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Di(2-ethylhexyl) phthalate (DEHP)

Assessment Values in Biological Material – Translation of the German version from 2018

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Di(2-ethylhexyl) phthalate (DEHP)

BAT Value Documentation

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area evaluated di(2-ethylhexyl) phthalate [CAS No. 118-81-7] in 2017 and derived a biological guidance value at the workplace (BLW) for the combined urinary concentration of the four major DEHP metabolites mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), mono(2-ethyl-5-oxohexyl) phthalate (5-oxo-MEHP) and mono(2-ethyl-5-carboxypentyl) phthalate (5-cx-MEPP). Available publications are described in detail.

Human studies are not available for deriving a quantitative relationship between the internal dose and the critical toxic effects of DEHP (tumour promotion in the liver, respiratory effects, reproductive and developmental toxicity). Therefore, the evaluation of the BLW was based on the relationship between DEHP uptake by inhalation at the level of the MAK value and the urinary excretion rates of MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP, using a conversion factor that defines this relationship. In accordance with this conversion factor external exposure to DEHP at the level of the MAK value corresponds to a combined urinary concentration of the four metabolites of approx. 4 mg/g creatinine at steady state. As the conversion factor has been derived from oral DEHP uptake and metabolite excretion data of only one male volunteer, the concentration of 4 mg/g creatinine is considered a BLW. Sampling time is for long-term exposure at the end of the shift after several shifts.

Keywords

di(2-ethylhexyl) phthalate; DEHP; bis(2-ethylhexyl) phthalate; DOP; dioctyl phthalate; mono(2-ethylhexyl) phthalate; MEHP; mono(2-ethyl-5-hydroxyhexyl) phthalate; 5-OH-MEHP; mono(2-ethyl-5-oxohexyl) phthalate; 5-oxo-MEHP; mono(2-ethyl-5-carboxypentyl) phthalate; 5-cx-MEPP; BAT value; BLW; biological guidance value; occupational exposure; toxicity

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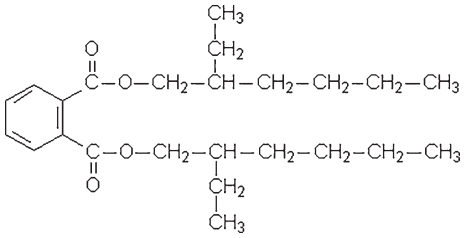
Di(2-ethylhexyl) phthalate (DEHP)

BLW (2017)	**4 mg (MEHP + 5-OH-MEHP + 5-oxo-MEHP + 5-cx-MEPP) (after hydrolysis)/g creatinine** Sampling time: for long-term exposures: at the end of the shift after several shifts
MAK value (2014)	**2 mg/m³ E**
Peak limitation (2014)	Category II, excursion factor 2
Absorption through the skin (2014)	H
Sensitization	–
Carcinogenicity (2014)	Category 4
Prenatal toxicity (2015)	Group C
Germ cell mutagenicity	–
Synonyms	Bis(2-ethylhexyl) phthalate DOP Phthalic acid bis(2-ethylhexyl) ester Di(2-ethylhexyl) phthalate 1,2-Benzenedicarboxylic acid bis(2-ethylhexyl) ester Di-sec-octyl phthalate DEHP
Formula	 $C_{24}H_{38}O_4$
Molecular weight	390.56 g/mol
Melting point	–50 °C
Boiling point	385 °C
Density at 20 °C	0.99 g/cm³

1 Metabolism and Toxikokinetics

1.1 Absorption, distribution and elimination

Di(2-ethylhexyl) phthalate (DEHP) can be absorbed through the lungs, from the gastrointestinal tract (as mono-(2-ethylhexyl) phthalate (MEHP)) and, to a limited extent, through the skin. Due to the low vapour pressure of DEHP, exposure to DEHP by inhalation probably mainly occurs in the form of particulate matter or an aerosol. Presumably also in the case of inhalation, a substantial proportion of DEHP is absorbed from the gastrointestinal tract. The systemic bioavailability of DEHP after inhalation is assumed to be 75%. The oral absorption rate is reported to be about 50% (EU 2008), while the studies by Koch et al. (2004 a, 2005), however, revealed a partly higher absorption rate (47–75%) following single-dose oral administration of ring-deuterated DEHP. The dermal absorption rate is estimated to be 5% (EU 2008).

Studies on the distribution of ^{14}C-DEHP in rats show that DEHP or DEHP metabolites are distributed throughout the organism without accumulating in individual tissues (EU 2008).

In the case of four male subjects (aged 28–61 years) who were administered a single oral dose of 645 ± 20 µg d_4-DEHP/kg, the DEHP half-life in blood was 4.3 hours (monophasic); MEHP was eliminated biphasically from the bloodstream with half-lives of 1.9 and 4.4 hours. Excretion indicated that the MEHP glucuronide is subject to enterohepatic recirculation (Kessler et al. 2012).

The DEHP metabolites are excreted in urine and faeces. DEHP in urine is eliminated biphasically after an oral dose, with half-lives of 5 to 24 hours for the five most important DEHP metabolites during the second elimination phase (Koch et al. 2005; s. Table 1).

1.2 Metabolism

The metabolism of DEHP differs among species and depends on the route of exposure, the level of exposure, age, gender, the health and nutritional status as well as other individual factors. While DEHP is broken down into MEHP and 2-ethylhexanol in the blood or in the liver after inhalation, DEHP is hydrolysed to its monoester after oral administration predominantly prior to intestinal absorption by pancreatic lipases in the intestines (EU 2008; Greim 2002, translated). Intestinal absorption is enhanced after hydrolysis to MEHP. DEHP that is absorbed unchanged in the intestines is hydrolysed in the liver or in blood (EU 2008). MEHP is oxidised in the liver at the longer branch of the 2-ethylhexyl residue by formation of the primary alcohol (ω-oxidation) or of secondary alcohols ((ω-1)- and (ω-2)-oxidation). The terminal alcohol is further oxidised to the dicarboxylic acid, while the secondary alcohols are further oxidised to ketones. The dicarboxylic acid is subject to α- or β-oxidation in mitochondria and peroxisomes. Both MEHP and the oxidative metabolites are largely excreted as glucuronic acid conjugates (EU 2008).

The quantitatively most important DEHP metabolites in humans after both inhalation and oral uptake are mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), mono-(2-ethyl-5-oxyhexyl) phthalate (5-oxo-MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (5-cx-MEPP) (see

Figure 1) (Dirven et al. 1993 a; Koch et al. 2004 a, 2005; Kurata et al. 2012). To a lesser extent, several other oxidation products are formed (Koch et al. 2005; Kurata et al. 2012).

After inhalation, an average of 26.2% MEHP, 33.8% 5-OH-MEHP, 18.2% 5-oxo-MEHP and 21.8% 5-cx-MEPP was found in the urine of five workers. The proportions of free MEHP varied between 20% and 100%. 5-OH-MEHP and 5-oxo-MEHP were found in all persons almost entirely in the conjugated form, 5-cx-MEPP only to 32–45%. (ω-1)-oxidation thus proved to be the preferred route of degradation (Dirven et al. 1993 b).

Table 1 Mean renal excretion rates after 24 h and estimated elimination half-lives of five DEHP metabolites, determined after administration of three different doses of deuterium-labelled DEHP to a subject (Koch et al. 2005)

	Renal excretion rates	Half-lives of renal excretion during the second elimination phase
	[%]	[h]
MEHP	5.9	5
5-OH-MEHP	23.3	10
5-oxo-MEHP	15.0	10
5-cx-MEPP	18.5	12–15
2-cx-MMHP[1]	4.2	24

[1] Mono-[2-(carboxymethyl)hexyl] phthalate

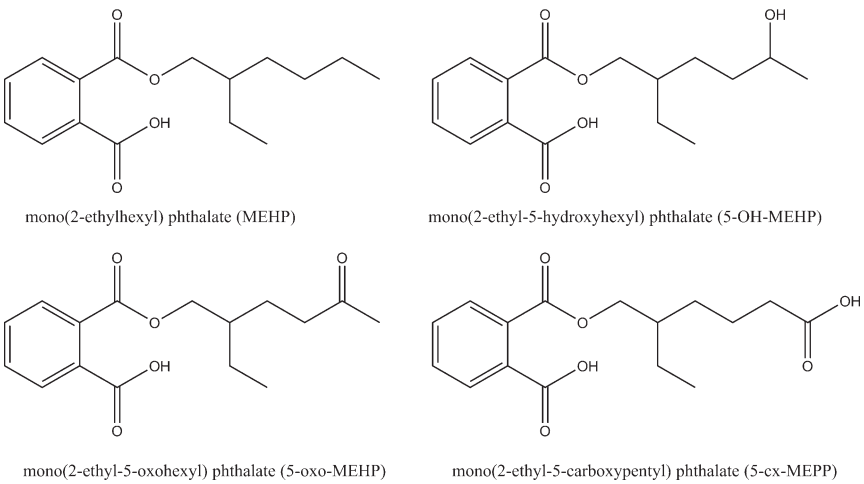


Figure 1 The quantitatively most important DEHP metabolites

After oral DEHP uptake, more than 70% of metabolites were excreted in the urine in the form of 5-OH-MEHP, 5-oxo-MEHP, 5-cx-MEPP and mono-[2-(carboxymethyl) hexyl] phthalate (Koch et al. 2005) (see Table 1). After oral administration, the proportion of glucuronidated metabolites was 65% (Schmid and Schlatter 1985) and 99% (Bronsch 1987, quoted from EU 2008), respectively, in two studies; according to a recent study, it was 77.6% in men and 84.2% in women (Kurata et al. 2012).

2 Critical Toxicity

Critical effects of DEHP identified in animal studies are carcinogenic effects on the liver, effects on the respiratory tract as well as reproductive and developmental toxicity. Detailed information on the toxicity can be found in IARC Monographs (IARC 2010, 2012), an EU Risk Assessment Report (EU 2008), ECHA's compilation of safety data sheets (ECHA 2013) as well as in the MAK Value Documentations (Greim 2002, translated; Hartwig 2015, translated, 2016, translated).

The MAK value of 2 mg/m^3 was derived from a 90 day oral study in rats for lack of adequate human data and due to insufficient inhalation studies. Thus, a bioavailable dose of 15 mg (given 75% absorption by inhalation) per working day by additional inhalation is tolerable (Hartwig 2015, translated).

3 Exposure and Effects

There are no human studies available from which a quantitative relationship between the internal exposure to DEHP – determined on the basis of the urinary excretion of DEHP metabolites – and the critical systemic effects (tumour-promoting effect on the liver, effects on the respiratory tract, reproductive and developmental toxicity) can be derived. Thus, data required to derive a threshold value from the relationship between internal exposure and response is lacking.

For the derivation of a threshold value, inhalation exposure at the level of the MAK value is taken as a basis. Background exposure must be taken into consideration.

Data on the inhalation exposure to DEHP in the workplace and on the urinary excretion of DEHP metabolites are available from studies by Liss et al. (1985), Dirven et al. (1993 a) and Fong et al. (2014).

In their study, Liss et al. (1985) determined the external exposure to DEHP and phthalic acid anhydride in 95 workers at a DEHP manufacturing plant by personal air sampling during a work shift as well as the overall phthalate concentration after hydrolysis of the phthalic acid esters and derivatisation. The research protocol did not include the quantification of the individual oxidised DEHP metabolites. The analytical detection limit for DEHP of 10 µg/sample was exceeded in the air samples of six workers only (concentration range in these samples 20–4110 µg/m^3, mean value 71 µg/m^3). The attempt to detect MEHP in individual urine samples with the highest overall phthalate concentration remained fruitless. Due to the mixed exposure and analytical shortcomings, the study by Liss et al. (1985) is not suitable for deriving a relationship between inhalation exposure to DEHP and the urinary excretion of DEHP metabolites.

Dirven et al. (1993 a) determined the external exposure to DEHP and the concentrations of MEHP, 5-OH-MEPH, 5-oxo-MEHP and 5-cx-MEPP in the urine of nine boot factory workers and of six workers at a cable factory. The external exposure to DEHP was determined by two-hour personal air sampling on the first day of the working week (cable factory) and on the first and the last day of the five-day working week (boot factory), respectively. Urine samples were taken on the first and last day (boot factory) and on the first and fourth day (cable factory), respectively, before the beginning of the shift and after the end of the shift. At the boot factory, the mean airborne concentrations in the workplace were 261 µg/m³ (100–1214 µg/m³) during the mixing process and 120 µg/m³ (48–278 µg/m³) during the extrusion process. At the cable factory, the mean concentrations were 180 µg/m³ (9–809 µg/m³) during the granulation process and 239 µg/m³ (10–1266 µg/m³) during the extrusion process. Although the urinary concentrations of all four metabolites increased on all measurement days in the course of the shift (1.2- to 2.3-fold at the boot factory (significantly), 1.2- to 4.5-fold at the cable factory (insignificantly)), on the fourth and fifth day of the working week, however, only the median concentrations measured in the post-shift urine of the cable factory workers were higher than the concentrations in the post-shift urine measured at the beginning of the week (no information provided on the significance). The authors point out that there was no discernible relationship between the airborne concentrations of DEHP in the workplace and the urinary metabolite concentrations. Besides, as the mean workplace air concentrations only marginally exceeded the estimated maximum intake caused by non-occupational exposure to DEHP (see Table 2), this study is not suitable either as a basis for deriving a threshold value.

On the basis of all measured air concentrations, Dirven et al. (1993 a) determined a mean airborne concentration of 137 µg DEHP/m³. They used this value to calculate a maximum inhalation exposure to DEHP of 1.9 mg/day (27 µg/kg BW), based on 100% pulmonary absorption and a respiratory volume of 13.7 m³ per eight-hour shift (see Equation (2)). Based on the median differences between the concentrations of the four DEHP metabolites in the post-shift and pre-shift urine samples and on the assumption of a mean creatinine excretion rate of 16 mmol/24 h, they calculated an overall metabolite excretion of 0.49 mg. The conversion factor for the metabolic degradation of DEHP into the four aforementioned metabolites is thus 0.258 for inhalation exposure and not 0.631 as it was determined from the excretion data after oral DEHP administration (Koch et al. 2005).

The study by Fong et al. (2014) covered 66 high-exposure workers and 23 low-exposure workers at a PVC production plant. On the last day of a five-day working week, exhaled air samples obtained by personal air sampling (for the duration of a shift) as well as pre-shift and post-shift urine samples were taken from the workers and analysed. The analysis of the DEHP metabolites included MEHP, 5-OH-MEHP and 5-oxo-MEHP. The measured values obtained are listed in Table 2.

Table 2 shows that variations in inhalation exposure were very wide: both in the high-exposure group and in the low-exposure group, inhalation exposure levels were measured that differed by three orders of magnitude. The mean inhalation exposure in the high-exposure group of this study was approximately 1%, while it was 0.26% of the MAK value in the low-exposure group. The urinary concentrations of the DEHP metabolites also varied considerably (one to two orders of magnitude). The post-shift concentrations were consistently significantly higher than the pre-shift ones, and with the exception of the MEHP concentrations, the concentrations of

the DEHP metabolites in the post-shift urine samples of the high-exposure group were also significantly higher than the urinary concentrations in the low-exposure group. The high-exposure group exhibited a significant correlation (correlation coefficients 0.71–0.78) between inhalation exposure and the creatinine-adjusted urinary concentrations of the DEHP metabolites, while in the low-exposure group this only applied to MEHP. For all workers, the correlation coefficients were 0.59 (MEHP), 0.71 (5-OH-MEHP) and 0.68 (5-oxo-MEHP). A correlation formula was not provided.

Based on a linear two-compartment model (David 2000; Kohn et al. 2000) and the assumption of steady-state conditions, the authors calculated the daily DEHP intake from the metabolite excretion rates according to the following Equation (1) by Koch et al. (2006):

$$DI_{urine} = \frac{UE_{sum} \cdot CE}{F_{UE}} \cdot M_{DEHP} \quad (1)$$

Abbreviations:

DI = daily DEHP intake based on urinary data (µg/(kg body weight · d))

UE_{sum} = total amount of the three DEHP metabolites in night-shift urine (µmol/g creatinine)

CE = daily urinary creatinine excretion, calculated on a body weight basis (g/(kg body weight · d))

F_{UE} = $0.442 = 0.059_{MEHP} + 0.233_{5\text{-OH-MEHP}} + 0.150_{5\text{-oxo-MEHP}}$ (molar fraction of the three DEHP metabolites relative to the amount of DEHP taken up, according to Koch et al. (2004 a, 2005))

M_{DEHP} = molar mass of DEHP (390 g/mol)

Table 2 Inhalation exposure to DEHP for PVC production workers and urinary concentrations of DEHP metabolites (mean values and range) in the study by Fong et al. (2014)

n	DEHP	MEHP	5-OH-MEHP	5-oxo-MEHP
	[µg/m³]	[µg/g creatinine]		
23	5.27			
(low-exposure group)	(0.10–236.8)			
pre-shift		10.4	32.5	25.6
		(3.1–55.7)	(9.8–108.4)	(8.2–85.1)
post-shift		16.5	57.1	42.8
		(0.5–141.2)	(23.8–481.1)	(7.3–364.0)
66	32.7			
(high-exposure group)	(1.26–1581.9)			
pre-shift		18.2	68.1	56.7
		(1.5–201.6)	(11.4–534.6)	(7.8–341.7)
post-shift		25.1	97.1	77.4
		(0.5–390.9)	(10.8–677.5)	(5.3–466.4)
89	20.4			
(all workers exposed)	(0.10–1581.9)			
pre-shift		15.8	56.3	46.2
		(3.1–201.6)	(9.8–534.4)	(7.8–341.7)
post-shift		22.5	84.6	66.4
		(0.5–390.9)	(10.8–677.5)	(5.3–466.4)

To determine the share of DEHP intake by inhalation of the overall DEHP exposure based on the personal air sampling data, intake by inhalation was calculated according to the following Equation (2) (Wormuth et al. 2006; Xu et al. 2010):

$$DI_{air} = \frac{C_{air} \cdot IR \cdot AF}{BW} \cdot T \quad (2)$$

Abbreviations:

DI_{air} = daily DEHP intake by inhalation based on personal air monitoring data

C_{air} = airborne DEHP concentration of personal exposure in the workplace (µg/m³)

IR = inhalation rate (18 m³/day)

AF = assumed absorption rate (100%)

BW = body weight

T = exposure time (8/24)

The intake values for DEHP calculated according to the equations above are listed in Table 3.

As outlined above, the mean value of inhalation exposure determined in the study by Fong et al. (2014) is approximately 1% of the MAK value and even the maximum exposure concentration (1581.9 µg/m³) barely reaches 80% of the threshold value (Table 2). Besides, the study provides no indication as to whether the maximum inhalation exposure (1581.9 µg/m³) correlates with the maximum post-shift urinary concentration of the DEHP metabolites (5.2 µmol/g creatinine). Linear extrapolation from the mean inhalation exposure and the corresponding concentrations of the DEHP metabolites in the post-shift urine samples to a hundredfold higher inhalation exposure is problematic due to error amplification. For the reason set out above, this also applies to the extrapolation from the respective extreme values measured (1581.9 µg/m³ and 5.2 µmol/g creatinine) to inhalation exposure at the level of the MAK value (in the case of linear extrapolation, 2000 µg/m³ would correspond to 6.6 µmol/g creatinine).

Fong et al. (2014) calculated the DEHP intake per working day based on the urinary data (Table 3) using Equation (1) proposed by Koch et al. (2006), into which the mean excretion rates of the three DEHP metabolites MEHP, 5-OH-MEHP and 5-oxo-MEHP listed in Table 1 are incorporated as molar fractions ($F_{UE} = 0.442 = 0.059_{MEHP} + 0.233_{5\text{-OH-MEHP}} + 0.150_{5\text{-oxo-MEHP}}$). Koch et al. (2006) derived this equation from two studies, in which single oral doses of ring-labelled d_4-DEHP were each applied to a male volunteer (Koch et al. 2004 a, 2005). In the first study, 48.1 mg of d_4-DEHP were applied, in the second study d_4-DEHP doses of 0.35 mg (4.7 µg/kg BW), 2.15 mg (28.7 µg/kg BW) and 48.5 mg (650 µg/kg BW). The highest dose in the two studies thus corresponded to about the 3.25-fold of the tolerable daily intake of 15 mg by additional inhalation in the workplace (in the case of 75% absorption by inhalation) and thus also covers the threshold value range. The equation applied by Koch et al. (2006) can thus be used to derive a threshold value on the basis of the excretion data of the three DEHP metabolites mentioned. However, as the measured values used for that purpose were determined on the basis of merely one oral study with one volunteer only and as an inter-individual variance has to be

Table 3 DEHP intake by inhalation for PVC production workers per working day and overall DEHP intake (Fong et al. 2014)

	low-exposure group (n = 23)	high-exposure group (n = 66)	all workers exposed (n = 89)
DEHP intake by inhalation per working day based on personal air monitoring data			1.8 µg/(kg BW · d) (mean value) (0.01–123.0 µg/(kg BW · d))
Overall DEHP intake per working day based on urinary data		cf. Hines et al. 2011: 17.0 µg/(kg BW · d) (mean value)	13.5 µg/(kg BW · d) (mean value)
	7.56 µg/(kg BW · d) (median)	14.0 µg/(kg BW · d) (median)	12.5 µg/(kg BW · d) (median) (1.5–102.3 µg/(kg BW · d))
Contribution of inhalation exposure to DEHP relative to body burden	4.8%	20.8% the higher the metabolite excretion, the higher the contribution of inhalation exposure (in the 4th quartile 46.7%)	

assumed, the values are considered insufficient for deriving a BAT value. However, they can be used as a basis for deriving a BLW (biological guidance value).

The excretion of the metabolite mono-(2-ethyl-5-carboxypentyl) phthalate (5-cx-MEPP), which is quantitatively one of the most important degradation products of DEHP and should thus be included in the biomonitoring, has not been taken into account yet by Koch et al. (2006) when deriving the equation. If the mean renal excretion rates of the four quantitatively most important DEHP metabolites at medium and high doses are included in the study by Koch et al. (2005), this would yield a value of 0.631 ($F_{UE} = 0.058_{MEHP} + 0.234_{5\text{-OH-MEHP}} + 0.138_{5\text{-oxo-MEHP}} + 0.2005_{5\text{-cx-MEPP}}$) for F_{UE} instead of a value of 0.442.

By solving the equation for UE,

$$DI_{urine} = \frac{UE_{sum} \cdot CE}{F_{UE}} \cdot M_{DEHP} \quad (1)$$

yields

$$UE_{sum} = \frac{DI_{urine} \cdot F_{UE}}{M_{DEHP} \cdot KE} \quad (3)$$

This Equation (3) is used to evaluate a biological guidance value (BLW) (see Chapter 7).

4 Selection of Indicators

Basically, the internal exposure to DEHP is best assessed by a quantitative analysis of as many urinary DEHP metabolites as possible. However, this would require an undue analytical effort due to the numerous metabolites identified. The above-mentioned derivation is based on the quantitative determination of the four DEHP metabolites MEHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate (5-OH-MEHP), mono-(2-ethyl-5-oxohexyl) phthalate (5-oxo-MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (5-cx-MEPP). They account for the major share of DEHP metabolites excreted in urine. The equation by Koch et al. (2006) does not take into account the excretion of 5-cx-MEPP. Due to the quantitative importance of this metabolite, however, its excretion was incorporated into the derivation of the BLW. MEHP cannot be measured free of interference as the ubiquitous DEHP can be hydrolysed to this primary metabolite both in the environment and during the pre-analytical phase. However, these contaminations are likely to be negligible in the case of exposure at the level of the proposed BLW. Therefore, the sum of the concentrations of MEHP and of the three MEHP oxidation products 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP in urine is used for the biomonitoring of exposure to DEHP.

5 Methodology

For the simultaneous analysis of MEHP and the DEHP oxidation products in urine, both capillary GC-MS/MS (Hoppe et al. 2010) and HPLC-MS/MS methods (Blount et al. 2000; Koch et al. 2003) are used. Irrespective of the detection system, the methods in the pre-analytical phase require enzymatic hydrolysis as the metabolites are partly excreted as glucuronides.

The analytical methods have been verified and published in the loose-leaf collection of the working group "Analyses in Biological Material". The limits of quantitation are 1.5 µg/l urine each (Hoppe et al. 2010).

6 Background Exposure

Data on the general population's exposure to DEHP are available from various countries. Table 4 provides an overview of the internal exposure of the German and U.S. general population to DEHP.

For the threshold value derivation, the non-occupational exposure to DEHP has to be considered, unless it is negligible compared to the inhalation exposure in the workplace at the level of the MAK value. Non-occupational exposure to DEHP comprises inhalation exposure in the environment, dietary intake as well as dermal exposure by using textiles, cosmetics and other DEHP-containing products. According to estimates by Heinemeyer et al. (2012), the DEHP uptake from various non-occupational sources is 10–37 µg/ (kg BW · d) in juveniles and 13–31 µg/ (kg BW · d) in adults, although in individual cases even considerably higher DEHP levels were observed. The daily non-occupational DEHP uptake rate is thus 0.6–2.22 mg for

Table 4 Concentrations of MEHP, 5-OH-MEHP, 5-oxo-MEHP, 5-cx-MEPP and 2-cx-MMHP (mono-[2-(carboxymethyl)hexyl] phthalate) measured in urine samples taken from the general population (median and 95th percentile (in brackets))

n (age)	Country	MEHP	5-OH-MEHP	5-oxo-MEHP	5-cx-MEPP	2-cx-MMHP	Source
289 (20–60 y)	USA	2.7[a] (21.5[a]) 2.7[b] (15.2[b])	n. s.	n. s.	n. s.	n. s.	Blount et al. 2000
2541 (≥ 6 y)	USA	3.20[a] (23.8[a]) 3.08[b] (18.5[b])	n. s.	n. s.	n. s.	n. s.	Silva et al. 2004
85 (7–64 y)	Germany	10.3[a] (37.9[a])	46.8[a] (224[a])	36.5[a] (156[a])	n. s.	n. s.	Koch et al. 2003
50	USA	4.5[a]	35.9[a]	28.3[a]	n. s.	n. s.	Barr et al. 2003
36 (2–6 y) 19 (20–59 y)	Germany	6.6[a] (14.6[a]) 9.0[a] (29.0[a])	49.6[a] (107[a]) 32.1[a] (64.0[a])	33.8[a] (71.0[a]) 19.6[a] (36.7[a])	n. s.	n. s.	Koch et al. 2004 b
254 (3–14 y)	Germany	7.18[a]/5.85[b] (29.7[a]/23.7[b])	52.1[a]/39.9[b] (188[a]/170[b])	41.4[a]/30.5[b] (139[a]/119[b])	n. s.	n. s.	Becker et al. 2004
127	USA	< LOD (20.4[a])	17.4[a] (220[a])	15.6[a] (243[a])	n. s.	n. s.	Kato et al. 2004
19	Germany	9.8[a]	47.5[a]	39.7[a]	85.5[a]	36.6[a]	Preuss et al. 2005
150 m 150 f	Germany 2007–2015	2.3[a] 2.0[a]	7.4[a] 6.8[a]	4.5[a] 4.9[a]	6.9[a] 7.3[a]	n. s. n. s.	Koch et al. 2017
30 m 30 f	Germany 2015	1.2[a] 1.0[a]	4.5[a] 4.2[a]	2.8[a] 3.3[a]	3.6[a] 4.0[a]	n. s. n. s.	Koch et al. 2017

[a] µg/L
[b] µg/g creatinine
Abbreviations: m = male; f = female; n. s. = not specified; y = years

a juvenile weighing 60 kg and 0.91–2.17 mg for an adult weighing 70 kg. The upper limit of the daily non-occupational DEHP uptake is thus approximately 15% of the tolerable bioavailable dose of 15 mg after inhalation exposure at the level of the MAK value. The non-occupational DEHP uptake is thus negligible, particularly as the distance to the NOAEL from animal studies was additionally increased by applying the *preferred value approach* when deriving the MAK value.

7 Evaluation of the Biological Guidance Value (BLW)

Reliable studies on the relationship between the internal exposure to DEHP and systemic DEHP effects are not available. Therefore, the relationship between DEHP intake and the excretion of the four DEHP metabolites MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP determined in oral human studies in due consideration of the known toxicity can only be used to derive the BLW (Greim 2002, translated; Hartwig 2015, translated, 2016, translated). The derivation obtained in this way presupposes that this relationship also applies to inhalation exposure to DEHP at the level of the MAK value. Non-occupational oral, inhalation and dermal exposure to DEHP is negligible in the case of inhalation exposure to DEHP at the level of the MAK value. As the DEHP metabolites are excreted to a varying extent as conjugates, the assessment of the internal exposure to DEHP requires the hydrolysis of the conjugates in the pre-analytical phase. The conversion factor derived by Koch et al. (2006) on the basis of an equation set up by David (2000) describing the relationship between the excretion data and the daily DEHP intake takes into account the creatinine excretion related to body weight.

For a male person weighing 70 kg (standardised creatinine excretion 23 mg/kg BW · d), Equation (3) yields a creatinine-related molar excretion of the four DEHP metabolites of

$$UE_{sum}\ (\text{mol/g creatinine}) = \frac{15\ \text{mg}\cdot 0.631}{390\ \text{g/mol}\cdot 23\ \text{mg/kg}\cdot 70\ \text{kg}} \tag{4}$$

= 15.1 µmol/g creatinine

For a female person weighing 70 kg (standardised creatinine excretion 18 mg/kg BW · d) the resulting value is

19.3 µmol/g creatinine

If concentrations are given in mg/g creatinine for practical reasons, the result is a concentration of 4.53 mg/g creatinine for a male person weighing 70 kg and a concentration of 5.79 mg/g creatinine for a female person weighing 70 kg. The values are based on a mean molar mass of 300 g/mol in due consideration of the quantitative evaluation of the four urinary metabolites. After rounding down to the nearest integer, the BLW is 4 mg/g creatinine. Although this value has been derived from the elimination rates of the metabolites of one male volunteer only, an additional safety factor is not deemed necessary as the LOAEL used to derive the critical inhalation exposure level for DEHP (MAK value) was ten times higher than the NOAEL in animal studies.

A cumulative urinary concentration of the four DEHP metabolites MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP of

4 mg (after hydrolysis)/g creatinine

is thus set as the **BLW**.

In the case of long-term exposure, concentrations of the DEHP metabolites should be measured in spontaneously voided urine samples at the end of the shift after several previous shifts.

8 Interpretation of the Data

The excretion of the four DEHP metabolites MEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP specifically indicates the DEHP uptake from occupational and non-occupational sources. The maximum non-occupational DEHP uptake estimated to be approximately 2 mg leads to an overall urinary concentration of the four DEHP metabolites of approximately 2 µmol/g creatinine and 0.6 mg/g creatinine, respectively. Even though metabolite concentrations below 0.6 mg/g creatinine do not exclude an occupational exposure to DEHP, an occupational exposure can reasonably only be assumed when this concentration is exceeded. However, the assessment of an occupational exposure to DEHP is not affected by this as such exposure levels are well below the BLW. Only if the BLW is exceeded is it imperative to take measures to reduce the exposure to DEHP.

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