures in humans have been linked to changes in sex hormone levels, altered development of genitals and low sperm count and quality. Phthalates have also been linked with obesity, reduced female fertility, preterm birth and low birth weight, a worsening of allergy and asthma symptoms and altered toddler behaviour. Other phthalates, like DiDP, have been linked to other types of birth defects (Moore *et al.*, 2016).

Toxicity of diethylhexyl phthalates (dehp) in animals

DEHP causes skeletal, cardiovascular and eye abnormalities; neural tube defects; intrauterine death; increased postnatal death; and decreased intrauterine and postnatal growth in rodent pups whose dams received DEHP in feed or by gavage during pregnancy. Thus, foetal toxicity could occur without evidence of maternal toxicity after oral exposure. The most sensitive system is the reproductive tract of immature males. Pathologic changes in the testes and decreased sperm numbers are consistent effects across studies. Changes in weight of

the testes, vacuolization of sertoli cells and atrophy of the seminiferous tubules have been observed in rodent pups exposed to DEHP in utero via dietary exposure of dams. A rodent study of intravenous exposure found histologic abnormalities in sertoli cell endoplasmic reticulum and changes in spermatocyte structure.

Toxicity of diisodectylphthalates (dinp) in animals

The evidence on the toxicity of DINP is not as complete as that on the toxicity of DEHP. In general, DINP shows similar patterns of developmental toxicity, but at higher exposure levels. DINP has not been shown to cause reproductive toxicity. DINP causes skeletal and genitourinary abnormalities when rodent pups are exposed in utero at maternal oral doses of 500 to 1000 mg/kg per day (LOAEL), and as with DEHP, fetal toxicity can be seen at lower doses than can maternal toxicity (Whyatt *et al.*, 2009).

Other toxicities of phthalates

Human exposure to phthalates is associated with endocrine disruption, delays in fertility, impairment in foetal development, increased risk of allergies, asthma, and cancer. The current tolerable daily intake (TDI) values for DEHP, DBP, and BBP established by the EU Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) are based on studies of reproductive toxicity.

Reproductive and developmental toxicity

Phthalates that have a long alkyl side-chain in the *ortho* position have a potential for reproductive and developmental toxic effects in humans. These include DEHP>DBP>BBP (in the order of their toxic potential), as well as diisononyl phthalate (DiNP), di-*n*-hexyl phthalate (DnHP), and diisobutyl phthalate

(DiBP). This and other reproductive effects such as cryptorchidism and decreased semen quality could be owed to the ability of phthalate monoesters to cross the placental barrier and enter the umbilical cord blood of the foetus. Several studies have indicated that changes in male reproductive parameters, such as DNA sperm damage, decreased reproductive hormone levels, and anogenital distance (AGD, a biomarker of prenatal androgen exposure in male newborns) could be related with environmental exposure to phthalates.

Low-dose testicular effects

Histological damage to the rat testes was seen upon prenatal exposure to low levels of dietary DEHP. Male offspring showed severe dose-dependent histological damage including the disorganization of the seminiferous tubules and the absence of spermatocytes; these effects were only partially reversible. Within the testes, the interaction between Sertoli cells (specialized testicular cells that provide nutrients to sperm-producing structures) and gonocytes (precursors of spermatogonia) is essential for the normal maturation of sperm (Wolff *et al.*, 2010).

DEHP as a hepatotoxin

DEHP is a well-known hepatotoxin in rodents. The mechanisms of this hepatotoxicity have been extensively studied. DEHP is a peroxisome proliferator, a compound that stimulates hepatic peroxisomes and produces liver hypertrophy, hyperplasia and liver tumors, in rodents. These effects result from DEHP stimulation of a nuclear receptor protein called PPAR. Stimulation of PPAR results in alterations in hepatic enzyme activities, proliferation of abnormal cellular structures, and interference with apoptosis, the normal destruction of damaged cells. Thus, the peroxisome

proliferation and induction of hepatocarcinoma in the rodent liver by DEHP is dependent on this mechanism involving PPAR. Low dose hepatic effects have also been found in primates (Main *et al.*, 2006).

Indoor "fogging": a special case

The phenomenon known as indoor "fogging" has occurred since the mid-1990s: Within a few days or weeks black deposits begin to cover the surfaces of walls, ceilings or furnishings in residences (UBA 2005). The black film appears primarily after renovation work or upon initial occupancy of a dwelling. It is believed that a basic cause are semi-volatile organic compounds (SVOC), which are increasingly contained in products used in construction and renovation as well as in home furnishings, in replacement of volatile organic compounds (VOC). SVOC—to which the phthalates belong—escapes from the products and form a slimy film directly on the product, or on walls or ceilings. This film binds suspended dust particles to create a sooty deposit. The negative aesthetic implications and the expense associated with these deposits can be high in some cases. It is therefore advisable to rely on products that are low in contaminants. Fogging effects also occur in new vehicles, as temperatures in the interior of a car can rise dramatically, especially on sunny days. Besides the appearance of deposits from SVOC, elevated concentrations of contaminants may occur in the air of the car's interior; this is perceived as the typical "new car smell".

Environmental concern of phthalates...

Phthalates are released to the environment from multiple sources including industrial releases, the disposal of manufacturing, processing and industrial wastes, municipal solid waste, land application of sewage sludge, and release from products containing

phthalates. The data also indicate that the volume of releases to particular media generally ranks in the following order (from highest to lowest release volume): land, air, water.

Phthalates used as plasticisers have been released in the environment for the last 50 years. Fortunately, they are prone to bio, photo, and anaerobic degradation, which mean that they do not survive long in the environment.

Some facilities report relatively high releases and may create potentially high localized environmental concentrations of phthalates. Due to their pervasive use and release, as well as the propensity for global transport of plastics, many of which contain phthalates, phthalates are found in most environmental media, for example ambient air, surface water, soil, sediment, etc. Aquatic organisms, fish and terrestrial animals have evident exposure to DEHP (Staples *et al.*, 1997).

Phthalates may also pose risks for aquatic and terrestrial ecosystems particularly in the vicinity of phthalate processing industries. Some phthalates are bio-accumulative and have been detected in aquatic organisms. For example, BBP has been shown to be toxic to aquatic organisms and may cause long-term adverse effects in aquatic environments. Studies suggest BBP may have endocrine disrupting effects in fish.

In conclusion we are living in a plastic world. Plastics have been beneficial for the development of modern civilization. It is nearly impossible in most industrialized nations to avoid daily use of plastic. Unfortunately, some of the constituents in plastics like phthalates leach out into our environment and foods. It is time to take pause and analyze its deleterious effects on animals, humans and wildlife health.

Phthalates as a plasticizer is extensively used in toys, medical devices, cling wrap, nail polish, adhesives etc. They produce wide range of adverse effect on human, animals and other animal particularly involving reproductive and endocrine system of the body apart from neuro-chemical changes including diabetes and cancer. It is not possible to completely stop the use of phthalate from our daily life which is actually next to impossible. At best, we can follow a more rational and informed use of phthalates containing plastic in our daily life so that its deleterious effects can be minimized. Getting a suitable substitute of phthalates is not easy, as it is difficult to get, all the qualities of phthalates in other chemical. But, before using any substitute in medical industry, comprehensive toxicological investigation is essential so that a substitute itself may not become a second source of harmful chemical to the patients.

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