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Human exposure to phthalates via consumer products

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Summary

Phthalate exposures in the general population and in subpopulations are ubiquitous and widely variable. Many consumer products contain specific members of this family of chemicals, including building materials, household furnishings, clothing, cosmetics, pharmaceuticals, nutritional supplements, medical devices, dentures, children's toys, glow sticks, modelling clay, food packaging, automobiles, lubricants, waxes, cleaning materials and insecticides. Consumer products containing phthalates can result in human exposures through direct contact and use, indirectly through leaching into other products, or general environmental contamination. Historically, the diet has been considered the major source of phthalate exposure in the general population, but all sources, pathways, and their relative contributions to human exposures are not well understood. Medical devices containing di-(2-ethylhexyl) phthalate are a source of significant exposure in a susceptible subpopulation of individuals. Cosmetics, personal care products, pharmaceuticals, nutritional supplements, herbal remedies and insecticides, may result in significant but poorly quantified human exposures to dibutyl phthalate, diethyl phthalate, or dimethyl phthalate. Oven baking of polymer clays may cause short-term, high-level inhalation exposures to higher molecular weight phthalates.

Introduction

Phthalates are a family of chemicals used in many consumer products, including building materials, household furnishings, clothing, cosmetics, personal care products, pharmaceuticals, nutritional supplements, herbal remedies, medical devices, dentures, children's toys, glow sticks, modelling clay, food packaging, automobiles, lubricants, waxes, cleaning materials and insecticides. Phthalates provide plasticity to otherwise rigid materials such as polyvinyl chloride and other polymers. They also lubricate, act as solvents, and otherwise impart favourable characteristics to products.

Annually, more than three million metric tonnes of phthalates are produced globally (Bizzari *et al.*, 2000). Uses of the various phthalates depend in part on their molecular weight (MW). Higher MW di-(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) are the phthalates produced in highest volume for use in construction material, clothing and furnishings. By far, their largest application is to impart flexibility to polyvinyl chloride plastic (PVC). Relatively low MW phthalates such as diethyl phthalate (DEP), dimethyl phthalate (DMP) and dibutyl phthalate (DBP) tend to be used as solvents and in adhesives, waxes, inks, cosmetics, insecticides and pharmaceuticals. Single applications may also use mixtures of phthalates.

Because of their widespread use, all populations of people, domestic animals, and wildlife regularly encounter opportunities for exposure to phthalates. This paper reviews data regarding various sources and pathways of human exposure to phthalates from consumer products. Data gaps are numerous, which makes it difficult to explain fully the relative contributions of various sources of phthalates to exposures reported in the general population (CDC, 2005).

Routes of exposure to phthalates

The physicochemical characteristics of phthalates vary with the chemical structure and may include a vapour phase, although vapour pressures are generally low. Phthalates are generally lipophilic, which influences their leaching and environmental partitioning characteristics.

Ingestion, inhalation, intravenous injection 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 (Aurela *et al.*, 1999) or intravenous fluids, or by general contamination of the ambient environment.

Ingestion

Phthalate ingestion may occur via food, including enteral nutritional formulas, pharmaceuticals, nutritional supplements, sucking children's toys and other mouthing objects.

Food

Dietary intake from contaminated food is likely to be the largest single source of phthalate exposure in the general population. Phthalate levels in food, however, are widely variable, and data are often old and may not reflect current exposure levels. Estimates include: DBP maximal daily intake 0.48 μg/kg/day (MAFF, 1996), DEHP 4.9–18 μg/kg/day (Meek & Chan, 1994), butyl benzyl phthalate (BBP) 0.11–0.29 μg/kg/day (MAFF, 1996).

Medical devices

Medical devices made of polyvinyl chloride softened with DEHP for administering i.v. solutions, blood, nutritional formulas and respiratory gases leach varying amounts of the phthalate. Solutions containing lipids facilitate leaching. Enteral formula containing lipid emulsion stored in a polyvinylchloride (PVC)/DEHP bag and delivered through PVC/DEHP tubing is estimated to result in a maximal daily DEHP exposure of about 9.5 mg/day, or 0.14 mg/kg/day in adults, whereas neonatal infants may be exposed to 2.5 mg/kg/day via this pathway (FDA, 2001).

Pharmaceuticals, herbal preparations, nutritional supplements

Pharmaceutical preparations are often coated with a polymer that influences the timing and location of drug delivery in the gastrointestinal tract. Eudragit is an ammonia methacrylate copolymer coating that remains intact in low gastric pH but breaks down in the higher pH of the lower intestine (Chourasia *et al.*, 2003). Various plasticizers, including DBP and DEP, may be added to Eudragit to influence drug delivery in the intestine. An internet search of the US Patent Office data base (http://www.patentstorm.us/) produces many examples of pharmaceutical products that may have phthalate plasticizers, including DBP and DEP, in their coatings. Among them are commonly used antibiotics, antihistamines and laxatives. Patented herbal preparations and nutritional supplements, including those intended for use during pregnancy, may also incorporate phthalates in the formulation.

A case report identified high levels (16 868 ng/mL) of the monoester metabolite of DBP in the urine of a man who had taken Asacol for ulcerative colitis (Hauser *et al.*, 2004). This concentration is two orders of magnitude higher than the 95th percentile in the US population-based NHANES report. Commonly used pharmaceuticals, herbal preparations and nutritional supplements may be important uninvestigated sources of phthalate exposure in the general population.

Toys

Polymer toys softened with phthalates are a source of potential oral exposure in children. The European Union has temporarily banned marketing of all children's toys and child-care articles containing DEHP, DBP, and BBP as well as toys containing DiNP, di-*n*-octyl phthalate (DnOP) and DiDP intended for children <3 years old. Primarily DiNP is used in toys in the US. Estimates of mean DINP exposure resulting from children's mouthing activities range from 5.7 to 44 μg/kg/day depending on assumptions and statistical techniques. The 99th percentile estimate ranges from 40 to 173 μg/kg/day (Kavlock *et al.*, 2002a).

Inhalation

Medical devices

DEHP may be transferred into respiratory gases passing through PVC tubing, although quantification of exposure has rarely been attempted. Hill estimates exposure to DEHP via respiratory therapy at 28.4–94.6 μg/day, based on direct measurement under experimental conditions (Hill, 1997).

Baking modelling clay

Polymer modelling clay is formed and then cured by baking in an oven. A complex mixture of phthalates imparts a soft consistency to the material at room temperature. Ten samples of Sculpey and Fimo clay contained total phthalate levels ranging from 3.5% to 14% by weight. Individual phthalates identified included DnOP, di-*n*-hexyl phthalate, BBP, DEHP and terephthalic acid (Maas *et al.*, 2004). Air concentrations of the phthalates after baking were reported for BBP (32–2667 $\mu g/m^3$), and DnOP (ND-6670 $\mu g/m^3$). DEHP and/or chemically similar analogues were detected at 6.05–4993 $\mu g/m^3$. For short-term exposures, the US EPA recommends using a mean of 1.0 m^3/h as an estimate of respiratory volume in children <18 years of age. For a 1-h exposure period, this would result in maximal inhalation exposures for BBP,

DnOP and DEHP or similar compounds of 2667, 6670 and 4993 μg respectively.

House dust and indoor air

Indoor air and dust contains phthalates that leach from building products, household furnishings, toys, clothing, accessories (e.g. children's PVC backpacks), and inside automobiles from plasticized components. General environmental contamination with phthalates contributes to some unspecified degree to food, water and indoor dust levels.

Rudel *et al.* (2001) reported total phthalate concentrations in dust from one office and five homes ranging from 0.3 to 524 μg/g dust. Phthalate air concentrations from samples from other locations ranged from 0.005 to 28 $\mu g/m^3$.

Becker *et al.* (2004) reported levels of DEHP in the house dust of 254 children whose urinary metabolites of DEHP were also measured. The mean house dust level was 508 μg DEHP/gm dust, with no correlation between house dust levels and urinary levels of DEHP metabolites in the sample, suggesting that house dust is not a major contributor to total DEHP exposure. Another study of phthalate exposure via inhalation using personal air monitors also found no significant correlation between DEHP air levels and the urinary monoester metabolite, mono ethylhexyl phthalate (MEHP). However, a significant correlation for DEP, DBP and BBP was identified, suggesting that inhalation may be an important pathway of exposure for lower molecular weight phthalates (Adibi *et al.*, 2003).

Oie *et al.* (1997) reported a mean of 960 μg total phthalates/g dust in 38 homes in Norway (range 130–2920 μg/g dust). DEHP was the largest contributor (mean 640 μg/g dust; range 100–1610). They estimated mean adult inhalation exposure to DEHP from this source to be 0.76 μg/day. Ingestion of dust contaminated at 640 μg DEHP/g dust ×100 mg dust ingestion/day would yield a dose of 64 μg/day.

Otake *et al.* (2004) analysed phthalate levels in indoor air of 27 houses in Tokyo. They reported median concentrations of DEP, DBP, BBP, dicyclohexyl phthalate, and DEHP of 0.10, 0.39, 0.01, 0.07, and 0.11 $\mu g/m^3$ respectively. For an adult breathing 20 m^3/day, these would result in inhalation exposures of 2, 78, 0.2, 1.4 and 22 μg/day respectively. Inhalation of contaminated dust will result in larger inhalation exposures.

Intravenous

A variety of medical devices made of PVC plasticized with DEHP are used to deliver medical care. Bags and/or tubing deliver intravenous fluids, nutritional formulas, blood and are used for extracorporeal membrane oxygenation and dialysis. Leaching of DEHP from the device varies with lipid content, temperature, storage time and agitation (FDA, 2001). Table 1 shows the estimates of parenteral exposure to DEHP that may result from various procedures. Individual studies show some variability in exposure levels, depending on specific conditions and equipment choices. For example, DEHP exposure from extracorporeal membrane oxygenation (ECMO) can be reduced considerably by using heparinized PVC/DEHP tubing (Karle *et al.*, 1997).

Table 1 Intravenous exposures to DEHP from select medical procedures using medical devices made of PVC containing DEHP (modified from FDA, 2001)

	Adult	Neonate
	DEHP dose (mg/kg/day)	
Crystalloid i.v. solutions	0.005	0.03
Total parenteral nutrition		
Without added lipid	0.03	0.03
With added lipid	0.13	2.5
Blood transfusion		
Trauma patient	8.5	
Transfusion/ECMO	3.0	
Exchange transfusion		22.6
Replacement transfusion		0.3
Coronary artery bypass graft	1	
ECMO		14

Calafat *et al.* (2004) measured DEHP metabolites in the urine of six premature infants receiving intensive medical therapy, including i.v. infusions, and reported that the median level of the metabolite MEHP (129 ng/mL) in these children was significantly higher than the median in the general population NHANES study (2.7 ng/mL). Green *et al.* (2005) measured DEHP metabolites in the urine of 54 newborn children in two neonatal intensive care units. This study documented higher levels of urinary metabolites of DEHP with increasing intensity of care and more frequent use of DEHP-containing devices. Mean urinary MEHP levels in low, medium and high intensity care infants were 9.3, 41, 139 ng/mL respectively.

Skin absorption

Skin may come into direct contact with phthalate-containing clothing, cosmetics, sunscreens, insecticides, other personal care products, modelling clay, toys, yoga pads, waxes, cleaning products and denture material (Munksgaard, 2004).

In general, transdermal absorption depends on chemical concentration, chemical structure, water solubility, octanol : water partition coefficient between the

formulation vehicle and stratum corneum, the formulation vehicle, and the anatomic area of application (US EPA, 1992). Skin absorption of chemicals from the face, axilla and scrotum, for example, may be up to 10-fold higher than the arm.

Studies using rodent skin show that absorption of phthalates is generally slow. An in vitro comparison demonstrated that human skin is less permeable to phthalates than is rat skin, although studies of human skin are few (Scott *et al.*, 1987; Elsisi *et al.*, 1989). An in vivo study of DBP absorption through human upper arm skin showed a maximum flux of 10 $\mu g/cm^2/h$ (mean = 3.8) when applied as a saturated solution of DBP in propylene glycol (Hagedorn-Leweke & Lippold, 1995). The authors concluded that the octanol : vehicle partition coefficient is the largest determinant of skin absorption.

Dimethyl phthalate and DBP have been used topically as insect repellants (Ware & Whitacre, 2004). DBP, DEP, DMP and DnOP are currently on the US EPA's list of 'potentially toxic inerts', and may be used along with other ingredients in insecticides or repellants, causing dermal or inhalation exposures.

Quantification of internal exposures to phthalates from commercially available products that are applied to the skin is not generally available.

Data gaps

Significant data gaps make it difficult to identify with certainty the various sources, exposure pathways and their relative contributions to observed human phthalate levels in the general population. Dietary phthalate data are outdated. Exposures from pharmaceutical products, herbal remedies and nutritional supplements are generally not quantified. The relative contribution of transdermal and inhalation pathways from cosmetics, other personal care products and insecticides is unknown. Foetal exposures to DEHP from medical care or other sources during pregnancy have not been quantified, although DEHP and its metabolites are known to cross the placenta (Latini *et al.*, 2004).

The presence of phthalates in consumer products may not be apparent, even in cosmetics that are subject to strict labelling requirements. One study analysed 72 cosmetics and personal care products purchased directly from stores (http://www.nottoopretty.org/). Phthalates were not identified on any of the labels. Phthalates were present in 52 of the products, including deodorants, fragrances, hair gels, mousses, hair sprays, and hand and body lotions. Nail polish may also contain high concentrations of unlabelled DBP.

Koch et al. have recently demonstrated that DEHP is metabolized into at least five metabolites, including MEHP, 5OH-MEHP, 5oxo-MEHP, mono(2-ethyl-5-carboxypentyl)phthalate, and mono[2-(carboxymethyl)hexyl]phthalate (Koch, 2005). Earlier attempts to quantify total DEHP exposure that relied on measuring fewer metabolites undoubtedly resulted in underestimates, as the newly identified carboxy-metabolites comprise approximately 22% of the molar concentration of all metabolites. However, the pathway of exposure to DEHP and individual and age-related variability in metabolic pathways are likely to influence metabolite profiles (Schmid & Schlatter, 1985; Anderson *et al.*, 2001; Barr *et al.*, 2003; David, 2003; Koch *et al.*, 2003, 2004).

Conclusions

Consumer products containing phthalates can result in human exposures through direct contact and use, by leaching into other products, or via general environmental contamination. Phthalate exposures in the general population and in subpopulations are ubiquitous and sources are widely variable.

In the general population, the diet is generally considered the major pathway of exposure but all sources, pathways, and their relative contributions to measured body burdens of phthalates are not well understood. Phthalates may be present but unidentified in many consumer products, including cosmetics, personal care products, home furnishings, pharmaceuticals, nutritional supplements and insecticides. In some instances, these may be important but unquantified sources of exposure. Oven baking of polymer clays may cause short-term, high-level inhalation exposures. Medical devices made of PVC containing DEHP are an important source of exposure to this reproductive and developmental toxicant in susceptible populations.

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Discussion

Dr NE Skakkebæk (Copenhagen, Denmark)
What proportion of the daily intake of phthalates is derived from food and drink?

Dr T Schettler (Newburyport, MA, USA)
Food has traditionally been considered to be the major single source of exposure to DEHP and other phthalates. However, new data on metabolites of phthalates in humans have revealed, in some cases, higher exposures than previously estimated in the general population. For some phthalates non-food sources may be more important, but the relative contributions from each source are still not well understood.

Dr D de Kretser (Melbourne, Australia)
Given the considerable time that the postulate that phtalates may adversely affect reproduction, it is surprising that there is no evidence about a mechanism of action. Given their structure, it should be possible to radioactively label these compounds and ascertain whether they bind to target tissues. Could they, for instance, bind to putative orphan steroid receptors that lack a defined ligand?

Dr H Leffers (Copenhagen, Denmark)
I fully agree that it is crucial to elucidate the mode of action of phthalates in the testis. However, a few studies have looked at the distribution of DEHP and metabolites (for example *Ono et al.*, *The Journal of Toxicological Sciences*, 2004; 29: 113). Also, reports on interactions between the toxic metabolites (the monophthalates) and different receptor systems, incl. PPAR receptors, are beginning to emerge (for example *Hurst & Waxman*, *Toxicological Sciences*, 2003; 74: 297). Nevertheless, much more knowledge is clearly needed to understand the apparently very restricted effects on Leydig cells, and thus their effects on male reproduction.