Health Effects Review

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Phthalates

Introduction

Phthalates are a ubiquitous class of compounds used most commonly as a softener for products made with polyvinyl chloride (PVC). The term "phthalate" refers to the di-ester derivatives of phthalic acid and thus represents a group of different though structurally related compounds. Between 1985 and 1990, 300 million pounds a year of phthalates were manufactured annually.[1] The most commonly used phthalate is di (2-ethylhexyl) phthalate or DEHP, chiefly used to soften PVC and make it more flexible.[1] Flexible PVC is used in everything from medical devices such as intravenous tubing and blood transfusion bags, to plastic wraps for food, shower curtains, and some types of floors and walls. DEHP is also known as bis (2-ethylhexyl) phthalate or dioctyl phthalate (DOP), which has led to some confusion with another phthalate, di-n-octylphthalate (DnOP), used in adhesives, coatings, and floors. The similarity in names may have resulted in overestimation of concentrations in the environment for the much less frequently used DnOP.[2] Another phthalate, di-n-butylphthalate (DBP), is used as a softener for PVC resins found in toys, pipes, wallpaper, furniture, raincoats, glue, nail polish and hair spray.[3] Yet another phthalate, butylbenzylphthalate (BBP) is in widespread use in flooring, paints, coatings, adhesive formulations and printing inks.[5]

Phthalates are a widespread environmental micropollutant in Europe and North America, including in the Great Lakes Basin. Studies that demonstrate toxicity of phthalates in animals have raised questions about possible human health effects. This review will briefly summarize the sources of phthalate exposure and selected toxicology as it relates to the potential for human health effects.

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Sources of Exposure

Water contamination

Phthalates are so ubiquitous in the environment that the laboratory air or equipment used for specimen, collection, storage, and analysis of phthalate levels may themselves be contaminated. Before 1980, many studies did not consider this phenomenon, and many published reports did not detail preventative measures to avoid laboratory contamination.[6] Numerous studies conducted since 1980, however, have documented the presence of phthalates in the sediments and surface waters of Europe and the U.S., including the Great Lakes Basin ecosystem. In 1990, DEHP, DnOP and DBP were found at Fort Erie and Niagara-on-the-Lake (at ng/L or : g/L concentrations). [7] DEHP and DBP have been found in effluent from petrochemical plants along the St. Clair River.[8] BBP, DnOP and DBP have been demonstrated in Detroit River sediments.[9] Finally, fish in U.S. Great Lake harbors are contaminated with DEHP and DBP.[10]

Soil and air contamination

The primary route for DEHP release into soil is through disposal of industrial and municipal waste at landfills. The majority of this is municipal waste, which harbors DEHP-containing plastics (an estimated 230 million pounds released from this route, according to reports in 1988 to the Toxic Release Inventory).[1] Industrial releases also contribute to soil contamination. The migration and deposition patterns of phthalates in general, once released into the environment, vary according to their water solubility and other physical characteristics, which in turn, depend on their specific chemical structures. From landfills, DEHP, for example, tends to bind to soil, and does not migrate far from where it is released.[1] The leachate from a landfill can range from less than 0.01 to 150 ppm DEHP.[11] In the presence of solvents, lipids, or other hydrophobic compounds, the solubility phthalates in ground and surface waters increases. Air concentrations (at ng/m3 levels) have been measured in remote areas.[1]

Human Exposure

The primary sources of human exposure to phthalates are through food, indoor air, and through use of selected medical devices.[14] Food contamination occurs because of the use of PCV in wrapping materials and food processing. Phthalates are found in meat, fish, milk products, and other foods with a high fat content.[14] Phthalate exposure through ingestion has been estimated at 0.25 mg/day. Indoor air sources include new floor and wall coverings, and car materials (up to 0.2 to 0.3 mg DEHP/m3 in rooms with freshly installed floors[14]). Medical procedures which deliver the highest doses of DEHP include hemodialysis, transfusions, and extracorporeal membrane oxygenation (ECMO) in infants. Estimates for infant exposure from chewing on soft PVC toys vary widely, with a recent estimate for DINP exposure of 5.7 : g/kg/day for child 3-12 months old. 30 The contribution of phthalate exposure from ambient air, drinking water and agricultural contamination unrelated to plastic packaging, is unknown, but it is less in magnitude than the above sources.

Phthalates documented in human adipose tissue

Measurable levels of DEHP have been found in human adipose tissue of a sizable proportion of the U.S. population.[1] According to a study by the National Human Adipose Tissue Survey, 31% of 46 composite human adipose tissue specimens analyzed had detectable levels of DEHP.15 Persons receiving medical care may be exposed to much higher concentrations of phthalates than the general population.

Toxicology of Phthalates

DEHP causes animal toxicity in many organ systems, including the liver, male and female reproductive organs, heart, lungs, kidneys, and developing embryo and fetus. The toxicities which appear to be of most concern for humans, based on the potential for effects from low doses of exposure, are hepatic and testicular. For both, human data are very limited, so we must primarily rely on animal studies.

Phthalates as a reproductive toxin

There are almost no data currently available for the reproductive or developmental effects of phthalates in humans. In animals, investigations since the 1940's have demonstrated loss of spermatogenesis in male mice and rats, inhibition of estrogen-producing granulosa cells in female rats, and developmental and teratogenic effects to prenatally exposed rodents. These abnormalities occurred at high doses of exposure. Current efforts at defining a threshold of exposure below which adverse effects do not occur have demonstrated subtle reproductive toxicity in male rodents at low doses of exposure.

Low-dose testicular effects

Histological damage to the rat testes was seen upon prenatal exposure to low levels of dietary DEHP.[16] After exposure of females to an estimated 3.0-3.5 and 30-35 mg DEHP/kg/day in drinking water from day 1 of pregnancy to day 21 post delivery, 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. They were not observed in adult male rats exposed to the same concentrations of DEHP. These and other data suggest that the developing fetal and neonatal testes is more susceptible to the testicular toxicity of DEHP than mature animals, and that the fetal and neonatal stages are critical periods for exposure to DEHP.

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. The effect of the DEHP metabolite, MEHP, on this interaction was studied by Li et al, who exposed co-cultures of rat neonatal Sertoli cells and gonocytes to micromolar concentrations of MEHP (0.01, 0.1, or 1.0 ?M) for 48 hours. They observed disruption of the normal adhesion of gonocytes to Sertoli cells, and decreased proliferation of Sertoli cells, in a dose-dependent manner. These effects were not seen with exposure of the cell culture to the parent compound, DEHP. These investigators demonstrated a disruption of the normal activities of cell structures required for sperm production by a DEHP metabolite at very low concentrations. In humans, if similar toxicity occurred, adverse function might be subtle (for example, impaired fertility) and might not become manifest for many years, until adulthood is reached.

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.[22] Thus, the peroxisome proliferation and induction of hepatocarcinoma in the rodent liver by DEHP is dependent on this mechanism involving PPAR".

(Continued on page 2)

Low dose hepatic effects have also been found in primates. In a small study, immature rhesus monkeys receiving plasma transfusions from DEHP-containing PVC blood bags over a six-month or one-year period (yearly dose of 50 - 1,500 mg) had abnormalities in liver histology and function that persisted up to 26 months after treatment.[19, 20] These effects were absent from control animals and those receiving transfusions using polyethylene-stored platelets.

Relevance of liver peroxisome proliferation questioned in humans

Humans are relatively insensitive to peroxisome proliferators, probably due to minimal expression of PPAR" in the human liver. Many investigators have questioned the relevance of peroxisome proliferation-dependent hepatic carcinogenicity, which has been well demonstrated in rodents, to human disease. However, very limited human data suggest the possibility of human hepatotoxicity associated with DEHP exposure occurring from the use of medical devices. Liver biopsies for patients undergoing chronic hemodialysis for one year showed peroxisome proliferation; these abnormalities were not seen after one month of dialysis.[21]

IARC downgrades DEHP re carcinogenicty

Based on the above understanding of the mechanism of hepatic carcinogenicity, the International Agency for Research on Cancer (IARC) recently downgraded the classification of the carcinogenicity of DEHP from Group 2B (possibly carcinogenic to humans) to Group 3 (not classifiable as to carcinogenicity), due to the absence of demonstrated peroxisome proliferation in humans.[24]

Other mechanisms of toxicity may be relevant to humans

Animal studies indicate that not all DEHP effects are fully mediated by PPAR". Using "knock-out" mice (which are deficient in PPAR"), investigators have demonstrated DEHP-induced toxicity in the testis, kidney, fetus and embryo.[25, 26]

In this regard, the recent findings by Maloney and Waxman[22] are of great interest. Their results suggest the possibility that DEHP-induced testicular toxicity results from MEHP activation of another nuclear receptor, PPAR(1. Furthermore, because this receptor is plentiful in adipose tissue, where a lipophilic compound like DEHP may accumulate, these findings may have other implications, not yet appreciated, for mechanisms of DEHP-related toxicity and, possibly, human disease. However, very limited human data suggest the possibility of human hepatotoxicity associated with DEHP exposure occurring from the use of medical devices. Liver biopsies for patients undergoing chronic hemodialysis for one year showed peroxisome proliferation; these abnormalities were not seen after one month of dialysis.[21]

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Conclusions

Current guidelines

In light of data adverse health effects in animals exposed to phthalates, many governmental bodies have set guidelines for maximum concentrations in drinking water and standing water. The Great Lakes Water Quality Agreement of 1978 lists phthalic acid esters as persistent toxic substances and calls for standing water standards of 0.6 : g/L (or 0.6 ppb) for DEHP, 4.0 : g/L for di-butylphthalate, and 0.2 : g/L for the other phthalic acids, for the protection of aquatic life in the Great Lakes Basin ecosystem

Environment Canada has draft interim standing water quality guidelines for DEHP (1.0 : g/L)[27] and for DBP (19 : g/L)[28] for the protection of freshwater aquatic life. The U.S. EPA also has set standards for DEHP (6 ppb) and DBP (34,000 ppb) in drinking water. The California EPA's Office of Environmental Health Hazard Assessment has set a public health goal for drinking water of 12 ppb for DEHP.

Data needs

At the moment, the public health threat due to phthalates is not clear. The lack of relevant studies on phthalates in humans has made it difficult to fully characterize the risk of these compounds to human health. An upcoming study by the Centers for Disease Control will attempt to establish a reference range of phthalates in the U.S. population. The European Union is in the process of completing a risk assessment on various phthalates that is due soon. Others have suggested studies that include: pre- and postnatal development studies after oral exposure in non-rat species; toxicokinetic studies of primates after oral exposure; a complete multigenerational study of rodents which examines the effects on reproductive development and structure and fertility; and a study of non-rodents using non-oral routes of administration.[29] With further data on the toxicology of phthalates, and the human burden of exposure, we will hopefully be able to more accurately characterize the potential for human effects from these ubiquitous environmental contaminants.

Abbreviations used

BBP: Butylbenzyl phthalate, DBP: Di-n-butylphthalate
DEHP: di-ethylhexylphthalate, DnOP: di-n-octyl phthalate
FSH: follicle stimulating hormone, MEHP: mono-ethylhexyl phthalate
PPAR: peroxisome proliferator-activated receptor

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