HEALTH EFFECTS FROM PHTHALATES: EPIDEMIOLOGICAL EVIDENCE

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Introduction

Phthalates are compounds that are based on 1,2-benzene-dicarboxylic acid where one or both OH-groups are substituted with various atoms or functional groups. The following considerations apply to phthalate esters where the functional groups are alkyl groups of different length. Phthalates are used as plastic softeners or solvents in many different consumer and medical products. They can be absorbed through the skin, inhaled, ingested when they contaminate food or when children suck on toys, and are directly administered to patients from some PVC medical devices.

Due to the lipophilic nature of longer chain dialkyl phthalates dermal or pulmonary tissue are no barrier to absorption. Dialkyl phthalates are metabolized to the monoesters by enzymes present in most tissues, however, complete hydrolysis to phthalyc acid occurs in the liver. Although short length monoesters may directly be excreted, reduction of polarity is necessary for the longer chains that seems to be accomplished by glucuronidation and/or oxidation of the residual chain. Persistence of phthalates is comparably short in liver and longer in fat tissue. However, detailed study of excretion has become possible only recently by synthesis and analysis of secondary metabolites (Gilsing et al. 2002; Koch et al. 2003a; Silva et al. 2003).

Exposure

Due to multiple routes of exposure, estimation of internal exposure from measurement of phthalates in the environment is difficult. Measurement of internal exposure, on the other hand, especially from exposure to DEHP, which is of most widespread use, has been hampered by two problems: first of all this compound is ubiquitous and contaminates analytes as well as containers such that high blanks occurred in analyses, and second, only a small fraction is excreted as monoester.

During the last few years metabolites have been synthesized and excretion of these oxidized products has been monitored in several studies. From these analyses (Koch et al. 2003b) a higher intake has been estimated and a considerable fraction (more than 10%) of the population seems to be exposed above the TDI (tolerable daily intake, 37 µg/kg body weight/day). Furthermore, age-specific measurements were possibly biased due to different patterns of uptake and metabolization in children and adults. Recently, by assessing DEHP-metabolites in children and adults, significantly higher concentrations were found in children (Koch et al. 2004).

Table 1: Some important phthalates

Name	Abbreviation
Diethyl phthalate	DEP
Dibutly phthalate	DBP
Benzylbutyl phthalate	BzBP (BBP)
Dicyclohexyl phthalate	DCHP
Di-2-ethlyhexyl phthalate	DEHP
Di-n-octyl phthalate	DOP (DNOP)
Di-isononyl phthalate	DINP
Di-isodecyl phthalate	DIDP

Epidemiological evidence

There are more than 1000 studies of in vitro and in vivo effects of phthalates. However, there is almost no evidence from human and epidemiological studies. In the following paragraphs recent studies about effects of phthalates on the male reproductive system, on preterm breast development in females, on pulmonary function and on duration of human pregnancy will be presented.

Despite decade long controversy about a possible cancer link of phthalate exposure there are only few studies about occupational exposures. One case-control study (Ohlson & Hardell 2000) reported an increased risk for seminoma, one type of testicular cancer, in plastic workers exposed to PVC. Studies in rats and mice indicated an increased risk of liver cancer, however, it was implicated that this is due to peroxisome proliferation that is thought to be of no importance in human carcinogenesis (Doull et al. 1999). Because proliferation of peroxisomes has not been established as an obligatory step in the carcinogenicity of DEHP, this contention should be viewed as a still unvalidated hypothesis that DEHP poses no carcinogenic risk to humans (Melnick 2001).

Duty et al. (2003) presented results of semen analyses in 168 men who were part of subfertile couples. Sperm concentration and motility was evaluated according to the WHO criteria, morphology according to the strict Tygerberg criteria. Eight phthalate metabolites were measured by HPLC and tandem mass spectrometry. There was a dose dependent relationship between monobutyl and monobenzyl phthalate and one or more semen parameters. Monomethyl phthalate was weakly associated with semen morphology.

TABLE 4. Associations of Below-Reference Value Sperm Concentration, Sperm Motility and Sperm Morphology with Tertiles of Phthalate Monoester Levels (N = 143)*

Specific gravity adjusted phthalate tertile	Sperm Concentration N	Crude OR	95% CI	Adj. OR†	95% CI	Sperm Motility N	Crude OR	95% CI	Adj. OR†	95% CI	Sperm Morphology N	Crude OR	95% CI	Adj. OR†	95% CI
Butyl phthalate (MBP), tertile															
1‡	6	1.0		1.0		15	1.0		1.0		12	1.0		1.0	
2	6	1.3	0.4–4.6	1.4	0.3–6.0	22	1.8	0.8–4.5	1.8	0.7–4.6	12	1.5	0.5–3.4	1.5	0.5–4.5
3	10	2.3	0.8–6.6	3.3	0.9–12.6	17	2.9	1.2–6.9	3.0	1.1–7.6	15	2.0	0.8–5.3	2.2	0.8–6.1
P for trend			0.10		0.07			0.02		0.02			0.2		0.1
Benzyl phthalate (MBP), tertile															
1‡	3	1.0		1.0		18	1.0		1.0		16	1.0		1.0	
2	6	1.1	0.3–4.1	1.4	0.3–6.0	21	1.1	0.5–2.5	1.1	0.5–2.6	6	0.4	0.1–1.2	0.4	0.1–1.4
3	11	3.0	0.9–10.2	5.5	1.3–23.9	24	1.8	0.9–4.3	2.1	0.8–5.3	19	1.8	0.7–4.7	2.2	0.9–6.0
P for trend			0.07		0.02			0.2		0.1			0.2		0.1
Methyl phthalate (MMP), tertile															
1‡	4	1.0		1.0		9	1.0		1.0		4	1.0		1.0	
2	5	1.6	0.3–7.4	1.7	0.3–11.1	13	1.8	0.6–5.9	2.1	0.6–7.7	6	1.9	0.4–9.5	1.5	0.3–7.4
3	5	1.6	0.3–7.4	0.7	0.1–5.5	11	1.6	0.5–5.1	1.2	0.5–4.6	10	3.2	0.8–12.9	2.4	0.5–11.7
P for trend			0.6		0.8			0.5		0.8			0.1		0.3

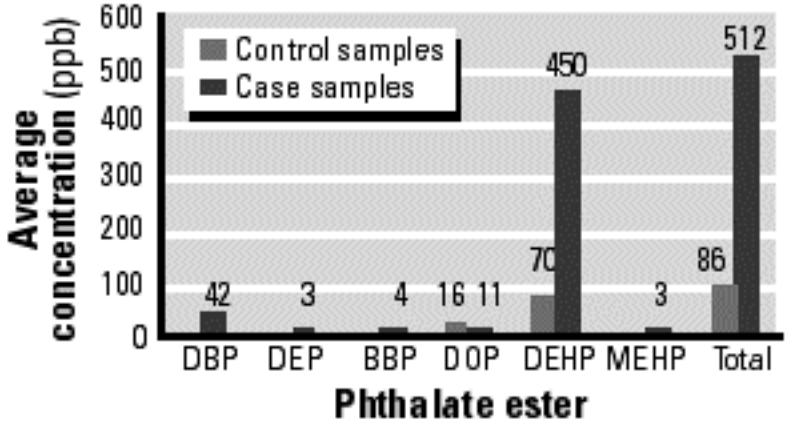
Tertile cut-points (ng/ml): butyl = 0–11.64, 12.24–20.13, 20.16–403.93; benzyl = 0–5.50, 5.54–12.94, 13.04–540.24; methyl = 0–4.30, 4.43–10.18, 10.29–32.46.
* Comparison group is subjects at or above reference value for sperm concentration (≥20 million/ml), motility (≥50% motile) and morphology (≥4% normal morphology. Excludes 25 people with extreme specific gravity (<1.010 or >1.030).
† Adjusted for age (continuous), abstinence time (5 categories: ≤2 days, 3, 4, 5 and 6 days) and smoking (current, former and never).
‡ Reference category.

Table 2: From Duty et al. 2003

These data are consistent with animal studies except for MMP, where no indication of testicular toxicity has been found. The results must be interpreted with caution because only one spot measurement of phthalate urinary excretion has been performed. Nevertheless, it offers some evidence that phthalates at environmental exposure levels may exert effects on the male reproductive system.

Puerto Rico has the highest known incidence of premature thelarche. No explanation has been found for this phenomenon. Colon et al. (2000) investigated 41 patients with thelarche between 6 months and 8 years and 35 control subjects. Phthalate concentration in serum samples was analysed by GC/MS. Results indicate a multifold higher serum phthalate concentration in patients as compared to controls.

Figure1: Serum concentration of different phthalates in thelarche patients and controls (Colon et al. 2000)



Because there were patients without increased levels of phthalates (32%) that are known to have estrogenic and anti-androgenic activity, phthalates are likely not the only factor responsible for the high incidence of preterm breast development, however, a causative action cannot be ruled out.

It has been implicated that DEHP when inhaled and locally hydrolyzed to MEHP results in increased risk of airway inflammation due to mimicking the inducing prostaglandins and thromboxanes. In fact, association with respiratory symptoms has been found in young children (Jaakkola et al. 1999; Ponsonby et al. 2003) and beauticians (Hollund 2001), with potentially higher exposure to phthalates. Recently Hoppin et al. (2004) reported spirometric measurements in adults related to urinary concentrations of phthalate metabolites measured by GC/MS. Monoethyl phthalate and monobutly phthalate but not monoethylhexyl phthalate were associated with lower FVC and/or FEV1 in males but not females. Analysis according to smoking status revealed inconsistent findings. The study provides no evidence for airway inflammation in adults exposed to phthalates, however, only the monoesters have been measured that are not the major metabolites.

Latini et al. (2003) investigated the possible role of DEHP exposure during pregnancy and pregnancy outcome. DEHP and MEHP levels were measured in cordblood of 84 consecutive births. In 77% DEHP or MEHP was found in the samples. Newborns that were MEHP positive had lower gestational age as compared to MEHP negative infants. Findings suggest that exposure can begin in utero and that it may affect fetal development.

Table 3: From Latini et al. (2003)

Table 2. DEHP- and/or MEHP-positive versus -negative infants: comparisons between groups (range in parentheses).

Infants' characteristics	DEHP+	DEHP−	*p*-Value	MEHP+	MEHP−	*p*-Value
Mean birth weight (g)	3206.15 ± 692.68 (1,150–4,350)	3284.74 ± 626.50 (1,950–4,350)	NS	3,158 ± 698.68 (1,150–4,100)	3475.26 ± 566.74 (2,550–4,350)	NS
Mean gestational age (weeks)	38.37 ± 2.33 (27–42)	38.58 ± 1.84 (35–42)	NS	38.18 ± 2.34 (27–42)	39.35 ± 1.35 (37–42)	0.033
Total	65	19		65	19	

Abbreviations: −, negative; NS, not significant; +, positive.

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