

Derivation of human biomonitoring (HBM) values based on tolerable intake doses.

Part III: HBM values for di(2-ethylhexyl)phthalate (DEHP)

Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency (Umweltbundesamt)

1 Introduction

Phthalates (phthalic acid diesters) are used as softeners in dispersions, paints, and varnishes, as emulsifiers, repellents and carrier fluids in biocides, in cosmetics and perfumes, and for many other common applications. DEHP (di(2-ethylhexyl)phthalate) is one of the phthalates most commonly used [1].

In animal experiments on chronic toxicity, testicular, renal and hepatic effects have been observed following intake of extremely low doses of DEHP. In addition to pronounced reproduction toxicity, DEHP has embryotoxic, fetotoxic and teratogenic effects on the offspring of exposed rodents. In vitro and in vivo studies have shown that DEHP can influence hormonal regulation, leading to estrogenic/anti-androgenic effects and delayed sexual maturity [2, 3]. Phthalates are currently discussed in environmental medicine as a priority substance group for human biomonitoring, since reliable analytic methods [4] are now available, and data on the exposure of the general population [5, 6] indicate a need for the toxicological assessment of individual exposure.

In the following text, the way of derivation of HBM values based on tolerable intake doses described in Part II [7] is applied to di(2-ethylhexyl)phthalate (DEHP). The present paper explicitly refers to the Commission's recently published monograph on DEHP [8].

In Chapter 2, the methodological requirements for deriving an HBM value based on tolerable intake doses (TDI/ADI) are checked [7], and in Chapter III, an HBM I value is proposed.

2 Checking the methodological requirements for deriving an HBM value

2.1 Tolerable/acceptable daily intake

Various organisations have published a TDI value for DEHP referring to testicular toxicity, based on the NOAEL (No Observed Adverse Effect Level) of 4.8 mg DEHP/kg bw/day found by Wolfe and Layton in a multigenerational study in Sprague-Dawley rats [2]. This study focused on reproduction toxicity resulting in a reduced number of offspring, lower birth weights, male and female genital malformations, and infertility. This study is widely regarded as being more valid than studies such as that of Poon et al [9] who found a NOAEL of 3.7 mg/kg bw/day in a classical toxicity study which measured testicular toxicity (Sertoli cell vacuolisation, atrophy of the seminiferous tubules) and hepatotoxicity (peroxisome proliferation) in rats.

The Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR), in accordance with the European Food Safety Authority (EFSA), has defined a TDI value of 0.05 mg/kg bw/day [10, 11] for DEHP on the basis of the Wolfe and Layton NOAEL [2]. At the request of the Federal Environment Agency (UBA), a corresponding tolerable resorbed dose (TRD) was estimated (0.03 mg/kg bw/day, equivalent to an intake of 0.05 mg/kg bw/day). This dose was also supported in an experts' meeting report [12]. The aforementioned Wolfe und Layton NOAEL of 4.8 mg/kg bw/day [2] was also referred to by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) that derived a TDI value of 0.048 mg/kg bw/day [13, 14]. A total extrapolation factor of 100 [12, 13, 14] was used for each of these derivations. Tolerable DEHP intake doses defined by other organisations are listed in table 1.

According to current European and German assessments, an HBM value is derived based on a TDI of 20 µg/mg/kg bw/day for women of childbearing age and 50 µg/mg/kg bw/day for children and the remaining general population.

Conclusion: A generally accepted tolerable/acceptable daily intake value is available at the national and international level.

Table 1 Tolerable intake doses of DEHP		
Term, Institution, Year [Source]	Value (µg/kg bw/day)	Underlying NOAEL (µg/kg bw/day), Year [Source]
TDI ^{a)} (MPR ^{b)} NL RIVM 2002 [27]	4	3.7; 1997 [9]
RfD ^{c)} US EPA 1991 [28]	20	20; 1953 [29]
TDI ^{a)} WHO 2003 [30]	25	2.5; 2003 [30]
TDI ^{a)} EU CSTEE 1998 [13]	37	3.7 ; 1997 [9] and ca. 3.5 LOAEL; 1998 [31]
TDI ^{a)} ECB/EU (RAR-DEHP) 2004 [32]	20 (0–3 months old infants; women of childbearing age) 25 (3-12 months old infants) 48 (all other population groups)	4.8; 2003 [2]
TDI ^{a)} Health Canada 1994 [33]	44	44 ; 1984 [34]
TRD ^{d)} German UBA, 2003 [12]	50	2.9 (intake: 4.8); 2003 [2]
TDI ^{a)} BfR, 2005 [10] and EFSA, 2005 [11]	50	4.8; 2003 [2]
MRL ^{e)} US ATSDR, 2002 [35]	60	5.8; 2000 [36]
<p>^{a)} Tolerable Daily Intake ^{b)} Maximum Permissible Risk Level ^{c)} Reference Dose (for chronic exposure) ^{d)} Tolerable Resorbed Dose ^{e)} Minimal Risk Level (for chronic exposure duration)</p>		

2.2 Exposure levels for the general population and basic toxicokinetic data

In several countries, renal excretion of DEHP metabolites in various population groups has been studied (see section 2.3), most of them in Germany. The German studies have investigated both adults and children (see table 2). In virtually all of the morning urine samples, the DEHP metabolites 5-oxo-MEHP and 5-OH-MEHP could be detected, with median levels ranging 20-40 µg/l for the former and 30-50 µg/l for the latter. Maximum urine concentrations found were 544 µg/l for 5-oxo-MEHP and 818 µg/l for 5-OH-MEHP.

Author [source]	Age groups (years)	Sample size	5-oxo-MEHP (µg/l) Median (P 95)	5-OH-MEHP (µg/l) Median (P 95)
Koch et al. [37] Koch et al. [6]	7 – 64	85	36.5 (156)	46.8 (224)
Koch et al. [38]	20-59	19	19.6 (36.7)	32.1 (64.0)
	2-6	36	33.8 (71.0)	49.1 (107.0)
Becker et al. [39]	3-14	254	41.4 (138)	52.1 (185)

P 95 = 95th percentile

Mammals rapidly convert DEHP into numerous metabolites. In the oral cavity, salivary enzymes start hydrolysis of DEHP into MEHP and 2-ethylhexanol. The latter compound is completely metabolized via a series of intermediate steps.

Oxidative MEHP metabolism begins with hydroxylation at five locations along the ethylhexyl side chain, resulting in the formation of primary and secondary alcohols which are then oxidized into ketones or carboxylic acids.

After human oral exposure to 30 mg DEHP, 12 metabolites were analysed. Their interrelationships and concentrations showed to be influenced by the way of application (oral, intravenous). The main DEHP metabolites – in addition to MEHP - are 5-oxo-MEHP and 5-OH-MEHP, the latter of which accounts for 50-66 percent of DEHP metabolites in urine [15, 16, 17].

A HBM study using isotope-marked DEHP found that 47 percent of the applied dose could be found in urine, with MEHP amounting to 7 %, 5-oxo-MEHP to 15 % and 5-OH-MEHP to 25 %. Thus 40 percent of the applied DEHP dose was excreted as 5-oxo-MEHP or 5-OH-MEHP [16].

As in rodents, a certain amount of biliary excretion can be supposed in humans, too.

The aforementioned DEHP metabolites are excreted in urine with a half-life of approximately 12 hours. The secondary DEHP metabolites' concentration in urine is clearly higher than MEHP concentration, and their half-lives are also longer.

Conclusion: Basic human toxicokinetic data are available, and the relationship between intake and urinary excretion is known.

2.3 Analytical aspects

MEHP and secondary DEHP metabolites in urine are assayed using gas chromatography-mass spectrometry [15] as well as high pressure liquid chromatography-mass spectrometry [4, 18]. However, only secondary DEHP metabolites in urine (and in blood) can be measured reliably since during the pre-analytic phase or under ambient conditions MEHP is readily formed from DEHP through various hydrolytic processes. This does not occur with secondary metabolites.

Conclusion: An established assay method is available for a readily accessible human biological matrix.

3 Derivation of an HBM I value for DEHP

HBM values for DEHP metabolites in urine are derived based on 5-oxo-MEHP and 5-OH-MEHP referring to the sum of these two metabolites. 40 percent of the applied (oral) DEHP dose are excreted in urine in form of these two metabolites [16, 17].

Concentration data are generally based on mass, thus the metabolite values must be adapted according to molecular weights, which are 390 g/mol for DEHP, 292 g/mol

for 5-oxo-MEHP, and 292 g/mol, for 5-OH-MEHP. This can be simplified by using a molecular weight of 293 g/mol for these metabolites.

Derivation of the HBM value is in a first step based on the assumption that an adult's daily intake of DEHP amounts to the TDI value (50 µg/kg bw/day), i.e., this adult's intake is supposed to be 50 µg DEHP per kg body weight per day. 40 percent of the applied dose is excreted renally as the two metabolites 5-oxo-MEHP and 5-OH-MEHP (1 mol DEHP corresponds to ~ 0.4 mol Σ(5-oxo-MEHP + 5-OH-MEHP)). When expressed on a mass basis (µg/l), the ratio between the molecular weights (MW) of DEHP and its metabolites must be taken into account. The molecular weight of DEHP is 390 and the mean molecular weight of both 5-oxo-MEHP and 5-OH-MEHP is 293, thus the molecular weight ratio is 0.75.

$$\Sigma(5\text{-oxo-} + 5\text{-OH-MEHP}) \text{ in urine} = \text{TDI} \times \frac{\text{Molecular weights of the metabolites}}{\text{Molecular weight of DEHP}} \times 0.4$$

$$\Sigma(5\text{-oxo-} + 5\text{-OH-MEHP}) \text{ in 24-h urine} = 50 \text{ µg/kg bw/day} \times 293/390 \times 0.4 = 15 \text{ µg/kg bw/day.}$$

Thus of the 50 µg/kg bw/day of DEHP (TDI value) hypothetically ingested by an average adult, 15 µg x kg bw are excreted renally over a 24-hour period as the two metabolites 5-oxo-MEHP and 5-OH-MEHP. This excretion corresponds to the HBM I value for adults. Accordingly, this derivation leads to different tolerable excretion values for population subgroups such as women with different TDI values as a starting point. The HBM value derived in this way represents an HBM I value because it was derived from a NOAEL (which means according to current assessment no concern when not exceeded) [19].

Ideally, the HBM values should refer to the amount of a substance (µg/day) in a complete 24-hour urine sample. For reasons of simplicity, in accordance with the procedure described in Part II of the present report [7], the metabolites' excretion as calculated above is referred to a body weight-related urine excretion of 30 ml/kg bw/day for children and 20 ml/kg bw/day for all other population subgroups [20]. The resulting value is recommended to be used as an HBM I value for the sum of the

concentrations of 5-oxo-MEHP and 5-OH-MEHP (in µg/l) in morning urine samples (see table 3). As the ratio between renal elimination of DEHP metabolites and creatinine is unknown, the HBM value is not “standardised” referring to the creatinine concentration of the urine samples (also see [21, 22]).

Table 3			
Derived HBM I values for the sum of the metabolites 5-oxo-MEHP and 5-OH-MEHP			
Population group	Tolerable daily intake (µg/kg bw/day)	Urine volume (l/kg bw/day)	HBM I value (µg/l) in morning urine*
Children aged 6-13	50	0.030	500
Women of childbearing age	20	0.020	300
All other population groups	50	0.020	750

* Calculation method: Tolerable daily intake x concentration in urine (f = 0.4) x the ratio of molecular weight (0.75) to urine volume (ml/kg bw).

Keeping in mind that the physiology of children and adults differs, and it is not known whether metabolic ratios in adults and in children under the age of six are the same, the Commission refrains from deriving an HBM value for children below 6 years of age as long as it is unclear whether or not the metabolites' ratios differ between small children and adults.

A comparison of these HBM I values and the current reference values for the DEHP metabolites 5-oxo-MEHP and 5-OH-MEHP published by the Commission [8] can be found in table 4.

Table 4		
Comparison of the HBM I values and the sum of the current reference values for the DEHP metabolites 5-oxo-MEHP and 5-OH-MEHP		
Population group	HBM I value (ug/l)	Reference value (µg/l) [8]
Children aged 6-13	500	5-oxo-MEHP: 150 5-OH-MEHP: 220
Women of childbearing age	300	
Males 14 years of age and older, and remaining general population	750	Σ: 370

4 Summary and outlook

We recommend that DEHP exposure be assessed on the basis of the sum of the DEHP metabolites 5-oxo-MEHP and 5-OH-MEHP in morning urine ($\mu\text{g/l}$) using the HBM I values described in the present report.

Recent studies on health effects in pregnant women exposed to phthalates [23, 24] indicate that 2 to 36 months old male infants might exhibit reduced anogenital distance at DEHP exposures substantially lower than the US EPA's reference dose of 20 $\mu\text{g/kg bw}$. The results of these studies have not yet been considered in risk assessment [25]. If new findings modify the risk assessment of DEHP and, consequently, the TDI values, the HBM I values will also have to be adjusted according to the way of derivation as described in the present report.

First studies [26] have shown that groups of the general population are exposed to endocrine-active phthalates such as DnBP, DiBP, BBzP, and DiNP [26]. These phthalates should be included in a comprehensive assessment of phthalate exposure. However, an HBM I value for the sum of all endocrine-active phthalates cannot be derived at present due to the different toxicity of the respective compounds and a lack of knowledge on the underlying mechanisms of action.

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