Annex 2. Phthalates

di(2-ethylhexyl) phthalate (DEHP, CAS n° 000117-81-7, EINECS n° 204-211-0)
di-isononyl phthalate (DiNP, CAS n° 068515-48-0//028553-12-0, EINECS n° 271-090-9//249-079-5)
di-isodecyl phthalate (DiDP, CAS n° 068515-49-1//026761-40-0, EINECS N° 271-091-4//247-977-1)

Commission Regulation (EU) n° 10/2011 gives following specifications:

- The specific migration limit (SML) for DEHP is 1.5 mg/kg food. DEHP is only to be used as a plasticiser in repeated use materials and articles contacting "non-fatty" foods[1], or as a technical support agent in concentrations up to 0.1% in the final product.
- An SML(T) of 9 mg/kg is defined for the sum of DiDP and DiNP. They are only to be used as a plasticiser in repeated use materials and articles, in single-use materials and in articles contacting "non-fatty" foods[1] except for infant formulae and follow-on formulae as defined by Commission Directive 2006/141/EC or processed cereal-based foods and baby foods for infants and young children as defined by Commission Directive 2006/125/EC, and as a technical support agent in concentrations up to 0.1 % in the final product

Notice that Commission Regulation *(*EU*)* No 10/2011 *replaces Directive 2002/72/EC from 1 May 2011. Before this date use of DEHP, DiNP and DiDP was not restricted to materials and articles contacting "non-fatty" foods.*

2.1. Hazard identification

Phthalates are a class of synthetic compounds used widely in a variety of industrial and consumer applications. They were developed primarily as plasticizers, with the major use in polyvinyl chloride (PVC), which came onto the market nearly a century ago. Today, phthalates are found in building materials (such as flooring, roofing, paints, and adhesives), packaging materials (including food packaging), personal care products (such as cosmetics and lotions), medical devices (such as tubing and catheters), and the coatings of pills. It has been estimated that phthalate plasticizers comprise approximately 92% of plasticizer production in the world, with di(2-ethylhexyl) phthalate (DEHP) alone accounting for approximately 50% of this amount (Becker *et al*., 2009).
The industrial applications of phthalates are related to the length of their ester chain. Higher-molecular-weight phthalates, such DEHP, di-isononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP), are primarily used as plasticizers to soften PVC products, while the lower-molecular-weight phthalates, such as diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP) and butyl benzyl phthalate (BBzP), are widely used as solvents to hold color and scent in various consumer and personal care products (Cao, 2010).

The general structure of phthalates, diesters of ortho-phthalic acid, manufactured by reacting phthalic anhydride with alcohols of desired carbon-chain length, is shown in **figure 1**.[2] DEHP is produced by the esterification of phthalic anhydride with 2-ethyl-hexanol (ECB, 2008). DINP is a mixture of esters of phthalic acid with C8-C10 alkyl alcohols (C9 rich), of which two different DINP types are used, that differ in their isomer (ECB, 2003a). Regarding DIDP there are two types of C9-C11 (C10-rich) branched alkyl esters (ECB, 2003b).

[1] i.e. a food for which in migration testing only food simulants other than food simulants D1 (ethanol 50% v/v/) or D2 (vegetable oil) as laid down in Table 2 of Annex V to Regulation (EU) N° 10/2011 (hence, vegetables processed in the form of purée, preserves, pastes or in its own juice (including pickled and in brine), but not not e.g. sauces such as mayonnaise, salad creams and other oil/water mixtures, vegetables preserved in an oily or an alcoholic medium)

[2] Note that polyethylene terephtalate known as PET, has nothing to do, chemically and physically, with the chemical group of phthalates; their chemical structures are different. Phthalates are the esters of ortho-phthalic acid, while para-phthalic acid (terephthalic acid) and/or meta-phthalic acid (isophthalic acid) is used in PET. Unlike some PVC products that need to be plasticized with phthalates to make them more flexible, PET bottles should be as strong and rigid as possible and thus phthalates are not used in the PET polymer (Cao, 2010).

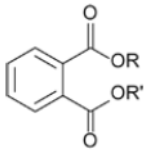

Figure 1. Generic chemical structure of phthalates. R and R´ are the same or different alkyl or aryl groups (e.g. ethyl groups for DEP and 2-ethylhexyl groups for DEHP)

For more information on e.g. the physico-chemical properties, the produced tonnage, uses, etc. reference is made to the risk assessment reports of the European Chemicals Bureau (ECB) for DEHP (ECB, 2008), DiNP (ECB, 2003a) and DiDP (ECB, 2003b).

2.1.1. Sources of exposure

Phthalates have become ubiquitous environmental contaminants due to volatilization and leaching from their widespread applications (Cao, 2010; Heudorf *et al*., 2007). **Figure 2** gives an overview of different possible sources of consumer exposure to phthalates. Dietary ingestion is regarded as the major pathway of exposure of the general population, particularly for the long-chain phthalates such as DEHP. For the short-chained phthalates inhalation might be an important route of exposure as well. Small children might be exposed via ingestion (house dust) and dermal contact with toys and consumer products (e.g. school supplies) (Cao, 2010; Wittasek *et al.*, 2010; Becker *et al*., 2009).

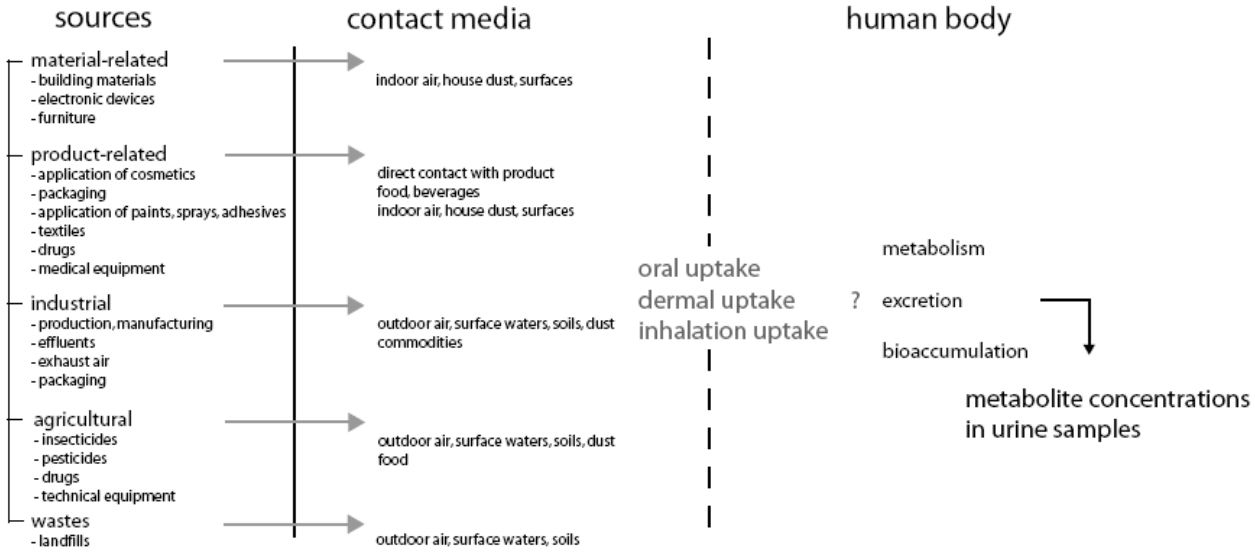

Figure 2. Possible sources of consumer exposure to phthalates (Wormuth *et al.*, 2006)

2.2. Hazard characterization

The acute toxicity of phthalates is very low with LD_{50} values[3] of 1–30 g/kg bw and higher (Heudorf *et al*., 2007; ECB, 2008 & 2003 a,b).
In short- and long-term rodent studies, dose-related adverse effects were found in liver, kidney, and – for selected phthalates – also in thyroid gland tissue and testes. Significant differences could be detected in different species and between males and females (Heudorf *et al*., 2007; Calafat & McKee, 2006).

[3] Lethal dose for 50% of the test animals

According to an evaluation of the International Agency for Research on Cancer (IARC), there is "sufficient evidence" in experimental animals but "inadequate evidence" in humans for the carcinogenicity of DEHP. Overall, the IARC evaluated DEHP as ''not classifiable as to carcinogenicity in humans'' (Group 3) (IARC, 2000). Although DiNP and DiDP are considered as animal carcinogens, there is no concern for a potential carcinogenic effect in humans. Neither the IARC nor the NTP (National Toxicology Program) has evaluated DiNP or DiDP with respect to human carcinogenicity (CDC, 2011).

All phthalates have been tested negative for mutagenicity and / or genotoxicity (Heudorf *et al.*, 2007; ECB, 2008 & 2003 a & b).

Phthalates are often classified as endocrine disruptors or hormonally-active agents because of their ability to interfere with the endocrine system in the body (U.S. EPA, 2007). Mechanisms of action differ among the phthalates, but several have anti-androgenic activity that can cause developmental toxicity, especially in males (Calafat & McKee, 2006). Although most reproductive tract abnormalities induced by phthalates occur at doses well above the estimated intake of the general population, the resemblance of phthalate effects with common human male reproductive disorders has raised concerns of a possible link between phthalate exposure and human disease. Moreover, recent experimental results indicate that biological changes can also be induced at low, human relevant doses and that different active phthalates can have cumulative effects. However, uncertainties in the epidemiological data base, difficulties in animal to human extrapolations and the lack of knowledge on the significance of low-dose effects for human health preclude a better understanding of the real risks for humans (Martino-Andrade & Chaoud, 2009).
According to Annex I of Council Directive 67/548/EEC, DEHP is classified into Category 2; R60-61, as toxic to reproduction (ECB, 2008)[4]. There is no classification for DiNP and DiDP.

2.2.1. Toxicokinetics

Phthalates are lipophilic compounds that appear not to bioaccumulate. After exposure, phthalates are metabolized and excreted with an elimination half life of ~8-10 hours in adults. Although the compounds are reported to be rapidly metabolized, concentrations in the body appear to remain fairly stable due to ongoing exposure.
After ingestion, the phthalate diesters are cleaved into the respective hydrolytic monoesters. In a second step, the alkyl chain of the resulting hydrolytic monoesters may further metabolize to more hydrophilic oxidative products. These metabolites can be excreted unchanged or can undergo phase II biotransformation to glucuronide conjugates. Metabolites and not the parent diesters are likely the bioactive species (Calafat & McKee, 2006; Mikula *et al.*, 2005).
Human metabolism studies have shown that the simple monoesters are the major urinary metabolites of the short-chain phthalates such as DnBP, DiBP or BBzP. Their urinary excretion represents approximately 70% of the oral dose. In the case of the long-chain phthalates such as DEHP, DiNP, and DiDP, the major share of the simple monoester is further metabolized to produce a number of oxidative metabolites (alcohols, ketones and carboxylic acids). Only between 2 and 7% of the dose is excreted as the simple monoester for these long-chain phthalates. The secondary, oxidized metabolites that are particularly formed by o-, o-1- and X-oxidation are the main metabolites excreted in human urine (Wittassek *et al.*, 2010; Koch & Calafat, 2009).
For the oral exposure route of DEHP, DiNP and DiDP the ECB selected a human systemic bioavailability of 50% and of 100% to calculate the internal exposure of adults and children respectively (ECB, 2008, 2003a&b).

[4] see also REACH website: http://www.reach-compliance.eu/english/legislation/docs/launchers/launch-annex-1-67-548-EEC.html

2.2.2. Toxicological Reference doses

Table 1 gives the exposure limit values for the considered phthalates established by the European Food Safety Agency (EFSA). The possibility of cumulative effects resulting from multiple exposures however, has raised additional concerns and needs to be addressed (ECB, 2008).

Table 1. Tolerable daily intakes (TDI) for phthalates established by the EFSA

Phthalate	CAS n°	TDI * (µg/kg bw/day)	Toxicological endpoint	Ref.
Di(2-ethylhexyl) phthalate (DEHP)	117-81-7	50	developmental and testicular toxicity in rats	EFSA 2005a
Diisononyl phthalate (DiNP)	28553-12-0 68515-48-0	150**	liver effects	EFSA 2005b
Diisodecyl phthalate (DiDP)	26761-40-0 68515-49-1			EFSA 2005c

* deduced from the NOAEL (no observed adverse effect level) by applying an uncertainty factor of 100; ** group-TDI for DiNP + DiDP based on related chemical structure and common mode of action (i.e. peroxisome proliferation in rodent liver)

2.3. Exposure assessment

2.3.1. Phthalate levels migrating from the packaging to food

a) Belgian monitoring data

Levels of DEHP, DiNP and DiDP were measured in various foodstuff packed in glass jars with PVC-lined metal lids, sampled on the Belgian market within the framework of the control programme of the FASFC. The analyses were performed in the laboratory of the Scientific Institute for Public Health (IPH) by means of a combined gas chromatographic/mass spectrometric (GC/MS) technique. In 2011 and 2012, phthalates were measured by Eurofins-Berlin. This implied an increase of the limit of quantification or LOQ from 0.05-0.1 to 1 mg/kg for DEHP, and from 0.5 -1 mg/kg to 5 mg/kg for DiNP and DiDP. Both laboratories were ISO 17025 accredited.

Between 2008 and 2012 a total of 161 food samples and of 130 baby food samples were analyzed. A statistical comparison of the results obtained between 2008 and 2012 showed no increase or decrease of the phthalate levels in function of time.[5, 6] Consequently, results obtained between 2008 and 2012 could be pooled for assessing the exposure. For DiNP, almost all results are below the LOQ, except for 2 vegetable (2.4 mg/kg, 2010; 25 mg/kg, 2011) and 2 fish samples (2.0 mg/kg, 2008 and 1.9 mg/kg, 2009). Only 1 cheese sample (1 mg/kg, 2010) and 1 vegetable sample (>200 mg/kg, 2011) exceed the LOQ for DiDP. Levels of DEHP measured in the different food categories considered for further evaluation of the exposure, are presented in **table 2**.

In addition, 2 non-food samples were analyzed in 2008, namely of a plastic film and of vinyl gloves. Results were in conformity for the 3 phthalates (< 0.60 mg/dm^2 for DEHP and < 1.0 mg/dm^2 for DiNP and DiDP).

[5] Statistical analysis was performed with SPSS 11.0 for Windows (SPSS Inc., USA). The Kolmogorov-Smirnov test was used to test normality. When data were normally distributed, means were compared using analysis of variance (one-way ANOVA) and Post Hoc Multiple Comparison tests (Tukey when variances were equal or Games-Howell when variances were unequal). Homogeneity of variances was tested using the Levene test. In case of non-normality Kruskal-Wallis test was used.

[6] Significant differences were observed in the food category 'sauces' between results obtained before and after 2011, which are mainly related to the higher LOQ of the analytical method applied from 2011 on.

Table 2. Levels of DEHP (mg/kg) analyzed in different food groups on the Belgian market (FASFC pooled data from 2008 - 2012)

		Baby food			**Sauces**		**Vegetables-**		
	total	*vegetables*	*fruit*	**total**	*pesto*	*other*	**in-oil**	**Cheese-in-oil**	**Fish-in-oil**
n	130	*84* [c]	*14* [c]	76	*15*	*61*	51	21	13
# > LOQ	23	*16* [c]	*6* [c]	19	-	*19*	12	6	3
median[a]	0.09	*0.05*	*0.35*	0.06	*0.05*	*0.06*	0.50	0.05	0.05
	(0.00-0.10)	*(0.00-0.10)*	*(0.00-0.35)*	(0.00-0.10)	*(0.00-0.10)*	*(0.00-0.10)*	(0.00-1.00)	(0.00-0.10)	(0.00-0.10)
average [a]	0.29	*0.21*	*0.37*	0.21	*0.17*	*0.23*	0.47	0.18	0.38
	(0.08-0.50)	*(0.08-0.33)*	*(0.25-0.50)*	(0.03-0.40)	*(0.00-0.33)*	*(0.04-0.41)*	(0.21-0.73)	(0.13-0.24)	(0.25-0.52)
upper average [b]	0.44	*0.41*	*0.58*	0.12	-	*0.12*	0.90	0.46	1.07
P90 [a]	0.50	*0.50*	*0.87*	0.50	*0.50*	*0.50*	0.50	0.70	1.10
	(0.11-1.00)	*(0.09-1.00)*	*(0.87-1.00)*	(0.07-1.00)	*(0.00-1.00)*	*(0.08-1.00)*	(0.43-1.00)	(0.70-0.70)	(1.10-1.16)
P95 [a]	0.80	*0.80*	*0.90*	0.50	*0.50*	*0.50*	1.15	0.70	1.24
	(0.80-1.00)	*(0.80-1.00)*	*(0.90-1.00)*	(0.09-1.00)	*(0.00-1.00)*	*(0.10-1.00)*	(1.15-1.15)	(0.70-0.90)	(1.24-1.24)
P97.5 [a]	0.90	*0.90*	*0.90*	0.50	*0.50*	*0.50*	2.50	0.80	1.27
	(0.90-1.00)	*(0.90-1.00)*	*(0.90-1.00)*	(0.11-1.00)	*(0.00-1.00)*	*(0.14-1.00)*	(2.50-2.50)	(0.80-0.95)	(1.27-1.27)
max [a]	0.90	*0.90*	*0.90*	1.00	*0.50*	*1.00*	3.10	0.90	1.30
	(0.90-1.00)[d]	*(0.90-1.00)*[d]	*(0.90-1.00)* [d]		*(0.00-1.00)* [d]			(0.90-1.00)[d]	

[a]: for results < LOQ a concentration of LOQ/2 is assumed (i.e. 'middle bound' scenario); lower (< LOQ = 0) and upper (< LOQ = LOQ) bound scenarios between brackets
[b]: average calculated by omitting results < LOQ, according to EFSA, 2006
[c]: for 32 samples of baby food the type (fruit/vegetable) is not recorded
[d]: due to the use of a method with a higher LOQ in 2011 and 2012 compared to former years

b) Discussion

Migration of plasticizers from food packaging and processing products is the major contamination path of phthalates into foods. Plasticizers are not bonded chemically to the polymer and can migrate when they are in contact with foods, especially fatty foods. Possible sources are PVC tubing, used in process equipment or for transfer of liquid food products between tanks (e.g. milk), the use of PVC gloves in the preparation of foods (which can contain up to 41.0% of DEHP and 74.8% of DiNP), thin packaging film or cling film used for wrapping a variety of foods, printing inks used for flexible food packaging, adhesives or glues used for paper and plastics, aluminium foil-paper laminates and closure seal in bottles (Cao, 2010; EFSA, 2005a; ECB, 2003a). Typical formulations of DEHP in flexible PVC-products are 30% (w/w) (ECB, 2008).
It has been established that the amount of phthalates found in foods or meals depends on the initial contamination of ingredients used in the production of the food, food production technologies, the period of storage (the time of contact with packaging materials), storage temperatures, ways of preparing dishes, the fat content of foods, and the type of packaging material used (Mikula *et al.*, 2005).

Several approaches to reduce leaching and migration of phthalates have been researched, such as the surface modification of polymers, encapsulation of phthalates, and the development of alternative plasticizers (Chung *et al*., 2009; Rahman & Brazel, 2004).

Regarding the Belgian data presented in **table 2**, DEHP is observed in 18% of the baby food samples, ranging from 0.05 to 0.9 mg/kg. Regarding the other food categories, DEHP is detected in 25% of the food samples. The SML of 1.5 mg/kg was only exceeded in one vegetable sample (3.1 mg/kg in garlic-in-oil)[7]. The food category vegetable-in-oil showed on average the highest DEHP levels.
The ubiquitous presence of phthalates in the environment poses an analytical challenge known as the phthalate blank problem. Phthalates are detected even in the cleanest laboratory chemicals, sampling equipment and analytical apparatus. These circumstances hamper the reliable quantification of phthalates in real-life scenarios. As a result, all ambient monitoring data and all data in general related to measurements of low levels of phthalate diesters have to be interpreted with utmost caution because of possible external contamination (Wittassek *et al.*, 2010). In so far a comparison can be made (e.g. influence of analytical method, foods considered in the food category, also inclusion of food not packed in glass jars, etc.), Belgian DEHP data are in the range of levels reported in literature. Wormuth *et al.* (2006) discussing the different exposure routes of phthalates retained for further evaluation of DEHP an average (range) value of 0.283 (0-1.64) mg/kg for commercial infant food, of 0.496 (0.041-1.23) mg/kg for cheese, of 0.013 (0.0023-0.29) mg/kg for fish/seafood and of 0.14 (0-0.14) mg/kg for vegetables based on reports in literature. In a review of Cao (2010) a range of 0.1-0.6 mg/kg is given for baby food, of 0.2-16.8 mg/kg for cheese, and of 40-160 µg/kg for canned fish.

2.3.2. Exposure to phthalates migrating from the packaging

a) Exposure via migration from PVC lined lids (Belgian data)

Since DiNP and DiDP were detected only in 4 and 2 samples respectively of the 291 food samples, an exposure assessment seems rather meaningless. Regarding DEHP, similarly to ESBO the P90 migration value is used as a conservative estimate of the concentration for estimating the chronic exposure of Belgian adults to DEHP. Besides the P90, calculations are also made for the average, the upper average (i.e. omitting the results with a concentration < LOQ) and the P95. Regarding the consumption, the P95 value for the whole population and for 'consumers only' from the Belgian Food Consumption Survey (BFCS) of 2004 (Devriese *et al.*, 2005) are considered (**table 3**). For infants (< 1 year) consumption data used in an EFSA opinion regarding the ESBO intake of infants (EFSA, 2004) are taken (**table 4**).

[7] Note: this is the same sample for which a high ESBO level was observed as well (see annex 2)

b) Exposure via migration from PVC films (Belgian data)

For DEHP, DiNP and DiDP, only 1 sample of cling film for food wrapping was analysed and showed no detectable phthalate level. Phthalates are not so much used in PVC cling films, particularly not intended for wrapping fatty food. Currently, polyadipates (replacing DEHA) rather than phthalates are used *(*internal communication, 23/10/2012).

c) Discussion

Levels of DiNP and DiDP are very low in the analyzed food samples, with ~ 98% of the samples having a level < LOQ. However, the tenfold higher LOQ of the analytical method used in 2011 and 2012 compared to the previous years, can have a significant influence on the conclusions of the risk assessment. Although DiNP and DiDP were not detected in baby food, a risk cannot be excluded for the results 2011-2012. Considering the group-TDI of 150 µg/kg bw per day and the P95 consumption value for infants of 53 g/kg bw per day, baby food can have maximally a DiNP + DiDP level of 2.8 mg/kg to exclude a risk, whereas the LOQ of the analytical method applied in 2011 and 2012 is almost twice as high.

The exposure of adults to DEHP is 5 to 50 times lower than the TDI for DEHP, even when only the consumers and not the whole population is considered. Omission of the results of 2011 and 2012 results in much lower exposures estimates. The exposure estimates for infants are much higher. Their exposure can in some cases exceed the TDI, particularly when other exposure routes are taken into account. Omission of the 2011-2012 results does not really affect the outcome of the risk evaluation.

In a BfR risk assessment, three different scenarios were elaborated for calculating the exposure to DEHP, DiNP and DiDP via the consumption of pesto, pasta sauce, dressing and pickled vegetables in jars (BfR, 2005 & 2007), namely (i) all considered foods have each the maximum measured phthalate concentration and are packed in jars with twist-off closure, (ii) a varying percentage of the considered foods are packed in jars with twist-off closure, and (iii) using the empirical distribution of all the measured phthalates concentrations. In scenarios (i) and (ii) the P95 consumption of the whole population and of consumers only were used. In scenario (iii) the whole distribution of consumption values was taken into account (probabilistic approach).
For the worst-case assumption that all considered foods had each the maximum measured phthalate concentration (i.e. DEHP: 195 mg/kg pesto; DiNP + DiDP: 86 mg/kg pasta sauce, 405 mg/kg vegetables-in-oil and 103 mg/kg pesto) and were all packed in jars with twist-off closures, the TDI was significantly exceeded for the most highly exposed individuals (P95, consumers only), up to 2.5-fold for DEHP and up to 2.4-fold to even up to 4.8-fold for children aged 4-9 years for the sum of DINP and DIDP. Assuming different percentages of in jar packed food, had only a minor impact on the exposure (intake estimates remained largely unchanged at a packing fraction >10%). Additionally, even with a more customized intake estimate (probabilistic calculation) the TDI was still exceeded for DEHP highly exposed individuals. Application of the first scenario on the Belgian data for DEHP results in an exposure of maximum 20% of the TDI (6.3 µg/kg bw/day for the population and 10.0 µg/kg bw/day when considering consumers only). Consequently, the other scenarios were not elaborated. Notice however, the high maximal levels measured in the BfR study. In this study as well, some relatively high levels were measured for DiNP and DiDP, although more than 98% of samples have a DiNP or DiDP level below the LOQ. Since further studies are needed to determine the relevance of such high concentrations that can be found in some studies, it was opted in the present study to use the P90 (P95) phthalate concentration instead of the maximum value for calculating the worst-case scenario.
Although the exposure of adults is far below the TDI of 50 µg/kg bw per day, it has to be emphasized that this report considers the presence of phthalates in food due to migration from the packaging only, more specifically glass jars with twist-off closures. As phthalates are ubiquitous, environmental contaminants, also other food categories should be considered in order to obtain a more correct estimate of the exposure through food intake. **Table 5** gives an overview of some dietary exposure studies of DEHP, DiNP and DiDP reported in literature.

Table 3. Exposure of adults to DEHP (µg/kg bw per day)[a] through in glass jars packed food (deterministic approach, based on FASFC control data (2008 - 2012) and BFCS data (Devriese *et al.*, 2005))

		Exposure population					Exposure consumers only				
		median	average	upper average [b]	P90	P95	median	average	upper average [b]	P90	P95
Sauces	**total**	0.10 (0.00-0.16)	0.34 (0.05-0.63)	0.19	0.80 (0.10-1.59)	0.80 (0.15-1.59)	0.11 (0.00-0.18)	0.39 (0.06-0.73)	0.22	0.92 (0.12-1.84)	0.92 (0.17-1.84)
	pesto	*0.00 (0.00-0.00)*	*0.00 (0.00-0.00)*	-	*0.00 (0.00-0.00)*	*0.00 (0.00-0.00)*	*0.03 (0.00-0.05)*	*0.09 (0.00-0.18)*	-	*0.27 (0.00-0.54)*	*0.27 (0.00-0.54)*
	other	*0.10 (0.00-0.16)*	*0.36 (0.06-0.66)*	*0.19*	*0.79 (0.13-1.59)*	*0.79 (0.16-1.59)*	*0.11 (0.00-0.18)*	*0.41 (0.07-0.76)*	*0.22*	*0.92 (0.15-1.84)*	*0.92 (0.18-1.84)*
Vegetables-in-oil		0.64 (0.00-1.28)	0.60 (0.27-0.93)	1.15	0.64 (0.55-1.28)	1.47 (1.47-1.47)	0.96 (0.00-1.91)	0.90 (0.40-1.39)	1.72	0.96 (0.82-1.91)	2.20 (2.20-2.20)
Cheese-in-oil		0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.04 (0.00-0.08)	0.15 (0.11-0.20)	0.37	0.58 (0.58-0.58)	0.58 (0.58-0.74)
Fish-in-oil		0.03 (0.00-0.06)	0.22 (0.14-0.29)	0.60	0.62 (0.62-0.65)	0.70 (0.70-0.70)	0.06 (0.00-0.11)	0.44 (0.28-0.60)	1.21	1.25 (1.25-1.32)	1.41 (1.41-1.41)
SUM		**0.77 (0.00-1.50)**	**1.16 (0.46-1.85)**	**1.94**	**2.06 (1.27-3.52)**	**2.97 (2.32-3.76)**	**1.17 (0.00-2.28)**	**1.88 (0.85-2.92)**	**3.52**	**3.71 (2.77-5.65)**	**5.11 (4.36-6.19)**

[a]: for results < LOQ a concentration of LOQ/2 is assumed (i.e. 'middle bound' scenario); lower (< LOQ = 0) and upper (< LOQ = LOQ) bound scenarios between brackets
[b]: average calculated by omitting results < LOQ, according to EFSA, 2006

Table 4. Exposure of infants (4-12 months) to DEHP (µg/kg bw per day) through in glass jars packed baby food (deterministic approach, based on FASFC control data (2008 - 2012) and consumption data used in EFSA opinion, 2004)

Consumption (g/kg bw/day)	Exposure 2008-2012 (µg/kg bw/day)					*Exposure 2008-2010 [f]* (µg/kg bw/day)	
	median	average	upper average [b]	P90	P95	*average*	*P95*
53 [c]	4.51 (0.00-5.30)	15.34 (4.15-26.53)	23.46	26.50 (5.83-53.00	42.40 (42.40-53.00)	*8.37*	*47.70*
43 [d]	3.66 (0.00-4.30)	12.45 (3.37-21.53)	19.03	21.50 (4.73-43.00	34.40 (34.40-43.00)	*6.79*	*38.70*
28 [e]	2.38 (0.00-2.80)	8.10 (2.19-14.02)	12.39	14.00 (3.08-28.00	22.40 (22.40-28.00)	*4.42*	*25.20*

[a]: for results < LOQ a concentration of LOQ/2 is assumed (i.e. 'middle bound' scenario); lower (< LOQ = 0) and upper (< LOQ = LOQ) bound scenarios between brackets; [b]: average calculated by omitting results < LOQ, according to EFSA, 2006; [c]: P95 consumers Donald study (Germany); [d]: P97.5 for "consumers", MAFF study (UK); [e]: average 4-6 months, Afssa (Anses) study (France); [f]: given the two times higher LOQ of the analytical method applied in 2011 and 2012 and the relatively high amount of results < LOQ, the exposure was also calculated with omission of the 2011 and 2012 results

In a UK study a mean and a P97.5 intake of 2.5 and 5 µg/kg bw/day respectively was calculated for an adult of 60 kg (MAFF, 1996 cited by EFSA, 2005a). Only the 10 food groups which make a major contribution to dietary fat intakes were selected for the UK analysis. Among these, carcass meat, eggs, poultry and milk were analyzed for individual concentrations of phthalates since these four food groups accounted for approximately 85% of the estimated dietary intake of total phthalates.
In a Danish assessment main dietary sources of exposure were estimated to be leaf crops (53%), root crops (13%), milk (12%) and fish (10%). Given the high contribution of vegetables reported in this latter study, the exposure estimated in the UK study probably is an underestimation as it considered only animal products (EFSA, 2005a).

Table 5. Overview of some dietary exposure studies regarding di(2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP) reported in literature

Mineral water stored in PET and glass bottles (Italian)	DEHP	The contribution from drinking water is < 0.01% of the RfD of 0.02 mg/kg bw per day (EPA, 2006)	Montuori *et al.* (2008)
Vegetable oils (Italy)	DEHP DiNP	DEHP and DiNP intake by oil consumption accounts to 1% and 0.6% of the TDI (EFSA, 2005a,b) respectively	Nanni *et al*. (2011)
Infants - infant formulae (+ baby food) [1]	DEHP	13 and 8 µg/kg bw/day for 0-3 months and 6+months old resp. (used in RA[2])	ECB (2008)
		Infant formula: 9.8 and 3.9 µg/kg bw/day for < and > 6 months resp. Baby food: 19.6 µg/kg bw/day = total of 23.5 µg/kg bw/day (6-12 months)	Müller *et al*. (2003)
	DiNP	1.8-2.6 µg/kg bw/day for 0->6 months	ECB (2003a)
		2.4 and 1.8 µg/kg bw/day for 0-6 and >6 months resp.	MAFF (1996 & 1998) cited by EFSA (2005b)
	DiDP	1.8 - 2.4 µg/kg bw/day for 0->6 months	ECB (2003b)
		2.4 and 1.8 µg/kg bw/day for 0-6 and >6 months resp.	MAFF (1996 & 1998) cited by EFSA (2005c)
Infants - breast milk [1]	DEHP	6.2-2.4 µg/kg bw/day for 0-3 months and 3-12 months old resp. (worst case)	ECB (2008)
Toddlers [1]	DiNP	2.0-2.4 µg/kg bw/day for 0-3 years old used in RA[1]	ECB (2003a)
	DiDP	2.3-2.4 µg/kg bw/day for 0-3 years old used in RA[1]	ECB (2003b)
Children	DEHP	**Belgium: 3.8 µg/kg bw/day (P50, probabilistic) and 5.7 µg/kg bw/day (P95, probabilistic) for 2.5-6 years**	Sioen *et al.* (2012)
		26 µg/kg bw/day (1-6 years) 11 µg/kg bw/day (7-14 years)	Müller *et al*. (2003)
(Adolescents-) children (3-15 years)	DiNP	0.1 µg/kg bw/day used in RA[2]	ECB (2003a)
	DiDP	0.1 µg/kg bw/day used in RA[2]	ECB (2003b)
Adults	DEHP	**Belgium: 1.6 µg/kg bw/day (P50, probabilistic) and 3.0 µg/kg bw/day (P95, probabilistic) for ≥ 15 years**	Sioen *et al.* (2012)
		2.4 µg/kg bw/day (median) 4.0 µg/kg bw/day (P95) for 14-60 years	Fromme *et al.* (2007)
		2.5 µg/kg bw/day (mean) 5 µg/kg bw/day (P97.5)	MAFF (1996) cited by EFSA (2005a)
		4.5 µg/kg bw/day	Müller *et al*. (2003)
		117 - 120 µg/kg bw/day (P95, max [DEHP])	BfR (2005)
	DiNP	< 0.17 µg/kg bw/day	MAFF (1996) cited by EFSA (2005b)
		5 µg/kg bw/day	Müller *et al*. (2003)
	DiDP	< 0.17 µg/kg bw/day	MAFF (1996 & 1998) cited by EFSA (2005c)
		3 µg/kg bw/day	Müller *et al*. (2003)
	DiNP + DiDP	90-150 µg/kg bw/day (P95, max [DiNP + DiDP])	BfR (2005)
Adult (total – food, water, air)	DEHP	1.93-18.8 µg/kg bw/day used in RA[1]	ECB (2008)

[1]: Infants = up to and including 11 months, toddlers = from 12 up to and including 35 months of age (EFSA, 2011; food consumption database); [2]: RA: risk assessment

d) PHTAL project

In the PHTAL project (Phthalates in food: inventarisation of their presence on the Belgian market, identification of contamination routes and exposure assessment for the Belgian population)[8] phthalates were identified in a wide range of foods purchased in Belgium; 400 food products, divided over 11 groups, were tested for eight phthalate compounds (DEP, DEHP, DiBP, DnBP, dimethyl phthalate or DMP, benzylbutyl phthalate or BBP, dicyclohexyl phthalate or DCHP, and di-n-octyl phthalate or DnOP). Hereto, phthalate extraction techniques were developed for high- and low-fat foods, water-based drinks and packaging materials.
DEHP was found in the highest concentration in almost every food group and appeared to be the most abundant phthalate compound, followed by DiBP, DnBP and BBP (Fierens *et al.*, 2012a). DEHP concentrations determined in the different food groups during the first measurement campaign are presented in **table 6**. A second measurement campaign was performed focusing on remarkable results obtained during the first campaign and possible contamination routes were looked at. Data of both measurement campaigns (572 food products in total) were used to assess the exposure of the Belgian population through food based on different scenario's (e.g. effect of preparation, maximum concentration, probabilistic, etc.) (Sioen *et al.*, 2012). The intake of DEHP was the highest (**table 5**), followed by DiBP. For DEHP, the 99th percentile of the intake distribution of preschool children in the worst case scenario (i.e. 37.5 µg/kg bw/day using the maximum concentration for each food group) was equal to 80% of the TDI (i.e. 50 µg/kg bw/day), which is not negligible, since other exposure routes of DEHP exist for children as well (e.g. mouthing of toys). Bread was the most important contributor to the DEHP intake. Since the origin of this phthalate in bread remains unclear, this may deserve further exploration. The dietary intakes of BBP, DnBP and DEP of Belgian preschoolers (2.5 – 6.5 years old) and adults (≥ 15 years old) were far below the TDI of 500, 10 and 500 µg/kg bw/day, respectively, and thus no health risks were to be expected (Sioen *et al.*, 2012).
Compared to the DEHP exposure calculated in the PHTAL project, results obtained in the present study are rather high considering they are only based on DEHP migration levels from lids of glass jars. The present study must be viewed as a screening of the situation, based on worst-case assumptions (e.g. all food contained the same DEHP level). The exposure determined in the PHTAL project is more refined, as it is based on levels in various food products taking the consumption and DEHP concentration distributions into account (i.e. probabilistic approach).

Table 6. DEHP concentrations (mg/kg fresh weight) determined in food sold on the Belgian market (Fierens *et al.*, 2012a).

Food group	# of samples	# of positive samples	median	min - max
Fruits and vegetables	27	13	ND	ND–1.413
Milk and dairy products	56	52	0.028	ND–0.743
Cereals and cereal products	47	45	0.063	ND–1.073
Meat and meat products	22	22	0.045	0.010–0.433
Fish and fish products	18	17	0.086	ND–5.932
Fat and oils	26	18	0.102	ND–1.827
Snacks	28	26	0.035	ND–0.308
Condiments and sauces	40	39	0.044	ND–2.154
Miscellaneous	22	15	0.016	ND–0.718
Baby food	17	16	0.022	ND–0.067
Beverages	85	48	0.000	ND–0.011
Packaging materials (ng/cm^2)[a]	12	12	32.0	1.1–319

ND: not detected, LOQ values depended on the type of food with an average LOQ of 0.145 mg/kg fat and of 0.008 mg/kg fat for high- and low-fat food respectively, and of 0.03 x 10^{-3} mg/kg fresh weight for aqueous food
[a]: including cardboard, tetra brick and plastic

Additionally, the project considered the effect of cooking (boiling, steaming, (deep-)frying or grilling) on the level of the eight phthalates in starchy products, vegetables, meat and fish (Fierens *et al.*, 2012b). In general, phthalate concentrations in foods declined after cooking, except in vegetables, where almost no effect was seen. Several factors influence the phthalate concentration after processing. A

[8] Performed at VITO (Vanermen G.) – UGent (S. De Henauw) and funded by the Belgian Federal Public Service of Health, Food Chain Safety and Environment (Contract No.: RT/08/1 PHTAL; 01/01/09 – 31/12/11)

decrease of phthalate concentrations can be due to a degradation of phthalates during cooking into phthalic acid with monoester phthalates as intermediates (more volatile compounds can also evaporate). Additionally, some food products lose fat during processing and phthalates, which are lipophilic and therefore tend to concentrate in the lipid phase of foodstuffs, can be removed together with the fat phase (e.g. minced meat). Phthalate concentrations can additionally be 'diluted' because food products take up water during cooking (e.g. pasta, rice). An increase of phthalate concentrations on the other hand, is also possible. This can be the result of migration from the cooking utensils used (e.g. coatings of non-stick cookware products) or from (contaminated) fat uptake during cooking. Some foodstuffs also lose weight during cooking (e.g. potatoes), causing a 'concentration' of the phthalate levels.

2.3.3. Phthalate exposure through other routes than food

The widespread exposure of the general human population has been demonstrated in several studies in the USA and Europe (Wittassek *et al.*, 2010; Koch & Calafat, 2009; Heudorf *et al*., 2007). In general, children are exposed to higher phthalate doses than adults. For the youngest children, additional or specific phthalate exposure routes and sources might be of importance due to children's behavioral patterns (e.g. crawling, mouthing habits). For the low-molecular weight phthalates, which can be found in personal-care products, associations between product use and hydrolytic monoester excretion both in children and adults have been reported (Koch & Calafat, 2009). In addition, high exposures can occur through some medications or medical devices (Wittasek *et al.*, 2010).
Wormuth *et al*. (2006) considering the different phthalate exposure routes estimated age-specific ranges (infants, toddlers, teenagers, and male and female teenagers and adults) in daily consumer exposure to eight phthalates in Europeans by a probabilistic scenario based approach. In this study, 15 different oral, dermal and inhalation exposure pathways were considered. Exposure media concentrations where they were available, were used and this often meant using data from countries outside of Europe and from studies having been conducted sometimes in the past decades. Exposure models and assumptions were also determined from a diverse range of literature, with varying degrees of certainty. In contrast to most other studies, also organ and situation-specific uptake rates were used for each pathway. With this range and diversity, for DEHP a medium exposure of ~2.7 µg/kg bw/day (P95 = 15.5 µg/kg bw/day) and of 1.78 µg/kg bw/day (P95 = 15.8 µg/kg bw/day) were quantified for adults and children respectively. The exposure value for adults was very similar to exposure levels determined by biomonitoring approaches. For DiNP and DiDP, clearly lower daily intakes were estimated with median exposure levels between 0.4 and 0.01 µg/kg bw/day.

2.3.4. Internal exposure: Biomonitoring [9]

Instead of characterizing exposure via a pathway analysis, other exposure assessments have focused on the measurement of phthalate metabolites in urine. Based on the varied toxicities of phthalates, internal dose measurements of specific phthalates and their monoester metabolites are important for exposure assessment, and ultimately for accurate human risk assessment. The major metabolites of DEHP are mono(ethylhexyl)phthalate (MEHP) and 2-ethylhexanol (2-EH) (ECB, 2008). For DiNP and DiDP, it can be assumed that the most relevant intermediate metabolite is monoisononyl and monoisodecyl phthalate respectively (ECB, 2003a & b).
Interpretation of biomonitoring studies must be conducted with caution since important differences may exist in study design (e.g. seasonal versus throughout-the-year collection, first-morning voids versus non-first-morning voids, convenience sampling versus nationally representative sampling). Second, the metabolite pattern is different for the short-chain phthalates compared with the long-chain phthalates. Third, when comparing urinary metabolite concentrations measured in subjects of different age, one has to make allowance for the biometric, physiological and potential toxicokinetic differences (e.g. children excrete generally higher urine volumes than adults and the same metabolite concentrations in the urine of young children, older children and adults therefore undoubtedly reflect a

[9] Human biomonitoring determines internal exposure (i.e. body burden) by measuring the chemicals, their metabolites or specific reaction products in human specimens (e.g. urine or blood). Biomonitoring represents an integral measure of exposure from multiple sources and routes.

higher body burden to phthalates per kg bw in the young children compared with the older children and adults). Fourth, creatinine excretion – often used as a corrective for urine dilution – is age and gender dependent. Fifth, oxidative metabolism was found to be age-dependent to a certain degree and slightly favoured in children compared with adults (Wittassek *et al.*, 2010).
Based on a review of biomonitoring studies, US and German data indicate that total phthalate exposure has decreased to a certain extent during the last decades. Exposure to some phthalates, e.g. DiBP and DiNP is on the rise, which can be explained by the substitution of DnBP with DiBP and DEHP with DiNP/DiDP (Wittassek *et al.*, 2010). Median daily intake values for DEHP deduced from urinary metabolite concentrations are in the range of 0.6 to 7.8 µg/bw bw per day (P95 between 3.1 and 25.2 µg/bw bw per day) – depending on metabolites analyzed. For DiNP a median intake in the range of <LOD to 0.7 µg/kg bw per day (P95 between 1.1 and 4.38 µg/kg bw per day) was back-calculated from urinary metabolite levels (Wittassek *et al.*, 2010).
Depending on the specific phthalate metabolite, children are exposed on an up to four fold higher level than adults. The investigation of the concentrations in different age-groups shows that the metabolite levels decrease with increasing age. This result gives reason for concern because the newborn and young children are said to be most sensitive to endocrine effects. Moreover, the concentrations of the phthalate metabolites in urine are correlated which indicates that children are exposed to a multiple mixture of phthalates simultaneously (Becker *et al*., 2009). The potential necessity of a cumulative risk assessment has already been addressed in both Europe (ECB, 2008) and the US (NRC, 2008).

2.3.5. Cumulative exposure assessment

In the report “Phthalates and cumulative risk assessment: The tasks ahead” of the US National Research Council, Committee on the Health Risks of Phthalates (NRC, 2008) an approach for cumulative risk assessment of phthalates (and other environmental chemicals) is suggested based on the common adverse outcomes of these chemicals (effect on the development of the male reproductive system, i.e. antiandrogens). A cumulative TDI value for all endocrine active phthalates is used instead of individual TDIs.
In addition, it has to be remarked that phthalates have been shown to act in a dose-additive or synergistic manner with other anti-androgens/endocrine disrupters (Wittassek *et al.*, 2010).

2.4. Risk evaluation

The exposure of Belgian adults to DEHP migrating into food packed in glass jars and bottles with metal lids sealed with PVC gaskets is very low. For DEHP exposures 5 to 50 times lower than the TDI of 50 µg/kg bw/day were observed. Even the worst case scenario where all considered foods had the P90 measured phthalate concentration and were frequently or highly consumed, resulted in an exposure of maximum 15% of the TDI. For infants on the other hand, the exposure via baby food packed in jars was much higher. In some cases an occasional exceeding of the TDI can be expected for DEHP, especially when other exposure routes are taken into account. Moreover, it has been reported that endocrine active phthalates could act synergistically with other endocrine disruptors.
DiNP and DiDP were detected in only ~ 2% of the analysed samples. Nevertheless, given the high LOQ of the analytical method used in 2011 and 2012, a risk for infants cannot be totally excluded in case of a high consumption.

In the present study, only the exposure through the migration from the metal lids sealed with PVC gaskets into food packed in glass jars and bottles was estimated. Other contamination routes of food were not considered, but discussed. Reference is made to the project PHTAL. In addition, exposure routes other than food were neither considered, but were briefly discussed.

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