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Exposure Assessment Articles

Modeling Human Exposure to Phthalate Esters: A Comparison of Indirect and Biomonitoring Estimation Methods

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ABSTRACT

Humans are potentially exposed to phthalate esters (PEs) through ingestion, inhalation, and dermal contact. Studies quantifying exposure to PEs include "biomarker studies" and "indirect studies." Biomarker studies use measurements of PE metabolites in urine to back-calculate exposure to the parent diester, while indirect studies use the concentration of the PE in each medium of exposure and the rate of intake of that medium to quantify intake of the PE. In this review, exposure estimates from biomarker and indirect studies are compiled and compared for seven PEs to determine if there are regional differences and if there is a preferred approach. The indirect and biomarker methods generally agree with each other within an order of magnitude and discrepancies are explained by difficulties in accounting for use of consumer products, uncertainty concerning absorption, regional differences, and temporal changes. No single method is preferred for estimating intake of all PEs; it is suggested that biomarker estimates be used for low molecular weight PEs for which it is difficult to quantify all sources of exposure and either indirect or biomarker methods be used for higher molecular weight PEs. The indirect methods are useful in identifying sources of exposure while the biomarker methods quantify exposure.

Key Words: phthalate ester, human exposure, biomarker.

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INTRODUCTION

Phthalate esters (PEs) are a diverse group of chemicals having a vast range of applications (Stanley *et al*. 2003). The higher molecular weight PEs are added to vinyl resin to improve its flexibility; di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) are the predominant PEs used as vinyl plasticizers. The lower molecular weight PEs have a considerable range of applications. Dimethyl phthalate (DMP) is used as a stabilizing diluent for the shipping and storage of organic peroxides. Diethyl phthalate (DEP) is used as a fixative or carrier for perfumes and fragrances and also in time-released pharmaceuticals. Dibutyl phthalate (DBP) and diisobutyl phthalate (DiBP) are used in vinyl acetate emulsion adhesives and in cellulose lacquers. Butyl benzyl phthalate (BBP) is normally used with other general-purpose plasticizers in polyvinyl chloride applications.

PEs have been measured in numerous media, including: surface water, groundwater, landfill leachate, drinking water, sediment, suspended particulate matter, soil, air (outdoor and indoor), dust, precipitation, wastewater, sewage sludge, food, vegetation, and wildlife (Clark *et al*. 2003a). Weathering of plastics and other PE-containing articles results in the release of PEs to the environment, including air and water (Bauer 1997; Michael *et al*. 1984; Tabor and Loper 1985). The source of PEs in indoor air, dust, or soil may be from weathering of products containing PEs or directly from household products containing PEs. Humans may be exposed to PEs simultaneously through a variety of exposure pathways, including ingestion of food, drinking water, dust, and soil; and inhalation of air (outdoors and indoors). The use of the lower molecular weight PEs in consumer products such as cosmetics and pharmaceuticals may result in their direct release to air or direct absorption through the skin or gastrointestinal tract. The number of household products containing PEs is not clear, nor is it clear how these products might contribute to overall exposure.

PEs have been measured in human milk, blood, and urine (Zhu *et al*. 2006; Hogberg *et al*. 2008; Koo and Lee 2005), and their metabolites have been measured in human urine, blood, amniotic fluid, and milk (Barr *et al*. 2003; Calafat *et al*. 2004, 2006; Teitelbaum *et al*. 2008). The largest database of metabolic concentrations in biological fluids is from the NHANES (National Health and Nutrition Examination Survey) analyses conducted by the Centers for Disease Control and Prevention (CDC 2001, 2003, 2005, 2009) in which the metabolites of the major PEs were measured relative to a unit of volume and in comparison to the amount of creatinine present. Other surveys of limited populations in Europe have also been published. While the attraction of using this information is high, there are limitations and difficulties in applying it to estimating exposure.

Numerous studies have quantified human exposure to PEs. These studies may be grouped into two types, "indirect" and "biomarker" studies. Indirect studies use the concentration of the PE in each medium of exposure (*e.g.*, air, water, food, consumer product, *etc*.) and the rate of intake of that medium (*e.g.*, inhalation or ingestion rates) to quantify the intake of the PE. Biomarker studies use measurements of PE metabolites in urine to back-calculate exposure to the parent diester.

The indirect studies require quality data concerning the concentration of the PE in every medium to which humans may be exposed and also the intake rate of each

medium. These estimates provide information on a population level because individual habits may vary from the intake estimated for each population. The indirect studies may help elucidate the source(s) of exposure and the relative importance of the various exposure pathways. They are, however, plagued by contamination issues and require rigorous sample handling to exclude PE contamination from sources inside and outside the analytical laboratory. In many studies, contamination issues lead to false high values.

The biomarker studies are less subject to concerns about contamination of samples with the diesters compared with the indirect studies because the metabolites are far less likely to arise from sample contamination. Biomarker studies, however, do not provide any information about the source(s) of exposure and are susceptible to physiological variability. The biomarker studies also require an understanding of the metabolism of the parent diester, which may differ for different PEs. Furthermore, normalizing urinary concentrations of metabolites to a constant such as excreted creatinine, which can account for variation in urinary output, is necessary for comparison. However, creatinine excretion can vary with age and gender, and possibly race (Barr *et al*. 2005). All these factors make using biomonitoring data a challenge. However, biomonitoring data can provide information on an individual basis, which may be useful to evaluate exposure-related effects.

In this article, estimates of exposure to PEs from indirect studies and biomarker studies are compiled for: DMP, DEP, DBP, DiBP, BBP, DEHP, and DiNP. The results are compared to determine if there are regional differences and to determine if one approach is preferred over the other.

METHODOLOGY

Indirect Studies

The general procedure used to estimate intake includes the following steps: description of exposure to the various media containing the PEs; assigning a concentration of the PE in each medium; and assigning an intake rate for that medium. Inclusion of absorption factors for the various media converts the estimated intakes into uptakes, facilitating a more direct comparison with the biomarker studies. Uptake is calculated for each medium and then summed, using the following equation:

$$D = \Sigma (C_i \times IR_i \times A_i / BW)$$

where: D = Absorbed dose of PE (μg/kg/d), C_i = Concentration of PE in medium (μg/g), IR_i = Intake rate of medium (g/d), A_i = Absorption factor (unitless), BW = Body weight (kg)

The intake rates and concentrations in each medium, used for the indirect exposure estimates, are summarized in Tables 1 and 2 and are discussed below. The source of information for intake rates is primarily Health and Welfare Canada (1993) and Health Canada (1995). Additional details and an explanation of the selected distributions are provided in Clark *et al*. (2003b). An absorption factor of 100% was used for all calculations; however, it is recognized that this will overestimate uptake.

Exposure via food may be evaluated by determining concentrations in a wide variety of foods (often called market basket surveys) and then quantifying typical

Table 1. Intake rates used to calculate indirect exposure.

		Adult (20 to 70 y)			Teen (12 to 19 y)			Child (5 to 11 y)			Toddler (0.5 to 4 y)			Neonate (0 to 0.5 y)		
Input Parameter	Units	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev
General receptor characteristics																
Body weight	kg	LN	71	14	LN	60	14	LN	27	7.3	LN	15	3.8	LN	7.5	3.2
Inhalation rate	m^3/d	LN	16	3.9	LN	16	4	LN	15	3.2	LN	9.3	2.6	LN	2.1	0.57
Receptor ingestion rates																
Tap water	L/d	LN	0.8	0.52	LN	1	0.67	LN	1.1	0.7	LN	0.7	0.46	LN	0.8	0.52
Beverages	L/d	LN	0.96	0.62	LN	0.43	0.28	LN	0.23	0.15	LN	0.12	0.08	—	—	—
Cereals	g/d	LN	27	16	LN	24	15	LN	34	22	LN	42	27	—	—	—
Dairy products (excl. milk)	g/d	LN	53	34	LN	50	33	LN	45	29	LN	38	25	—	—	—
Eggs	g/d	LN	32	21	LN	22	14	LN	21	14	LN	24	16	—	—	—
Fats and oils	g/d	LN	25	16	LN	29	19	LN	21	14	LN	11	7.1	—	—	—
Fish	g/d	LN	14	9	LN	11	7.3	LN	8.4	5.5	LN	3.4	2.2	—	—	—
Fruits	g/d	LN	190	120	LN	160	100	LN	200	130	LN	190	120	—	—	—
Grains	g/d	LN	160	100	LN	210	130	LN	190	120	LN	90	58	—	—	—
Meats	g/d	LN	95	61	LN	93	60	LN	55	36	LN	38	25	—	—	—
Milk	L/d	LN	0.23	0.15	LN	0.523	0.34	LN	0.564	0.37	LN	0.632	0.41	—	—	—
Nuts and beans	g/d	LN	28	18	LN	31	20	LN	24	15	LN	15	9.7	—	—	—
Other foods	g/d	LN	220	144	LN	250	160	LN	210	140	LN	270	180	—	—	—
Poultry	g/d	LN	21	14	LN	20	13	LN	17	11	LN	13	8.6	—	—	—
Processed meats	g/d	LN	22	14	LN	23	15	LN	19	12	LN	11	7	—	—	—
Vegetables	g/d	LN	230	150	LN	240	150	LN	190	120	LN	120	76	—	—	—
Infant formula (powder)	g/d	—	—	—	—	—	—	—	—	—	—	—	—	LN	130	85
Breast milk	L/d	—	—	—	—	—	—	—	—	—	—	—	—	LN	0.75	0.49
Total food	g/d	LN	2300	1495	LN	2100	1365	LN	1800	1170	LN	1500	975	LN	820	533
Incidental soil	mg/d	LN	40	100	LN	40	100	LN	40	100	LN	40	100	LN	40	100
Incidental dust	mg/d	LN	40	100	LN	40	100	LN	40	100	LN	40	100	LN	40	100
Exposure frequency																
Time spent indoors	h/d	U	20 to 24		U	20 to 24		U	20 to 24		U	20 to 24		U	20 to 24	

Dist = Distribution type; LN = log normal; U = uniform; References for information provided in Clark *et al.* (2003b).

Table 2. Concentrations used to calculate indirect exposure.

		DMP			DEP			DBP			DiBP			BBP			DEHP			DiNP		
Concentration	Units	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev	Dist	Mean	Std Dev
MEDIUM																						
Outdoor air	$\mu g/m^3$	LN	0.0033	0.0021	LN	0.013	0.0085	LN	0.012	0.008	LN	0.015	0.01	LN	0.002	0.001	LN	0.018	0.01	LN	0.01	0.007
Indoor air	$\mu g/m^3$	LN	0.923	0.60	LN	0.91	0.59	LN	1.06	0.69	LN	0.5	0.3	LN	0.042	0.027	LN	0.274	0.18	LN	0.011	0.007
Drinking water	$\mu g/L$	LN	0.027	0.018	LN	0.12	0.08	LN	0.19	0.12	LN	0.26	0.17	LN	0.06	0.04	LN	1.8	1.2	C	0	—
Ingested soil	$\mu g/g$	LN	0.0002	0.00013	LN	0.0023	0.0015	LN	0.011	0.007	LN	0.017	0.011	LN	0.0036	0.0023	LN	0.025	0.016	LN	0.011	0.007
Ingested dust	$\mu g/g$	LN	2.0	1.3	LN	25	16	LN	132	86	LN	86	56	LN	236	153	LN	901	586	LN	420	273
Food																						
Beverages excl. water	$\mu g/L$	C	0	—	—	—	—	—	—	—	LN	6	3.9	—	—	—	—	—	—	—	—	—
Cereals	$\mu g/g$	C	0	—	—	—	—	—	—	—	C	0	—	—	—	—	—	—	—	—	—	—
Dairy products	$\mu g/g$	C	0	—	—	—	—	—	—	—	C	0	—	—	—	—	—	—	—	—	—	—
Eggs	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.1	0.07	—	—	—	—	—	—	—	—	—
Fats and oils	$\mu g/g$	C	0	—	—	—	—	—	—	—	C	0	—	—	—	—	—	—	—	—	—	—
Fish	$\mu g/g$	LN	0.0012	0.0008	—	—	—	—	—	—	LN	0.011	0.008	—	—	—	—	—	—	—	—	—
Fruit products	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.03	0.02	—	—	—	—	—	—	—	—	—
Grains	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.13	0.08	—	—	—	—	—	—	—	—	—
Meats	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.05	0.03	—	—	—	—	—	—	—	—	—
Milk	$\mu g/L$	LN	0.7	0.5	—	—	—	—	—	—	LN	17	11	—	—	—	—	—	—	—	—	—
Nuts and beans	$\mu g/g$	C	0	—	—	—	—	—	—	—	C	0	—	—	—	—	—	—	—	—	—	—
Other foods	$\mu g/g$	C	0	—	—	—	—	—	—	—	C	0	—	—	—	—	—	—	—	—	—	—
Poultry	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.06	0.04	—	—	—	—	—	—	—	—	—
Processed meats	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.03	0.02	—	—	—	—	—	—	—	—	—
Vegetable products	$\mu g/g$	C	0	—	—	—	—	—	—	—	LN	0.005	0.003	—	—	—	—	—	—	—	—	—
Infant formula - powder	$\mu g/g$	C	0	—	C	0	—	LN	0.048	0.031	LN	0.06	0.04	LN	0.003	0.002	LN	0.15	0.10	C	0	—
Breast milk	$\mu g/g$	C	0	—	LN	0.00031	0.0002	LN	0.0015	0.001	C	0	—	LN	0.0008	0.0005	LN	0.148	0.096	C	0	—
Composite diet samples	$\mu g/g$	—	—	—	T	0.0001, 0.0002,	0.026	LN	0.033	0.021	—	—	—	LN	0.014	0.009	LN	0.39	0.25	LN	0.018	0.012

Dist. = Distribution type; LN = log normal; C = constant, T = triangular.
Measured concentrations obtained from numerous references, contained in ACC database (Clark 2008).

consumption of each of those foods; however, the market basket survey data for the PEs were collected 20 years ago (*e.g.,* Page and Lacroix 1995). Recent measurements of PEs in foods tend to be for composite diets (*e.g.,* Fromme *et al.* 2007b; Tsumura *et al.* 2001a,b and 2003; Wilson *et al.* 2001 and 2003; Petersen and Breindahl 2000) or for a few selected foods and not for a wide range of foods typical of the diets of most individuals.

Some of the indirect studies evaluate only selected exposure pathways (*e.g.,* ingestion of food and exposure to environmental media), whereas the Wormuth *et al.* (2006) study also includes exposure to consumer products via ingestion, inhalation, and dermal contact. Inclusion of consumer products provides a more comprehensive evaluation of potential exposures to the users of those products; however, it will overestimate exposures for individuals who are not product users. In addition, the estimates of exposure due to use of consumer products are confounded by very limited information concerning the concentrations of PEs in the products, the scenarios of use including intake rates, and absorption factors.

Human exposure to five PEs: DMP, DEP, DBP, BBP, and DEHP found in food, air, drinking water, soil, and dust was evaluated using information in the American Chemistry Council (ACC) database (Clark *et al.* 2003b). The exposure assessments have been updated using concentrations in the most recent version of the ACC database, as summarized in Table 2, and assessments are added for two additional PEs: DiBP and DiNP. The ACC database is comprised of more than 500 references reporting measurements of PEs in various media. The references have been reviewed and categorized in terms of data quality, on the basis of analytical and sampling methodologies and reporting of quality assurance and quality control measures; data categorized as "not reliable" are not included in the summary in Table 2.

As an example of the indirect study calculation, the mean daily uptake of DEHP for an adult, assuming 100% absorption for all exposure pathways, is:

$$\begin{aligned}\text{Total absorbed dose} &= \text{food} + \text{indoor air} + \text{outdoor air} + \text{drinking water} + \text{soil} + \text{dust}\\ &= (0.39\ \mu\text{g/g} \times 2300\ \text{g/d} \times 1 + 0.274\ \mu\text{g/m}^3 \times 16\ \text{m}^3\text{/d} \times 22\ \text{h/24 h} \times 1 + 0.018\ \mu\text{g/m}^3\\ &\times 16\ \text{m}^3\text{/d} \times 2\ \text{h/24 h} \times 1 + 1.8\ \mu\text{g/L} \times 0.8\ \text{L/d} \times 1 + 0.025\ \mu\text{g/g} \times 0.040\ \text{g/d} \times 1\\ &+ 901\ \mu\text{g/g} \times 0.040\ \text{g/d} \times 1)/71\ \text{kg} = 13\ \mu\text{g/kg/d}\end{aligned}$$

The above calculation uses the mean values of the distributions, presented in Tables 1 and 2, whereas the results of the calculations presented in Tables 3 to 10 were performed using the distributions of values with the software Crystal Ball™ (Oracle Corporation). Use of the distributions allows calculation of the median and 95th percentile values, which are the values presented in Tables 3 to 10. The preponderance of lognormal distributions as inputs results in median values that are less than the mean.

Biomarker Studies

Many of the papers reporting measurements of PE metabolites in urine also present estimates of the daily intake of the diesters and those estimates are presented herein. For studies reporting only measurements of PE metabolites in urine, the following equation, from David (2000) as expressed by Koch *et al.* (2003b), was used

Table 3. DMP exposure estimates.

Study	DMP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Update to Clark *et al.* (2003b), using concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 0.16 (0.48)	Age 12 to 19 y: 0.19 (0.60)	Age 5 to 11 y: 0.40 (1.2)	Age 0.5 to 4y: 0.47 (1.4)	Age 0 to 0.5 y: 0.22 (0.8)
Clark *et al.* (2003b)					
Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	Age 20 to 70 y: 0.7	Age 12 to 19 y: 0.7	Age 5 to 11 y: 1.4	Age 0.5 to 4y: 1.6	Age 0 to 0.5 y: 0.05
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.06; 0.94; 7.31 M: 0.08; 0.85; 5.99	Age 11 to 18 y: F: 0.07; 0.59; 3.50 M: 0.05; 0.53; 3.55	Age 4 to 10 y: 0.05; 0.46; 5.92	Age 1 to 3 y: 0.08; 0.76; 9.78	Age 0 to 1 y: 0.2; 1.27; 16.97
Fromme *et al.* (2007b)					
Germany (2005): intake estimated from composite dietary samples collected over 7 days; N = 50 (27 female + 23 male)	Age 14 to 60 y: 0.11 (median); 0.18 (95th percentile); 0.05–0.26 (range)		—	—	—

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Table 3. DMP exposure estimates. *(Continued)*

Study	DMP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Itoh *et al.* (2007)					
Japan:					
Based on ingestion of food and inhalation of indoor air; data compiled from various sources	0.38 (mean)	—	—	—	—
Calculated from urinary metabolite data for MMP (2004); N = 35	1.4 to 2.0 (range of means); 0.60 to 0.87 (range of geo means)	—	—	—	—
CDC (2005)[a]					
USA (NHANES 2001–2002): Calculated from urinary metabolite data for MMP; data format: geo mean (95th percentile)					
N = 2772	Age 6+ y: Total: 0.034 (0.25); Male: 0.034 (0.23); Female: 0.034 (0.28)			—	—
N = 1638	Age 20+ y: 0.031 (0.24)	—	—	—	—
N = 742	—	Age 12 to 19 y: 0.021 (0.12)	—	—	—
N = 392	—	—	Age 6 to 11 y: 0.028 (0.21)	—	—
Huang *et al.* (2006)					
Taiwan (undated): Calculated from urinary metabolite data for MMP; pregnant women; N = 28	0.3 (median)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.

Table 4. DEP exposure estimates.

Study	DEP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Update to Clark *et al.* (2003b), using concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 0.46 (1.0)	Age 12 to 19 y: 0.46 (1.3)	Age 5 to 11 y: 0.93 (2.8)	Age 0.5 to 4 y: 1.2 (3.8)	Age 0 to 0.5 y: 0.34 (1.2)
Clark *et al.* (2003b)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	Age 20 to 70 y: 2.5 (median)	Age 12 to 19 y: 3.0 (median)	Age 5 to 11 y: 5.7 (median)	Age 0.5 to 4 y: 10.6 (median)	Age 0 to 0.5 y: 0.2 (median)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.01, 4.06, 84.11 M: 0.02; 4.47; 49.27	Age 11 to 18 y: F: 0.01; 1.76; 20.94 M: 0.03; 1.53; 12.12	Age 4 to 10 y: 0.27; 1.23; 7.12	Age 1 to 3 y: 0.56; 2.46; 13.89	Age 0 to 1 y: 1.25; 4.37; 23.86
Fromme *et al.* (2007b)					
Germany (2005): intake estimated from composite dietary samples collected over 7 days; N = 50 (27 female + 23 male)	Age 14 to 60 y: 0.13 (median); 0.34 (95th percentile); 0.06–0.49 (range)		—	—	—
Fromme *et al.* (2007b)					
Germany (2002: Koch *et al.* 2003a): N = 85 Calculated from urinary metabolite data for MEP; data format: median (95th percentile)	Age 7 to 63 y: Female: 4.6 (38.5); Male: 2.0 (42.4)			—	—

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Table 4. DEP exposure estimates. *(Continued)*

Study	DEP Intake (μgkg^{-1}d^{-1})				
	Adult	Teen	Child	Toddler	Infant
Tsumura *et al.* (2001a)					
Japan (1999): Based on total diet study of hospital food; calculated using body weight of 50 kg.	0.007 (mean)	—	—	—	—
Itoh *et al.* (2007)					
Japan:					
Based on ingestion of food and inhalation of indoor air; data compiled from various sources	0.051 to 0.065 (range of means)	—	—	—	—
Calculated from urinary metabolite data for MEP (2004); N = 35	0.77 to 1.2 (range of means)	—	—	—	—
Calafat and McKee (2006)					
USA (NHANES 2001–2002; CDC, 2005): Calculated from urinary metabolite data for MEP; data format: geo mean (95th percentile)					
N = 2772	Age 6 to > 20 y: 5.5 (61.7); Male: 4.9 (69.0); Female: 6.2 (47.4)			—	—
N = 742	—	Age 12 to 19 y: 5.0 (44.1)	—	—	—
N = 392	—	—	Age 6 to 11 y: 1.8 (15.3)	—	—
Marsee *et al.* (2006)					
USA (2000–2003): pregnant women (N = 214): Calculated from urinary metabolite data for MEP	6.64 (median); 112.3 (95th percentile)	—	—	—	—
CDC (2003)[a]					
USA (NHANES 1999–2000): Calculated from urinary metabolite data for MEP; data format: geo mean (95th percentile)					
N = 2536	Age 6+ y: Total: 5.4 (64.7); Male: 5.4 (74.1); Female: 5.6 (57.4)			—	—
N = 1456	Age 20+ y: 5.9 (72.0)	—	—	—	—

N = 752	—	Age 12 to 19 y: 2.6 (28.3)	—	—	—
N = 328	—	—	Age 6 to 11 y: 1.7 (11.4)	—	—
Brock *et al.* (2002)[a]					
USA (2000): Intake calculated from urinary metabolite data for MEP; 19 children; 30 samples	—	—	—	Age 11.8 to 16.5 months: 6.3 (geo mean); 37 (95th percentile)	—
David (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MEP (Blount *et al.* 2000); N = 289	Age 20 to 60 y: 12.34 (geo mean); 93.33 (95th percentile)	—	—	—	—
Kohn *et al.* (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MEP (Blount *et al.* 2000); N = 289	Age 20 to 60 y: 12 (median); 110 (95th percentile)	—	—	—	—
Huang *et al.* (2006)					
Taiwan (undated): Calculated from urinary metabolite data for MEP; pregnant women; N = 28	3.01 (median)	—	—	—	—
Chen *et al.* (2008)					
Taiwan (undated): Calculated from urinary metabolite data for MEP; N = 60 (41 female, 18 male)	Age 21 to 67 y: nd (median); nd to 27.9 (range)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.
nd = Not detected.

Table 5. DBP exposure estimates.

Study	DBP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Update to Clark *et al.* (2003b), using concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 1.2 (3.0)	Age 12 to 19 y: 1.2 (4.0)	Age 5 to 11 y: 2.4 (8.1)	Age 0.5 to 4 y: 3.4 (12)	Age 0 to 0.5 y: 1.5 (5.7) formula-fed; 0.78 (4.0) breast-fed
Clark *et al.* (2003b)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	Age 20 to 70 y: 5.6 (median)	Age 12 to 19 y: 6.4 (median)	Age 5 to 11 y: 11 (median)	Age 0.5 to 4 y: 14 (median)	Age 0 to 0.5 y: 1.5 (formula-fed); 2.9 (breast-fed) (median)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 1.42; 5.33; 54.20 M: 1.63; 4.31; 25.82	Age 11 to 18 y: F: 0.19; 1.74; 17.35 M: 0.17; 1.37; 17.02	Age 4 to 10 y: 0.83; 2.41; 19.60	Age 1 to 3 y: 0.35; 2.62; 26.74	Age 0 to 1 y: 1.02; 7.37; 45.63
Franco *et al.* (2007)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	2.7 (median)	—	—	—	—
Based on ingestion of leaf and root crops, fish, beef, dairy, drinking water, and inhalation of outdoor air using the EUSES model and data from the Netherlands	0.21 (median)	—	—	—	—
Wilson *et al.* (2003)					
USA (1997): Based on ingestion of food, dust, and soil and inhalation of indoor and outdoor air	—	—	—	Age 2 to 5 y: 1.4 (mean); 0.745 to 2.85 (range)	—
Tsumura *et al.* (2003)					
Japan (2001): Based on total diet study of hospital food; calculated using body weight of 50 kg.	0.26	—	—	—	—

Tsumura *et al.* (2001a)					
Japan (1999): Based on total diet study of hospital food; calculated using body weight of 50 kg	0.29	—	—	—	—
Itoh *et al.* (2007)					
Japan:					
Based on ingestion of food and inhalation of indoor air; data compiled from various sources	0.44 to 0.75 (range of means)	—	—	—	—
Calculated from urinary metabolite data for MBP (2004); N = 35	1.7 (mean)	—	—	—	—
Fromme et al. (2007a and b)					
Germany (2005): N = 50 (27 female + 23 male)	Age 14 to 60 y:				
Calculated from composite dietary samples collected over 7 days	0.26 (median); 1.35 (95th percentile); 0.12–1.63 (range)		—	—	—
Calculated from urinary metabolite data for MBP; data format: median (95th percentile)	Total: 1.7 (4.2)		—	—	—
	Female: 1.7 (4.4); Male: 1.8 (3.9)		—	—	—
Fromme *et al.* (2007b)					
Germany (2002: Koch *et al* 2003a): N = 85	Age 7 to 63 y:				
Calculated from urinary metabolite data for MBP; data format: median (95th percentile)	Female: 6.0 (17.5); Male: 4.6 (15.9)			—	—
Wittassek *et al.* (2007b)					
Germany: Calculated from urinary metabolite data for MBP; male and female adults; data format: median; 95th percentile; (range)	Age 20 to 29 y:				
1988 (N = 60)	7.0; 24.2; (0.72–27.8)	—	—	—	—
1989 (N = 60)	7.5; 21.7; (1.5–70.1)	—	—	—	—
1991 (N = 60)	6.4; 14.3; (2.1–28.7)	—	—	—	—
1993 (N = 60)	6.6; 44.4; (1.5–56.3)	—	—	—	—
1996 (N = 145)	3.7; 15.5; (1.1–90.2)	—	—	—	—
1998 (N = 68)	3.1; 11.9; (0.22–20.3)	—	—	—	—
1999 (N = 60)	2.8; 16.2; (0.83–32.8)	—	—	—	—
2001 (N = 60)	2.5; 19.4; (0.81–116)	—	—	—	—
2003 (N = 59)	1.9; 5.3; (0.49–71.8)	—	—	—	—
Total male (N = 325)	3.7; 16.2; (NA)	—	—	—	—
Total female (N = 307)	4.6; 20.3; (NA)	—	—	—	—
Overall total (N = 632)	4.1; 19.1; (0.22–116)	—	—	—	—

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Table 5. DBP exposure estimates. *(Continued)*

Study	DBP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Wittassek and Angerer (2008)					
Germany: Calculated from urinary metabolite data for MBP; N = 102		Age 6 to 80 y: 2.1 (median); 230 (maximum)		—	—
Children: N = 239			Age 2 to 14 y:		
Creatinine-based model	—		4.1 (median); 76.4 (maximum)		—
Volume-based model	—		7.6 (median); 110 (maximum)		—
CDC (2005)[a]					
USA (NHANES 2001–2002): Calculated from urinary metabolite data for MBP; data format: geo mean (95th percentile)					
N = 2,772	Age 6+ y: Total: 0.65 (3.0); Male: 0.60 (2.5); Female: 0.71 (3.0)			—	—
N = 1638	Age 20+ y: 0.58 (2.6)	—	—	—	—
N = 742	—	Age 12 to 19 y: 0.39 (1.8)	—	—	—
N = 392	—	—	Age 6 to 11 y: 0.71 (2.9)	—	—
Marsee *et al.* (2006)					
USA (2000–2003): pregnant women (N = 214): Calculated from urinary metabolite data for MBP	0.84 (median); 2.33 (95th percentile)	—	—	—	—
CDC (2003)[a]					
USA (NHANES 1999–2000): Calculated from urinary metabolite data for MBP + MiBP; data format: geo mean (95th percentile)					
N = 2,541	Age 6+ y: Total: 0.81 (3.5); Male: 0.72 (2.7); Female: 0.93 (4.3)			—	—
N = 1,461	Age 20+ y: 0.74 (3.3)	—	—	—	—
N = 752	—	Age 12 to 19 y: 0.49 (1.8)	—	—	—
N = 328	—	—	Age 6 to 11 y: 0.84 (3.2)	—	—

Brock *et al.* (2002)[a]					
USA (2000): Intake calculated from urinary metabolite data for MBP; 19 children; 30 samples	—	—	—	Age 11.8 to 16.5 months: 2.45 (geo mean); 16.6 (95th percentile)	—
David (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MBP (Blount *et al.* 2000); N = 289	Age 20 to 60 y: 1.56 (geo mean); 6.87 (95th percentile)	—	—	—	—
Kohn *et al.* (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MBP (Blount *et al.* 2000); N = 289	Age 20 to 60 y: 1.5 (median); 7.2 (95th percentile)	—	—	—	—
Huang *et al.* (2006)					
Taiwan (undated): Calculated from urinary metabolite data for MBP; pregnant women; N = 28	9.28 (median)	—	—	—	—
Chen *et al.* (2008)					
Taiwan (undated): Calculated from urinary metabolite data for MBP; N = 60 (41 female, 18 male)	Age 21 to 67 y: 2.2 (median); nd to 23.5 (range)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.
NA = Not available
nd = Not detected

Table 6. DiBP exposure estimates.

Study	DiBP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Using method described in Clark *et al.* (2003b) and concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 0.76 (1.6)	Age 12 to 19 y: 0.98 (2.2)	Age 5 to 11 y: 2.1 (4.8)	Age 0.5 to 4 y: 2.6 (6.2)	Age 0 to 0.5 y: 1.3 (5.5)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.03; 0.45; 1.61 M: 0.03; 0.50; 1.82	Age 11 to 18 y: F: 0.05; 0.30; 0.98 M: 0.06; 0.40; 1.27	Age 4 to 10 y: 0.04; 0.39; 1.55	Age 1 to 3 y: 0.07; 0.69; 2.44	Age 0 to 1 y: 0.16; 1.53; 4.73
Fromme et al. (2007a and b)					
Germany (2005): N = 50 (27 female + 23 male)	Age 14 to 60 y:				
Calculated from composite dietary samples collected over 7 days	0.57 (median); 2.14 (95th percentile); 0.23–3.47 (range)		—	—	—
Calculated from urinary metabolite data for MiBP; data format: median (95th percentile)	Total: 1.7 (5.2)		—	—	—
	Female: 1.6 (4.7); Male: 1.8 (5.3)		—	—	—
Wittassek *et al.* (2007b)					
Germany: Calculated from urinary metabolite data for MiBP; male and female adults; data format: median; 95th percentile; (range)	Age 20 to 29 y:				
1988 (N = 60)	1.1; 3.6; (0.27–6.2)	—	—	—	—
1989 (N = 60)	1.0; 4.2; (0.30–12.9)	—	—	—	—
1991 (N = 60)	1.2; 8.7; (0.36–20.2)	—	—	—	—
1993 (N = 60)	1.2; 2.8; (0.39–4.8)	—	—	—	—
1996 (N = 145)	1.6; 8.4; (0.45–29.0)	—	—	—	—
1998 (N = 68)	1.4; 5.8; (0.10–12.2)	—	—	—	—
1999 (N = 60)	1.5; 4.4; (0.41–15.1)	—	—	—	—
2001 (N = 60)	1.6; 4.6; (0.29–12.6)	—	—	—	—
2003 (N = 59)	1.4; 3.9; (0.46–5.2)	—	—	—	—
Total male (N = 325)	1.3; 4.8; (NA)	—	—	—	—
Total female (N = 307)	1.4; 6.6; (NA)	—	—	—	—
Overall total (N = 632)	1.4; 5.7; (0.10–29.0)	—	—	—	—

Wittassek and Angerer (2008)					
Germany: Calculated from urinary metabolite data for MiBP; N = 102		Age 6 to 80 y: 1.5 (median); 27.3 (maximum)		—	—
CDC (2005)[a]					
USA (NHANES 2001–2002): Calculated from urinary metabolite data for MiBP; data format: geo mean (95th percentile)					
N = 2,772	Age 6+ y: Total: 0.09 (0.44); Male: 0.09 (0.46); Female: 0.09 (0.44)			—	—
N = 1,638	Age 20+ y: 0.08 (0.38)	—	—	—	—
N = 742	—	Age 12 to 19 y: 0.05 (0.26)	—	—	—
N = 392	—	—	Age 6 to 11 y: 0.10 (0.49)	—	—
Marsee *et al.* (2006)					
USA (2000–2003): pregnant women (N = 214): Calculated from urinary metabolite data for MiBP	0.12 (median); 0.41 (95th percentile)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.
NA = Not available

Table 7. BBP exposure estimates.

Study	BBP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Update to Clark *et al.* (2003b), using concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 0.50 (1.4)	Age 12 to 19 y: 0.49 (1.9)	Age 5 to 11 y: 0.97 (4.0)	Age 0.5 to 4 y: 1.5 (6.1)	Age 0 to 0.5 y: 0.51 (6.1) formula-fed; 0.53 (6.1) breast-fed
Clark *et al.* (2003b)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	Age 20 to 70 y: 3.7 (median)	Age 12 to 19 y: 5.7 (median)	Age 5 to 11 y: 7.9 (median)	Age 0.5 to 4 y: 9.3 (median)	Age 0 to 0.5 y: 1.5 (median)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.02; 0.24; 2.62 M: 0.02; 0.26; 2.97	Age 11 to 18 y: F: 0.02; 0.11; 2.24 M: 0.02; 0.13; 2.76	Age 4 to 10 y: 0.01; 0.13; 1.68	Age 1 to 3 y: 0.02; 0.44; 5.89	Age 0 to 1 y: 0.06; 1.16; 11.70
Wilson *et al.* (2003)					
USA (1997): Based on ingestion of food (composite samples), dust, and soil and inhalation of indoor and outdoor air	—	—	—	Age 2 to 5 y: 1.9 (mean); 0.744 to 2.88 (range)	—
Tsumura *et al.* (2003)					
Japan (2001): Based on total diet study of hospital food; calculated using body weight of 50 kg.	0.068	—	—	—	—
Tsumura *et al.* (2001a)					
Japan (1999): Based on total diet study of hospital food; calculated using body weight of 50 kg	0.094	—	—	—	—
Itoh *et al.* (2007)					
Japan:					
Based on ingestion of food and inhalation of indoor air; data compiled from various sources	0.062 to 0.083 (range of means)	—	—	—	—
Calculated from urinary metabolite data for MBzP (2004); N = 35	0.093 (mean)	—	—	—	—

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Fromme et al. (2007a and b)					
Germany (2005): N = 50 (27 female + 23 male)	Age 14 to 60 y:				
Calculated from composite dietary samples collected over 7 days	0.23 (median); 0.38 (95th percentile); 0.11–0.50 (range)		—	—	—
Calculated from urinary metabolite data for MBzP; data format: median (95th percentile)	Total: 0.2 (1.2)		—	—	—
	Female: 0.2 (1.5); Male: 0.2 (1.0)		—	—	—
Fromme *et al.* (2007b)					
Germany (2002: Koch *et al* 2003a): N = 85	Age 7 to 63 y:				
Calculated from urinary metabolite data for MBzP; data format: median (95th percentile)	Female: 0.6 (2.5); Male: 0.5 (2.4)			—	—
Wittassek and Angerer (2008)					
Germany: Calculated from urinary metabolite data for MBzP; N = 102	Age 6 to 80 y:				
	0.3 (median); 2.2 (maximum)			—	—
Children: N = 239		Age 2 to 14 y:			
Creatinine-based model	—	0.42 (median); 13.9 (maximum)			—
Volume-based model	—	0.77 (median); 31.3 (maximum)			—
Wittassek *et al.* (2007b)					
Germany: Calculated from urinary metabolite data for MBzP; male and female adults; data format: median; 95th percentile; (range)	Age 20 to 29 y:				
1988 (N = 60)	0.25; 0.77; (0.02–6.6)	—	—	—	—
1989 (N = 60)	0.30; 2.2; (0.07–2.8)	—	—	—	—
1991 (N = 60)	0.43; 1.6; (0.11–2.8)	—	—	—	—
1993 (N = 60)	0.27; 1.9; (0.07–2.2)	—	—	—	—
1996 (N = 145)	0.29; 5.5; (0.04–27.3)	—	—	—	—
1998 (N = 68)	0.22; 1.4; (0.01–4.0)	—	—	—	—
1999 (N – 60)	0.21; 3.7; (0.03–10.9)	—	—	—	—
2001 (N = 60)	0.22; 0.75; (0.02–0.99)	—	—	—	—
2003 (N = 59)	0.22; 0.91; (0.05–1.74)	—	—	—	—
Total male (N = 325)	0.25; 1.9; (NA)	—	—	—	—
Total female (N = 307)	0.28; 1.5; (NA)	—	—	—	—
Overall total (N = 632)	0.26; 1.6; (0.01–27.3)	—	—	—	—

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Table 7. BBP exposure estimates. *(Continued)*

Study	BBP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
CDC (2005)[a]					
USA (NHANES 2001–2002): Calculated from urinary metabolite data for MBzP; data format: geo mean (95th percentile)					
N = 2,772	Age 6+ y: Total: 0.47 (3.0); Male: 0.49 (3.1); Female: 0.47 (2.9)			—	—
N = 1,638	Age 20+ y: 0.40 (2.2)	—	—	—	—
N = 742	—	Age 12 to 19 y: 0.33 (1.8)	—	—	—
N = 392	—	—	Age 6 to 11 y: 0.70 (3.6)	—	—
Marsee *et al.* (2006)					
USA (2000–2003): pregnant women (N = 214): Calculated from urinary metabolite data for MBzP	0.50 (median); 2.47 (95th percentile)	—	—	—	—
Brock *et al.* (2002)[a]					
USA (2000): Intake calculated from urinary metabolite data for MBzP; 19 children; 30 samples	—	—	—	Age 11.8 to 16.5 months: 1.5 (geo mean); 6.4 (95th percentile)	—
CDC (2003)[a]					
USA (NHANES 1999–2000): Calculated from urinary metabolite data for MBzP; data format: geo mean (95th percentile)					
N = 2,541	Age 6+ y: Total: 0.47 (2.6); Male: 0.49 (2.8); Female: 0.46 (2.4)			—	—
N = 1,461	Age 20+ y: 0.39 (1.9)	—	—	—	—
N = 752	—	Age 12 to 19 y: 0.32 (1.3)	—	—	—
N = 328	—	—	Age 6 to 11 y: 0.73 (2.6)	—	—

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David (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MBzP (Blount, *et al.* 2000); N = 289	Age 20 to 60 y: 0.73 (geo mean); 3.34 (95th percentile)	—	—	—	—
Kohn *et al.* (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MBzP (Blount, *et al.* 2000); N = 289	Age 20 to 60 y: 0.88 (median); 4.0 (95th percentile)	—	—	—	—
Huang *et al.* (2006)					
Taiwan (undated): Calculated from urinary metabolite data for MBzP; pregnant women; N = 28	<0.1 (median)	—	—	—	—
Chen *et al.* (2008)					
Taiwan (undated): Calculated from urinary metabolite data for MBzP; N = 60 (41 female, 18 male)	Age 21 to 67 y: 0.2 (median); nd to 1.6 (range)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.
NA = Not available
nd = Not detected

Table 8. DEHP exposure estimates.

Study	DEHP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Update to Clark *et al.* (2003b), using concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 11 (31)	Age 12 to 19 y: 11 (42)	Age 5 to 11 y: 20 (81)	Age 0.5 to 4 y: 30 (124)	Age 0 to 0.5 y: 5.0 (27) formula—fed; 16 (66) breast—fed
Clark *et al.* (2003b)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	Age 20 to 70 y: 8.2 (median)	Age 12 to 19 y: 10 (median)	Age 5 to 11 y: 19 (median)	Age 0.5 to 4 y: 26 (median)	Age 0 to 0.5 y: 5.0 (formula— fed); 7.3 (breast—fed) (median)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.23; 2.06; 11.39 M: 0.26; 2.25; 12.93	Age 11 to 18 y: F: 0.10; 1.25; 10.40 M: 0.14; 1.68; 14.25	Age 4 to 10 y: 0.17; 2.00; 14.51	Age 1 to 3 y: 0.24; 4.91; 47.23	Age 0 to 1 y 0.54; 12.33; 106.67
Franco *et al.* (2007)					
Based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years	5.6 (median)	—	—	—	—
Based on ingestion of leaf and root crops, fish, beef, dairy, drinking water, and inhalation of outdoor air using the EUSES model and data from the Netherlands	0.68 (median)	—	—	—	—
Jensen and Knudsen (2006)					
Denmark: estimated intake due to exposure to consumer products and dust indoors	—	—	—	10–20 (typical); 50–250 (worst case)	—
Tsumura *et al.* (2003)					
Japan (2001): Based on total diet study of hospital food; calculated using body weight of 50 kg.	3.2	—	—	—	—

Tsumura *et al*. (2001a)					
Japan (1999): Based on total diet study of hospital food; calculated using body weight of 50 kg	10.4	—	—	—	—
Itoh *et al*. (2007)					
Japan:					
Based on ingestion of food and inhalation of indoor air; data compiled from various sources	2.1 to 2.8 (range of means)	—	—	—	—
Calculated from urinary metabolite data for MEHP (2004); N = 35	2.7 (mean)	—	—	—	—
Fujimaki *et al*. (2006)					
Japan (2003): pregnant women; N = 40	median (range)				
Calculated from urinary metabolite data: MEHP	10.4 (3.45–41.6)	—	—	—	—
Calculated from urinary metabolite data: MEOHP	4.55 (0.66–17.9)	—	—	—	—
Calculated from urinary metabolite data: MEHHP	3.51 (1.47–8.57)	—	—	—	—
Fromme et al. (2007a and b)					
Germany (2005): N = 50 (27 female + 23 male)	Age 14 to 60 y:				
Calculated from composite dietary samples collected over 7 days	2.43 (median); 3.95 (95th percentile); 1.0–4.80 (range)		—	—	—
Calculated from urinary metabolite data: MEHP	Total: 2.2 (median); 7.2 (95th percentile)		—	—	—
	Female: 1.9 (7.1); Male: 2.4 (7.6)		—	—	—
Calculated from urinary metabolite data: MEOHP	Total: 2.3 (median); 7.2 (95th percentile)		—	—	—
	Female: 2.3 (8.2); Male: 2.5 (6.5)		—	—	—
Calculated from urinary metabolite data: MEHHP	Total: 2.0 (median); 6.5 (95th percentile)		—	—	—
	Female: 1.7 (7.0); Male: 2.3 (6.0)		—	—	—
Fromme *et al*. (2007b)					
Germany (2002: Koch *et al*. 2003a): Age 7 to 63 y; N = 85	median (95th percentile):				
Calculated from urinary metabolite data: MEHP	Female: 4.0 (14.8); Male: 4.5 (20.5)			—	—
Calculated from urinary metabolite data: MEOHP	Female: 4.8 (16.2); Male: 6.3 (23.3)			—	—
Calculated from urinary metabolite data: MEHHP	Female: 3.7 (14.2); Male: 5.9 (23.6)			—	—

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Table 8. DEHP exposure estimates. *(Continued)*

Study	DEHP Intake ($\mu g kg^{-1} d^{-1}$)				
	Adult	Teen	Child	Toddler	Infant
Wittassek *et al.* (2007b)					
Germany: Calculated from sum of urinary metabolite data for MEHHP + MEOHP + MECPP + MCMHP + MEHP; male and female adults 20 to 29 y	median; 95th percentile; (range)				
1988 (N = 60)	3.9; 9.9; (0.78–39.8)	—	—	—	—
1989 (N = 60)	4.2; 10.0; (0.84–33.6)	—	—	—	—
1991 (N = 60)	4.0; 18.8; (1.2–23.6)	—	—	—	—
1993 (N = 60)	4.2; 12.9; (1.4–14.1)	—	—	—	—
1996 (N = 145)	3.7; 13.4; (0.76–30.4)	—	—	—	—
1998 (N = 68)	3.1; 8.1; (0.19–10.9)	—	—	—	—
1999 (N – 60)	2.7; 9.6; (1.0–13.9)	—	—	—	—
2001 (N = 60)	3.1; 7.4; (1.1–20.1)	—	—	—	—
2003 (N = 59)	2.4; 5.7; (0.82–7.1)	—	—	—	—
Total male (N = 325)	3.4; 10.2; (NA)	—	—	—	—
Total female (N = 307)	3.5; 10.5; (NA)	—	—	—	—
Overall total (N = 632)	3.5; 10.1; (0.19–39.8)	—	—	—	—
Wittassek and Angerer (2008)					
Germany: Calculated from urinary metabolite data for MEHHP + MEOHP + MECPP + MCMHP + MEHP; N = 102	Age 6 to 80 y: 2.7 (median); 42.2 (maximum)			—	—
Wittassek *et al.* (2007a)					
Germany: Calculated from urinary metabolite data for MEHHP + MEOHP + MECPP + MCMHP + MEHP; Children: N = 239 (paper contains additional breakdown of data by age and gender)		Age 2 to 14 y:			
Creatinine-based model	—	4.3 (median); 15.2 (95th percentile); 0.6–140 (range)			—
Volume-based model	—	7.8 (median); 25.2 (95th percentile); 0.4–409 (range)			—

Calafat and McKee (2006)					
USA (NHANES 2001–2002: CDC, 2005); data format: geo mean (95th percentile)	Age 6 to > 20 y: (N = 2,772)				
Calculated from urinary metabolite data: MEHP		0.9 (7.1)		—	—
Calculated from urinary metabolite data: MEHHP		2.1 (16.8)		—	—
Calculated from urinary metabolite data: MEOHP		2.2 (15.6)		—	—
		Age 12 to 19 y: (N = 742)	Age 6 to 11 y: (N = 392)		
Calculated from urinary metabolite data: MEHP	—	0.8 (5.5)	0.6 (3.7)	—	—
Calculated from urinary metabolite data: MEHHP	—	2.2 (11.6)	2.4 (13.2)	—	—
Calculated from urinary metabolite data: MEOHP	—	2.4 (12.6)	2.6 (12.8)	—	—
Germany (2001–2002: Becker *et al*., 2004); data format: geo mean (95th percentile)		Age 3 to 14 y: (N = 254)			
Calculated from urinary metabolite data: MEHP	—	0.7 (2.8)			—
Calculated from urinary metabolite data: MEHHP	—	2.6 (10.7)			—
Calculated from urinary metabolite data: MEOHP	—	3.1 (11.7)			—
Marsee *et al*. (2006)					
USA (2000–2003): pregnant women (N = 214)	median (95th percentile):				
Calculated from urinary metabolite data: MEHP	2.37; (16.8)	—	—	—	—
Calculated from urinary metabolite data: MEHHP	1.33; (9.11)	—	—	—	—
Calculated from urinary metabolite data: MEOHP	2.00; (12.8)				
Brock *et al*. (2002)[a]					
USA (2000): Intake calculated from urinary metabolite data for MEHP; 19 children; 30 samples	—	—	—	Age 11.8 to 16.5 months: 1.8 (geo mean); 7.0 (95th percentile)	—
CDC (2003)[a]					
USA (NHANES 1999–2000): Calculated from urinary metabolite data for MEHP; data format: geo mean (95th percentile)					
N = 2,541	Age 6+ y: Total: 0.73 (4.3); Male: 0.78 (5.8): Female: 0.71 (3.4)			—	—
N = 1,461	Age 20+ y: 0.71 (4.1)	—	—	—	—
N = 752	—	Age 12 to 19 y: 0.33 (1.6)	—	—	—
N = 328	—	—	Age 6 to 11 y: 0.67 (5.4)	—	—

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Table 8. DEHP exposure estimates. *(Continued)*

	DEHP Intake ($\mu g kg^{-1} d^{-1}$)				
Study	Adult	Teen	Child	Toddler	Infant
David (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MEHP (Blount, *et al.* 2000); N = 289	Age 20 to 60 y: 0.60 (geo mean); 3.05 (95th percentile)	—	—	—	—
Kohn *et al.* (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MEHP (Blount, *et al.* 2000); N = 289	Age 20 to 60 y: 0.71 (median); 3.6 (95th percentile)	—	—	—	—
Huang *et al.* (2006)					
Taiwan (undated): Calculated from urinary metabolite data for MEHP; pregnant women; N = 28	5.17 (median)	—	—	—	—
Chen *et al.* (2008)					
Taiwan (undated): Calculated from urinary metabolite data for MEHP; N = 60 (41 female, 18 male)	Age 21 to 67 y: 33.9 (median); 0.1 to 309.6 (range)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text. One half detection limit used for non-detect results.
NA = Not available

Table 9. DiNP exposure estimates.

	DiNP Intake ($\mu gkg^{-1}d^{-1}$)				
Study	Adult	Teen	Child	Toddler	Infant
Present evaluation					
Using method described in Clark *et al.* (2003b) and concentrations in Table 2. Median intake, based on ingestion of food, drinking water, dust/soil, and inhalation of air using data compiled from various countries and various years. Data format: median (95th percentile)	Age 20 to 70 y: 0.67 (2.0)	Age 12 to 19 y: 0.67 (2.6)	Age 5 to 11 y: 1.3 (5.5)	Age 0.5 to 4 y: 2.1 (8.7)	Age 0 to 0.5 y: 0.76 (9.9)
Wormuth *et al.* (2006) + suppl data					
Europe: based on oral, inhalation, and dermal exposure pathways, including consumer products; data format = low, intermediate, high estimate; F = female; M = male	Age 18 to 80 y: F: 0.01; 0.01; 0.26 M: 0.01; 0.01; 0.28	Age 11 to 18 y: F: 0.01; 0.01; 0.24 M: 0.01; 0.01; 0.29	Age 4 to 10 y: 0.00; 0.14; 6.22	Age 1 to 3 y: 0.01; 5.16; 75.34	Age 0 to 1 y: 0.02; 16.03; 152.40
Tsumura *et al.* (2003)					
Japan (2001): Based on total diet study of hospital food; calculated using body weight of 50 kg	0.094	—	—	—	—
Tsumura *et al.* (2001a)					
Japan (1999): Based on total diet study of hospital food; calculated using body weight of 50 kg	1.3	—	—	—	—
Gill *et al.* (2001)					
Estimates compiled from various sources					
Exposure due to mouthing of children's products	—	—	—	Age 1 to 3 y: 39 (average); 5–228 (range)	Age 0.3 to 0.5 y: 73.9 (95th percentile)
All sources other than mouthing children's products	—	—	—	Age 0.3 to 3 y: 50 (average)	—
Fromme *et al.* (2007b)					
Germany (2005): N = 50 (27 female + 23 male)	Age 14 to 60 y:				
Calculated from urinary metabolite data: MHiNP	Total: 0.7 (median); 3.5 (95th percentile)		—	—	—
	Female: 0.6 (3.5); Male: 0.8 (3.5)		—	—	—

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Table 9. DiNP exposure estimates. *(Continued)*

Study	DiNP Intake (μgkg^{-1}d^{-1})				
	Adult	Teen	Child	Toddler	Infant
Wittassek *et al*. (2007b)					
Germany: Calculated from sum of urinary metabolite data for MOiNP + MHiNP; male and female adults; data format: median; 95th percentile; (range)	Age 20 to 29 y:				
1988 (N = 60)	0.20; 1.4; (0.04–2.2)	—	—	—	—
1989 (N = 60)	0.24; 2.2; (0.03–12.9)	—	—	—	—
1991 (N = 60)	0.22; 4.5; (0.05–20.2)	—	—	—	—
1993 (N = 60)	0.27; 1.7; (0.04–2.6)	—	—	—	—
1996 (N = 145)	0.33; 1.6; (0.02–3.4)	—	—	—	—
1998 (N = 68)	0.30; 7.8; (0.06–11.7)	—	—	—	—
1999 (N – 60)	0.32; 1.9; (0.05–3.1)	—	—	—	—
2001 (N = 60)	0.34; 2.3; (0.10–4.4)	—	—	—	—
2003 (N = 59)	0.40; 1.5; (0.12–3.2)	—	—	—	—
Total male (N = 325)	0.27; 1.7; (NA)	—	—	—	—
Total female (N = 307)	0.32; 1.7; (NA)	—	—	—	—
Overall total (N = 632)	0.29; 1.7; (0.03–20.2)	—	—	—	—
Wittassek and Angerer (2008)					
Germany: Calculated from urinary metabolite data for MiNP + MOiNP + MHiNP + MCiNP; N = 102	Age 6 to 80 y: 0.6 (median); 36.8 (maximum)			—	—
CDC (2003)[a]					
USA (NHANES 1999–2000): Calculated from urinary metabolite data for MiNP; 95th percentile	Age 6+ y (N = 2,541): Total: 6.1; Male: 7.0; Female: 5.5			—	—
	Age 20+ y (N = 1461): 6.6	Age 12 to 19 y (N = 752): 1.5	Age 6 to 11 y (N = 328): 4.7	—	—
David (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MiNP (Blount *et al*. 2000); N = 289	Age 20 to 60 y: 0.21 (geo mean); 1.08 (95th percentile)	—	—	—	—
Kohn *et al*. (2000)					
USA (1988–1994; NHANES III). Intake calculated from urinary metabolite data for MiNP (Blount *et al*. 2000); N = 289	Age 20 to 60 y: 1.7 (95th percentile)	—	—	—	—

[a]Daily intake calculated from reported urinary metabolite data, as described in text.
NA = Not available

Table 10. Summary comparison of indirect and biomarker methods.

	PE Intake (μgkg^{-1}d^{-1})[a]	
PE	Indirect Studies	Biomarker Studies[b]
DMP	Diet only: 0.11	0.031 to 0.87 [0.38]
	Diet, air, dust: 0.16 to 0.38	
	Diet, air, dust, consumer products: 0.90	
DEP	Diet only: 0.007 to 0.13	0.77 to 12.3 [5.5]
	Diet, air, dust: 0.051 to 0.46	
	Diet, air, dust, consumer products: 4.27	
DBP	Diet only: 0.26 to 0.29	0.58 to 5.3 [1.7]
	Diet, air, dust: 0.44 to 2.7	
	Diet, air, dust, consumer products: 4.82	
DiBP	Diet only: 0.57	0.08 to 1.7 [1.45]
	Diet, air, dust: 0.76	
	Diet, air, dust, consumer products: 0.48	
BBP	Diet only: 0.068 to 0.23	0.093 to 0.88 [0.3]
	Diet, air, dust: 0.062 to 0.50	
	Diet, air, dust, consumer products: 0.25	
DEHP	Diet only: 2.43 to 10.4	0.60 to 33.9 [2.7]
	Diet, air, dust: 2.1 to 11	
	Diet, air, dust, consumer products: 2.16	
DiNP	Diet only: 0.094 to 1.3	0.21 to 0.7 [0.45]
	Diet, air, dust: 0.67	
	Diet, air, dust, consumer products: 0.01	

[a]Adult, median or geometric mean; see Tables 3 to 9 for source of information. Excludes studies of pregnant women.
[b]Format: range [median].

to estimate the daily intake:

$$DI = (UE \times CE)/(1000 \times F_{UE}) \times (MW_d/MW_m)$$

where: DI = daily intake of diester (μg/kg/d), UE = creatinine-corrected urinary metabolite concentration (μg/g), CE = creatinine clearance rate normalized by body weight (mg/kg/d), F_{UE} = molar conversion factor that relates urinary excretion of metabolite to diester, MW_d = molecular weight of diester (g/mol), MW_m = molecular weight of monoester (g/mol).

For short chain PEs (*e.g.*, DBP and BBP), the simple monoesters appear to be the major metabolites (Wittassek and Angerer 2008). Thus, for DMP, DEP, DBP, BBP, and DiBP, the estimates of intake are based on measurements of the following metabolites in urine: monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and monoisobutyl phthalate (MiBP), respectively.

For DEHP and DiNP, the oxidized (secondary) metabolites have been found to be more suitable biomarkers of exposure because they are produced in greater quantity compared with the primary metabolites and they are not susceptible to external contamination, as are the primary metabolites (Wittassek and Angerer 2008). For DEHP,

intake estimates are based on measurements of mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(2-carboxymethylhexyl) phthalate (MCMHP), and mono-2-ethylhexyl phthalate (MEHP). For DiNP, intake estimates are based on measurements of mono(hydroxyisononyl) phthalate (MHiNP), mono(oxoisononyl) phthalate (MOiNP), mono(carboxyisononyl) phthalate (MCiNP), and monoisononyl phthalate (MiNP). It should be noted that some DiNP is produced from a mixed isomeric alcohol unlike the other PEs, which are esters of single structures of alcohols. Therefore, DiNP is a blend of chromatographic peaks and this has limited the ability to accurately measure metabolites in the urine.

The values for F_{UE} are critical to the calculation of exposure. For example, a value of 0.059 for MEHP was derived by Koch *et al.* (2004) based on a single individual (as are the values for the oxidative metabolites of MEHP), while a value of 0.12 was derived by Anderson *et al.* (2001) using eight subjects (oxidative metabolites were not analyzed). Clearly, the value selected has an impact on the exposure calculated; additional volunteer studies are necessary to determine more accurate values. The following values were used in the above equation: 0.69 for MMP (Itoh *et al.* 2007); 0.69 for MEP (Calafat and McKee 2006); 0.69 for MBP and MiBP (Anderson *et al.* 2001); 0.73 for MBzP (Anderson *et al.* 2001); 0.12 for MEHP (Anderson *et al.* 2001); 0.233 for MEHHP, 0.15 for MEOHP, 0.042 for MCMHP, and 0.185 for MECPP (Koch *et al.* 2005); 0.02 for MiNP, 0.106 for MOiNP and 0.202 for MHiNP (Koch and Angerer 2007).

The values for creatinine clearance rate were: 23 and 18 mg/kg/d for male and female adults, respectively (Kohn *et al.* 2000); and 20, 11, and 9.8 mg/kg/d for all adults combined, children, and infants, respectively (Calafat and McKee 2006). Normalization to creatinine excretion per kg body weight is thought to reduce the diurnal variability in urinary output and the inter-individual variability in urinary output (David 2000).

As an example of the biomarker study calculation, the geometric mean daily intake for age 20+ years, for DMP, based on a creatinine-corrected urinary metabolite concentration of 1.00 μg/g, is:

$$\begin{aligned} DI &= (UE \times CE)/(1000 \times F_{UE}) \times (MW_d/MW_m) \\ &= (1.00 \times 20)/(1000 \times 0.69) \times 194.2/180.2 = 0.031\ \mu g/kg/d \end{aligned}$$

RESULTS

Presented in Tables 3 through 9 are the results of the comparison of the estimated daily intake for each diester via indirect and biomarker methods. For each study, where available, the location of the study population, the date, the scope of the study, and the number of individuals tested are presented. To facilitate comparison between studies, a central estimate of exposure (median or geometric mean) and a reasonable upper limit (usually the 95th percentile) are presented, if possible. Due to changes in patterns of use of the diesters and changes in analytical methods, the indirect exposure estimates are limited to those published from year 2000 to

the present. Note, however, some of the recently published indirect studies include some pre-2000 measurements due to a lack of more recent measurements.

Dimethyl Phthalate

When compared with the other diesters, fewer measurements of DMP in environmental media or of its metabolite, MMP, in human urine, are available. The frequency with which DMP is detected is also less than other PEs. This may reflect the overall use pattern of DMP as an industrial solvent, with little use in products. DMP has been evaluated in only a few foods (beverages, fish, milk, and infant formula and breast milk). In the Clark *et al*. (2003b) study, for foods in which DMP had not been detected, the concentration in that food group was assigned a value equal to one half the detection limit. This likely resulted in an overestimate of the intake of DMP. The concentrations used in the present evaluation are shown in Table 2. DMP has only been detected in fish and milk; for the remainder of the foods, a concentration of zero was used in the calculations.

As shown in Table 3, the highest intake in the present evaluation was estimated to be for the toddler, followed by the child, the infant, the teen, and the adult. For DMP, for all age groups, inhalation of indoor air represents the dominant exposure pathway, accounting for 95% or more of total exposure. Wormuth *et al*. (2006) estimated that infants had the highest intake of DMP, followed by female and male adults, toddlers, teens, and children (trend based on the intermediate estimates of uptake). For all age groups, inhalation of indoor air was the dominant exposure pathway; dermal contact and ingestion of personal care products represented 10 to 20% of exposure in teens and adults. The indirect study, based on only dietary exposure (Fromme *et al*. 2007b), produced daily intake estimates somewhat lower than those in the present evaluation and much lower than the Wormuth *et al*. estimates.

The highest estimated intake of DMP was found in the biomarker study in Japan (Itoh *et al*. 2007), while the estimated intake of DMP in Taiwan is somewhat less. The results of the biomarker study for the USA suggest a much lower intake of DMP (CDC 2005). In the USA study, adults had the highest intake, followed by children and teens. It is not known whether exposures are truly higher in Japan compared with other countries, as the available measurements of DMP in Japan are quite limited. Another possible explanation for the higher estimated intakes in Japan is that the results are based on a relatively small dataset. Variation between the indirect estimates and the biomarker estimates for DMP may be largely due to variability in the concentration of DMP in indoor air, due to varying patterns of use of products containing DMP.

Diethyl Phthalate

DEP has been measured in a wide variety of environmental media and foods in Europe, North America, and Japan/Asia; however, most of the data for individual foods are more than 20 years old. As shown in Table 4, the lowest estimates of daily intake of DEP are those based on diet (*e.g.*, Fromme *et al*. 2007b) or diet and inhalation of air (Itoh *et al*. 2007) or the present evaluation (diet, drinking water,

air, soil, and dust). In the present evaluation, ingestion of food accounts for 54% to 60% of the total intake for the adult, teen, child, and toddler with inhalation of indoor air accounting for most of the remainder. For the infant, food accounted for 7% of exposure, inhalation of indoor air 60%, and ingestion of dust 33%.

The estimates of Wormuth *et al.* (2006), which include exposure to personal care products, are very similar to the German study in which intake was estimated based on the biomarker MEP (Fromme *et al.* 2007b). The indirect exposure estimates, which do not include exposure to personal care products, underestimate the daily intake of DEP. These results are supported by the use pattern of DEP. DEP is commonly used in perfumes and fragrances (Shen *et al.* 2007).

Based on the biomarker data, intake of DEP is highest in the USA, followed by Germany, Taiwan, and Japan. This difference between regions is also apparent in the measured concentrations of DEP in indoor air; in the USA, the average concentration is approximately two times the average concentration in Europe and six times the average concentration in Japan. However, the average concentration of DEP in dust in the USA is less than that in Europe (by a factor of three or more); no data for DEP in dust are available for Japan. The concentration of DEP in composite diet samples is less in Japan compared with Germany. Although indoor air and diet may not represent the primary sources of exposure to DEP, regional differences in the concentrations in these media may reflect different use patterns of products containing DEP.

Dibutyl Phthalate

DBP is one of the most extensively evaluated PEs; concentration data are available for Europe, North America, and Japan/Asia for most media. However, as for most of the other PEs, recent data for a wide variety of foods are not available and the results of composite diet samples were used in the present evaluation. The lowest estimates of daily intake of DBP (see Table 5) are those based on diet only (*e.g.*, Tsumura *et al.* 2001a, 2003) or diet and inhalation of air (Franco *et al.* 2007; Itoh *et al.* 2007). In the present evaluation, ingestion of food accounts for approximately 75% of total exposure for the adult, teen, child, and toddler, with the remainder due to inhalation of indoor air and incidental ingestion of dust. For the formula-fed infant, ingestion of food accounts for 46% of exposure, followed by ingestion of dust (38%) and inhalation of indoor air (15%). For the breast-fed infant, ingestion of dust is the dominant exposure pathway (62% of total exposure), followed by inhalation of indoor air (25%) and ingestion of food (13%).

For the indirect estimates by Wormuth *et al.* (2006), ingestion of food is the dominant exposure pathway for adults, while for teens (especially female teens), dermal contact and ingestion of personal care products and inhalation of air are important exposure pathways, in addition to ingestion of food. For the three youngest age groups (children, toddlers, and infants), ingestion of food is the most important pathway, followed by inhalation of air, and ingestion of dust (toddlers and infants). The indirect estimates of Wilson *et al.* (2003) for the toddler, based on ingestion of food, dust, and soil and inhalation of air, are slightly lower than the estimates in the present evaluation and those of Wormuth *et al.* for the same age group.

The biomarker-based estimates vary by region; some biomarker estimates are higher than the indirect estimates and some are lower (see Tables 5 and 10). Using measurements of the metabolite MBP, the highest estimated intake of DBP is for Germany, followed by Taiwan, Japan, and the USA. This is supported by higher measured concentrations of DBP in environmental media in Europe compared with the USA (the concentration of DBP is five times higher in indoor air and more than six times higher in dust), suggesting greater use of DBP in Germany. The biomarker-based estimate of intake for Japan is also larger than the estimated intake for the USA and this is supported by the concentration of DBP in indoor air in Japan, which is approximately 50% higher than the concentration in the USA (no data for dust are available for Japan). Both the German and USA data show a decrease in DBP intake with time and both indicate that intake is higher for female adults compared with males. The gender difference may be due to the use of DBP in consumer products, including nail polish (Shen *et al*. 2007).

Di-isobutyl Phthalate

DiBP has been measured in a variety of environmental media and foods. In the present evaluation, for all age groups, food is the dominant source of exposure (especially grains, fruit, milk, and beverages). Inhalation of indoor air is also an important exposure pathway. As shown in Table 6, for the adult and teen, the estimated intake in the present evaluation is 50% to 2.5 times higher than the indirect estimates of Wormuth *et al*. (2006) and Fromme *et al*. (2007a,b). For the child and toddler, the estimated intakes in the present evaluation are three to five times higher than the estimates of Wormuth *et al*. (2006), while, for the infant, the estimates are similar. In the present evaluation, higher concentrations in several foods were used compared to those of Wormuth *et al*. (2006). Food was the predominant exposure pathway for all age groups in the Wormuth *et al*. estimates. For the youngest age groups (child and infant) ingestion of dust was also important.

The estimated intake of DiBP in Germany based on diet is approximately one third of the total estimated using the biomarker approach (Fromme *et al*. 2007a,b). Wittassek *et al*. (2007b) found that the intake of DiBP increased slightly between 1988 and 1996, and then remained relatively constant. They also found that female adults had significantly higher intakes of DiBP compared to male adults. The results of the biomarker studies indicate that the estimated intake of DiBP is more than an order of magnitude larger in Germany compared with the USA. This may be due to the use of larger quantities of DiBP in Germany compared with the USA and is supported by measurements of DiBP in dust and indoor air. No gender difference is apparent in the USA data. For the adult, the indirect estimates in the present evaluation are lower than the biomarker-based estimates for Germany and higher than the estimates for the USA.

Butyl Benzyl Phthalate

BBP has been measured in a variety of environmental media and foods. For most environmental media, BBP measurements are available for Europe and North America. Fewer data are available for Japan. In a recent dietary study in Germany, BBP was detected in only 35 of 350 composite samples (detection limit of 0.01 μg/g)

(Fromme *et al.* 2007b). Despite this low frequency of detection of BBP in composite foods, in the present evaluation, ingestion of food accounts for 68% to 77% of total exposure for the adult, teen, child, and toddler, with the remainder primarily due to incidental ingestion of dust and a minor contribution due to inhalation of indoor air. For both the formula-fed and breast-fed infants, ingestion of dust accounts for approximately 94% of exposure, with ingestion of food comprising most of the remainder. Ingestion of food represents approximately 60% of total exposure for the adult and inhalation of spray paints comprises most of the remainder in the estimates by Wormuth *et al.* (2006). For the teen, these two pathways are reversed in importance. For children, ingestion of food is the dominant exposure pathway, while for toddlers and infants, ingestion of dust is the most important pathway.

As shown in Table 7, for the present evaluation, the estimated intake to the toddler is equal to the biomarker-based estimate for toddlers in the USA using the data of Brock *et al.* (2002). It is also similar to the indirect estimates of Wilson *et al.* (2003) for toddlers in the USA. The indirect estimates of Wormuth *et al.* (2006), for the adult, are comparable to the biomarker-based estimates for German adults (*e.g.*, Fromme *et al.* 2007a,b; Wittassek *et al.* 2007b).

The biomarker-based estimates for the USA are higher than the German estimates and decrease by approximately 50% from the 1988–1994 study (NHANES III) to the studies in 1999–2000 and 2001–2002 (CDC 2003, 2005). Wittassek *et al.* (2007b) report only a slight decrease in the estimated intake of BBP over the period of 1988 to 2003 in German adults. The higher biomarker-based estimates for the USA compared with Germany are supported by differences in concentrations in indoor and outdoor air, drinking water, and soil. However, the average concentration in dust in the USA is approximately one half the average concentration in Europe. The lowest estimated intakes of BBP are reported for Japan (both indirect and biomarker-based). The data available for Japan indicate that the measured concentrations of BBP in indoor and outdoor air and composite diet samples are less than in the USA or Europe.

Di-2-ethylhexyl Phthalate

DEHP is the most widely studied PE and measured concentrations are available for all environmental media and food groups. However, as for the other PEs, few recent measurements of food are available. In the present evaluation, the highest estimated intake of DEHP is for the toddler, followed by the child. For the adult, teen, child, and toddler, ingestion of food is the predominant exposure pathway, accounting for approximately 95% of total exposure. Most of the remainder is due to incidental ingestion of dust. For the formula-fed infant, incidental ingestion of dust accounts for 63% of total exposure, ingestion of food 34%, and ingestion of drinking water 2%. For the breast-fed infant, ingestion of food accounts for 76% of total exposure and incidental ingestion of dust 24%. In the indirect estimates by Wormuth *et al.* (2006), ingestion of food accounts for more than 95% of total exposure to the adult, teen, and child. For the toddler and infant, ingestion of food and ingestion of dust are the predominant exposure pathways, having approximately equal importance.

As shown in Table 8, for all age groups except the infant, the intermediate estimates of Wormuth *et al*. (2006) are much less than those in the present evaluation. Wormuth *et al*. used minimum, mean, and maximum absorption fractions of 0.153, 0.552, and 0.95, respectively, whereas 100% absorption was assumed in the present evaluation. Thus, uptake of DEHP is likely overestimated in the present evaluation; if an oral absorption factor of 0.153 were used, the estimated intake for the adult would be lowered from 11 μg/kg/d to approximately 2 μg/kg/d. In addition to the difference in absorption factors, the concentration of DEHP in some of the individual foods in Wormuth *et al*. is also less than the concentration in the composite samples used in the present evaluation. The indirect estimates of Fromme *et al*. (2007a,b), based on diet only, are also considerably less than the estimates in the present evaluation.

The biomarker studies differ in the metabolites that were measured. The older studies (Brock *et al*. 2002; CDC 2003; David 2000; Kohn *et al*. 2000) evaluated only MEHP. The estimates of DEHP intake from those studies are generally the lowest. The exceptions are the studies of Huang *et al*. (2006) and Chen *et al*. (2008), which evaluated MEHP in the urine of pregnant women and male and female adults, respectively, in Taiwan. The intakes of DEHP, estimated from the MEHP concentrations in the Taiwanese studies, are larger than other studies with estimates based on MEHP. Using measurements of five metabolites of DEHP, Wittassek *et al*. (2007b) found that between 1988 and 1993, the intake of DEHP was nearly constant, but decreased after 1996. The estimated intakes in Wittassek *et al*. (2007a,b) are similar to other studies of the German population, but somewhat higher than the estimates for the U.S. population (CDC 2005).

Di-isononyl Phthalate

DiNP has been measured in water, soil, and air. It has been evaluated in a variety of foods, but is not often detected. Numerous studies have documented the presence of DiNP in indoor dust, at concentrations equal to approximately 50% of the level of DEHP. For the indirect studies, as shown in Table 9, the lowest median intake of DiNP for the adult is 0.01 μg/kg/d (Wormuth *et al*. 2006) due to ingestion of dust, inhalation of air, inhalation of spray paints, and dermal contact with gloves. Wormuth *et al*. (2006) used a value of zero as the concentration of DiNP in all foods except fish in their intermediate calculations; thus, food represents only a very small fraction of the total DiNP intake. Wormuth *et al*. (2006) estimated higher intakes of DiNP with decreasing age, with the highest intake estimated to be for the infant. For the infant, toddler, and child, the estimated intake is predominantly due to mouthing of toys.

In the present evaluation, the estimated median intake of DiNP to the adult is 0.67 μg/kg/d. The estimated intake for the teen and infant are comparable to the adult, but are higher for the child and toddler. For the adult, teen, child, and toddler, ingestion of food accounts for 61% to 71% of intake, depending on the age group. The remainder of the exposure for these age groups (and all of the exposure to the infant) is due to ingestion of dust. The estimated intakes of Tsumura *et al*. (2003, 2001a), based on dietary exposure in Japan decrease from 1999 to 2001 due to a decrease in the measured concentrations of DiNP in total diet samples. Gill *et al*.

(2001) estimated intakes of DiNP to the toddler and infant as follows: an average of 39 μg/kg/d for the toddler due to mouthing children's products and 50 μg/kg/d due to other sources. For the infant, Gill *et al.* estimated the 95th percentile intake to be 73.9 μg/kg/d, due to mouthing children's products. These estimates are in the range of the upper estimates by Wormuth *et al.* (2006).

The biomarker studies differ in the metabolites that have been measured. The older studies (CDC 2003; David 2000; Kohn *et al.* 2000) evaluated only MiNP. MiNP is reported to be only a minor urinary metabolite of DiNP, while the oxidative metabolites: mono(carboxyisooctyl) phthalate (MCiOP), MOiNP, and MHiNP are the major urinary metabolites in rats. Silva *et al.* (2006) analysed all four metabolites in the urine of adults and confirmed that the oxidative metabolites were found in higher concentrations compared to MiNP (which was not detected). Silva *et al.* concluded that human exposure to DiNP is underestimated by using MiNP as the only urinary biomarker of DiNP. This conclusion is supported by the biomarker data for the USA, where MiNP was rarely detected and only the 95th percentile concentrations are reported.

Over the period of 1988 to 2003, the median intake of DiNP to German adults, based on the sum of MOiNP and MHiNP, ranges from 0.20 to 0.40 μg/kg/d, with the intakes increasing with time (Wittassek *et al.* 2007b). Intakes are estimated to be higher for female adults than males. Based on measurements of only MHiNP, the estimated median intake of DiNP in adults in 2005 is 0.7 μg/kg/d, with males having a greater intake compared with females (Fromme *et al.* 2007b). Wittassek and Angerer (2007) estimated the median intake of DiNP, based on the sum of MOiNP, MHiNP, and MCiNP, to be 0.6 μg/kg/d.

The estimated median intake of DiNP to the adult in the present indirect evaluation (0.67 μg/kg/d) is comparable to the biomarker-based estimates for Germany using MHiNP (0.7 μg/kg/d in Fromme *et al.* 2007b) and using the sum of MiNP, MOiNP, MHiNP, and MCiNP (0.6 μg/kg/d in Wittassek and Angerer 2008). The above indirect and biomarker estimates are higher than those of Wittassek *et al.* (2007b).

DISCUSSION AND CONCLUSIONS

In Table 10 is presented an overall comparison of the estimated daily intake for each diester via indirect and biomarker methods. Selected results for three of the PEs (DEP, BBP, and DEHP) are presented in Figures 1 to 3.

In Figure 1 is presented the estimated intake of DEP from eight of the studies presented in Table 4. To facilitate comparison, the values presented in Figure 1 are the central (usually median) estimates for male and female adults. As shown in Figure 1 and Table 10, the intakes estimated in the indirect studies, which did not include exposure to personal care products (present evaluation; Fromme *et al.* 2007b; Itoh *et al.* 2007; Tsumura *et al.* 2001a), are much less than the indirect study that included such exposures (Wormuth *et al.* 2006) and less than the biomarker studies (Calafat and McKee 2006; Fromme *et al.* 2007b; Itoh *et al.* 2007).

In Figure 2 is presented the estimated intake of BBP for nine of the studies presented in Table 7. A comparison of Figures 1 and 2 shows that, for BBP, the indirect estimates are more similar to the biomarker-based estimates than was evident for

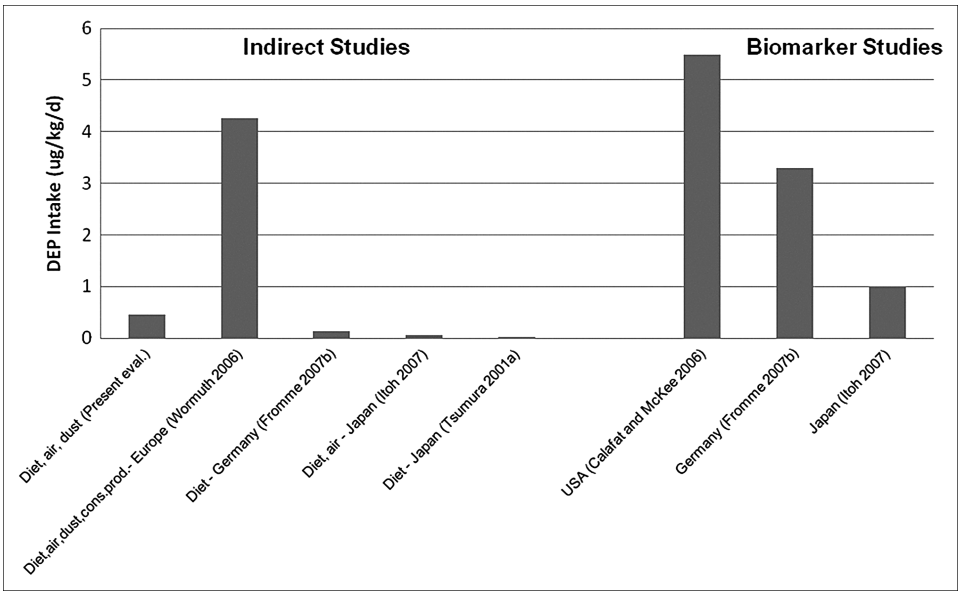

Figure 1. Estimates of median DEP intake to adults.

DEP. The indirect estimates of Wormuth *et al*. (2006) and Fromme *et al*. (2007b) are similar to the biomarker-based estimates for Germany (Fromme *et al*. 2007b; Wittassek *et al*. 2007b) and the indirect estimates for Japan (Tsumura *et al*. 2003; Itoh *et al*. 2007) are similar to the biomarker-based estimates (Itoh *et al*. 2007). The biomarker-based estimates suggest a higher intake in the USA, followed by Germany and then Japan.

The estimated intake of DEHP for 10 of the studies presented in Table 8 is presented in Figure 3. As shown in Figure 3, the present indirect estimates are higher than the other indirect estimates and higher than the biomarker-based estimates. This is due to the assumption of complete absorption following ingestion and/or elevated concentrations of DEHP in the composite food samples used in the calculations compared with the other indirect studies. That the intakes estimated by the other indirect studies and the biomarker studies are similar is shown in Figure 3. Although some regional differences were noted in the concentration data for DEHP, the biomarker estimates suggest similar intake in different regions. These regional differences in environmental concentrations may suggest greater use of DEHP in Europe versus North America and may support the slightly higher biomarker-based estimated intakes of DEHP for Germany (Wittassek *et al*. 2007b) versus the USA (Calafat and McKee 2006).

Based on both the indirect and biomarker methods, the volume and pattern of use of each PE vary with time and by region. As discussed, the biomarker-based estimates for several PEs (*e.g.,* DEP, DBP, DiBP, BBP) indicate that there are regional differences in exposure. In most cases, these differences are supported by regional differences in the concentrations of PEs in environmental media; however, there is generally insufficient data for all media (especially food) to generate region-specific

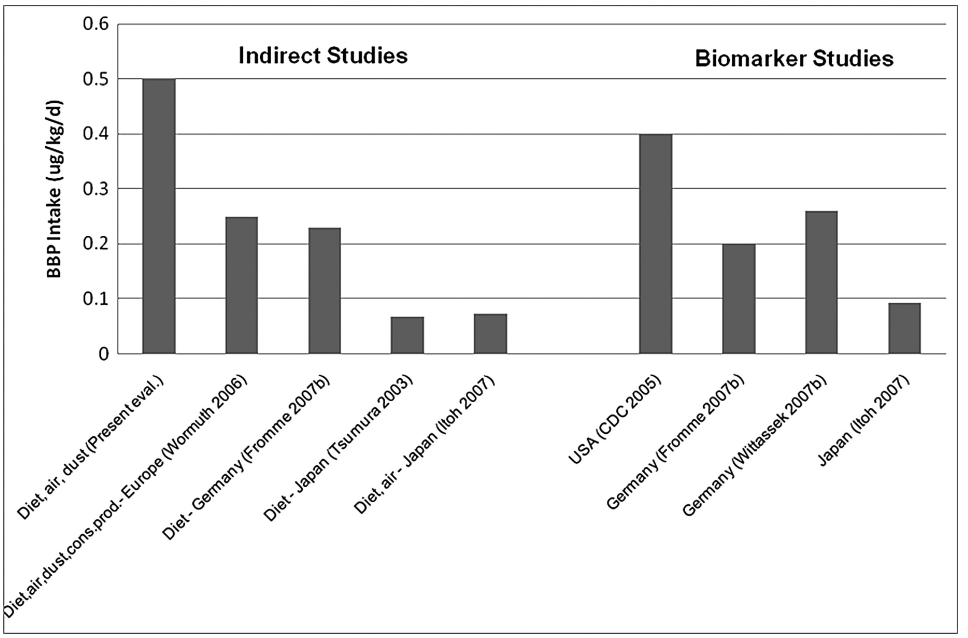

Figure 2. Estimates of median BBP intake to adults.

indirect estimates of exposure. Therefore, biomarker studies may have more value in assessing regional or temporal variations in exposure.

The importance of temporal changes in the use of PEs is shown in the work of Wittassek *et al.* (2007b) who analysed primary and/or secondary metabolites of DBP, DiBP, BBP, DEHP, and DiNP in the urine of adults in Germany. Archived

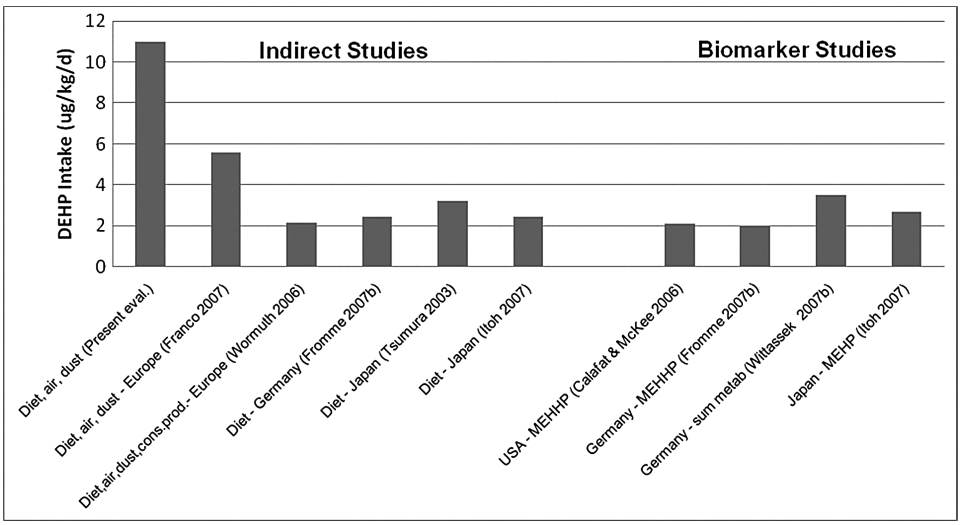

Figure 3. Estimates of median DEHP intake to adults.

samples, available for nine years in the period of 1988 to 2003, were analysed and the measurements were used to estimate the daily intake of the phthalate diesters. They found that between 1988 and 1993, the intake of DBP and DEHP was nearly constant, but decreased markedly after 1996. The intake of DiBP increased slightly over the period of study, while the intake of BBP decreased slightly. The intake of DiNP increased over the period of study. Female adults had significantly higher intakes of DBP and DiBP compared to male adults. Helm (2007) compared the estimated intake of DEHP from Wittassek *et al*. (2007b) for the years 1988 to 2003, with DEHP production data for Germany for the same time period and found a very high correlation between estimated intake and production. This suggests that changes in production volume should be considered when comparing intakes for different time periods.

The indirect estimates of Wormuth *et al*. (2006) incorporate absorption factors for ingestion, inhalation, and dermal contact with PEs. Minimum, mean, and maximum absorption factors are used for the ingestion pathways and, for some PEs, this range is very broad (ranging from 0.153 to 0.95 for DEHP). In contrast, the present evaluation has assumed 100% absorption for the ingestion and inhalation pathways (dermal contact is not included) and it is recognized that this will overestimate the intake for some PEs. This may also affect the relative importance of the various exposure pathways as the assumption of complete absorption may overestimate the relative contribution of food and dust ingestion compared to other pathways.

In summary, numerous estimates of the daily intake of PEs are available, using both indirect and biomarker methods. In many cases, these two methods agree with each other within an order of magnitude. Discrepancies between the two approaches are generally explained by one or more of the following factors: difficulties in accounting for use of consumer products in the indirect estimates, a lack of information concerning human absorption of PEs following ingestion, regional differences in the use of the PEs, and temporal changes in the use of PEs. Similarly, discrepancies when comparing the biomarker estimates with each other are generally explained by regional differences in concentrations of the parent diesters in the environment, suggesting different patterns of use, and temporal changes in use of PEs. No single method is identified as the preferred approach for estimating intake of all PEs; rather it is suggested that biomarker estimates be used for low molecular weight PEs for which it is difficult to quantify all sources of exposure and either indirect or biomarker methods be used for higher molecular weight PEs. The indirect methods are useful in identifying the sources of exposure while the biomarker methods can be used to quantify the amount of exposure. The indirect estimates would be improved by better characterization of the absorption factors and with current region-specific measurements of PEs in all media to which humans may be exposed.

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