



HBM4EU

science and policy  
for a healthy future

HORIZON2020 Programme  
Contract No. 733032 HBM4EU

## **SCOPING DOCUMENT**

**(1<sup>nd</sup> round of prioritization)**

**HBM4EU Priority Substance Group: Phthalates &  
Hexamoll® DINCH®**

**Chemical Group Leaders: Rosa Lange**

**Co-authors: Marike Kolossa-Gehring, Carolin  
Tschersich, Robert Barouki, Maria Uhl, Jana Klánová,  
Milena Horvat, Alessandro Alimonti, Denis Sarigiannis,  
Tiina Santonen, Erik Lebret, Greet Schoeters**

**Date: 07/01/2018**

**Document version: 3.1**

## 1. Prioritised substance group: Phthalates & Hexamoll® DINCH®

### 1.1. Background information

#### 1.1.1. Hazardous properties

Phthalates (or phthalate esters) and the non-phthalate substitute Hexamoll® DINCH® are a group of plasticizers with a production volume of millions of tons per year. Phthalates can cause a variety of adverse effects in humans and in laboratory animals (Koch and Calafat 2009, Mariana et al. 2016) of which the most prominent are the endocrine disrupting and reproductive effects. It has been shown that some phthalates, such as di(2-ethylhexyl) phthalate (DEHP), butylbenzyl phthalate (BBzP), di-n-butyl phthalate (DnBP), and di-iso-butyl phthalate (DiBP) induce the so-called phthalate syndrome already at low doses, which covers different reproductive abnormalities in male offspring of rats exposed during pregnancy with the critical time window of gestation day 15-17. The effects are among others malformations of the testes, epididymides and Gubernaculum Testis, cryptorchism, hypospadias, reduced semen count and others caused by interference of the development of fetal Leydig cells, reduced or inhibited testicular testosterone production and reduced production of insulin-like 3 peptide hormone (HBM Commission, 2011). Not all phthalates exhibit the reprotoxic and developmental effects described above and not all have the same endocrine disrupting potency. It seems that the molecular structure of the alkyl side chain is responsible for the exhibition of the effects, i.e. limited to phthalates with 3-7 (or 8) carbon atoms in the backbone of the side chain only. The most potent representative is di-n-pentyl phthalate (DnPeP), followed by DEHP, DnBP, DiBP, BBzP, and dicyclohexyl phthalate (DCHP) with a comparable potency. Di-iso-nonyl phthalate (DiNP) has a somewhat lower potency to act as an endocrine disruptor (Gennings et al. 2014). It must be assumed, that similar adverse effects are also caused in human, since the effects of the phthalate syndrome in rats have similarities with the observed testicular dysgenesis syndrome in humans (HBM Commission, 2011). In addition, several epidemiological studies conjecture an association between phthalate exposure and overweight, insulin resistance, asthma, attention deficit disorder and attention deficit hyperactivity disorder (Hatch et al., 2010; Engel et al., 2010; Wang et al., 2015, Franken et al., 2017). In terms of risk assessment it is important to note that mixtures of the above mentioned phthalates have direct additive effects (Howdeshell et al. 2017), but also additive effects with other endocrine disrupting chemicals has been demonstrated, even though they function via a different mode of action (Gray et al., 2006; Rider et al., 2010). Due to increased knowledge of the endocrine disrupting effects of the above mentioned phthalates, less harmful plasticisers became more important over the last decade including di(2-propylheptyl) phthalate (DPHP) and Hexamoll® DINCH®. DPHP due to its molecular structure is thought to have no anti-androgenic effects, but only minimal data is available. Hexamoll® DINCH® was introduced into the market in 2002 as a substitute mainly for DEHP and DiNP. The currently available data suggests that Hexamoll® DINCH® has no reproductive effects and is not an endocrine disrupter, but nephrotoxic effects were observed in a subchronic feeding study in rats EFSA (2006) considered these effects relevant for the derivation of a TDI of 1 mg/kg BW (Gennings et al., 2014). However, a study of women undergoing in vitro fertilization treatment by Mínguez-Alarcón al., 2016 showed suggestive negative associations between urinary MINCH concentrations and peak estradiol levels and numbers of total oocyte yields with stronger associations in older women compared to younger women (Mínguez-Alarcón al.,

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 3

2016). In animal studies effects on the thyroid gland are observed but were considered as secondary effects associated with liver enzyme induction and therefore of limited relevance to humans (EFSA, 2006).

### 1.1.2. Exposure characteristics

Phthalates, more specifically orthophthalates are the most commonly used plasticisers globally with an annual consumption of 8.4 million tons. Orthophthalates are made of alcohols with long alkyl chains and 1 million tons of orthophthalates are produced each year in Europe, which represent 80% of the plasticiser market. Depending on their molecular structure, they can be differentiated into low molecular weight orthophthalates (LMW) and high molecular weight (HMW) with different physico-chemical properties resulting in different applications. The latter include DEHP, DiNP, di-iso-decyl phthalate (DiDP) or di-2-propylheptyl phthalate (DPHP) of which the majority is used in flexible polyvinyl chloride (PVC) products such as flooring, wires and cables, sport equipment, toys, coated textiles, footwear, synthetic leather and others. DEHP is also used in PVC medical devices (Koch & Angerer, 2011). The LMW phthalates comprise DiBP, BBzP, DnBP, diethyl phthalate (DEP) and dimethyl phthalate (DMP) are more volatile and have plasticising and solvent-like properties. Therefore they have various other applications in addition to PVC products such as gelling plasticisers, paints, dispersions, and adhesives, but also as solvents in insect repellents (DMP) and in cosmetics (DEP). DEP and DnBP are also used in enteric-coated tablets/capsules as enteric film-coating materials or matrix binder (Wittasek, 2011). Hexamoll® DINCH®, due to its low toxicity and low migration rate, is used in soft PVC-containing medical devices such as blood bags, in food contact materials, such as artificial wine corks, in sports equipment and textile coatings, in wallpaper, paints and inks, adhesives and in cosmetics and toys. In the latter, Hexamoll® DINCH® is thought to be the most used plasticiser alternative.

However, DnBP, DiBP, BBzP, DEHP, DMEP, DnPeP, DiPeP are generally not allowed to be placed on the EU-market, when used as individual substances or in mixtures for supply to the general public when concentration limits are equal to or exceed 0,3%. In addition, DEHP, DnBP, BBzP, DEMP, DnPeP, DiPeP and DHNUP are prohibited for use in cosmetics in the European Union. Nevertheless, consumer articles (e.g. from Asia or USA) can contain phthalates since there is no such strict restriction for the use of phthalates in consumer articles up to now.

Since phthalates are not chemically bound to the (plastic) materials, they can leach, migrate or evaporate into indoor air and atmosphere, foodstuff or other materials and so are of ubiquitous presence in the environment (Heudorf et al. 2007). Therefore, plasticizers can be taken up by ingestion, inhalation and dermal contact. Whereas for HMW phthalates the main source of exposure is via food originating from contamination, e.g. via food contact materials (Wittassek et al. 2011; ECHA, Background document to the restriction proposal, 2017), especially for DEHP but also for DiNP, the exposure to LWM phthalates from food contribute to the overall exposure to a minor degree (Koch, 2011, Bdgbl). Inhalation of indoor air, exposure via ingestion of house dust by children and dermal contact with articles and dust can also be sources of exposure, especially for the short chain phthalates. Fromme et al., 2013b found significant correlations between phthalate concentrations in dust samples and urinary levels of DnBP, BzBP, but also for DEHP. In addition, medical treatment can lead to high exposure towards certain phthalates. For example, an exposure source for DEHP can be medical devices, such as tubes in blood transfusion. Long-term treatment with enteric-coated tables/capsules can lead also to high exposure of DEP and DnBP.

Several human-biomonitoring studies in the EU, US and Asia were conducted, showing that the ubiquitous use of phthalates lead to a continuous internal exposure of the general public. Phthalate metabolites are being detected in a high percentage of the study population, sometimes present in

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 4

each urine sample investigated (Bermann et al., 2013; Huang et al., 2016; Koch et al., 2017; Ye et al., 2008;). Comparison of exposure estimates between studies from the DEMOCOPHES project revealed a clear age difference. Levels of metabolites were in general higher in children than in mothers, which is confirmed also by other studies (ECHA, 2016; Hartmann et al., 2015; Frederiksen et al., 2013; Becker et al., 2009; Geens et al., 2014). The relative metabolite levels differed among countries, with Swedish children having higher urinary MBzP levels than the European average, Slovak children having two times higher concentrations of DEHP metabolite levels than the European average and Polish children showed highest levels of MnBP and MiBP. In Spain, average MEP levels were six times higher than the European average. However, exceedance of health-based guidance values, in particular HBM-I values and BE values, were only reported for few cases, i.e. for DEHP metabolites in mothers and children (Den Hond, 2015). Furthermore, results of some of the above-mentioned studies also suggest, that exposure to high levels of one phthalate metabolite is positively correlated with high exposure of one of the other phthalate metabolite (ECHA, 2016; Becker et al., 2009; Frederiksen et al., 2013). However, this cannot be confirmed by results of the DEMOCOPHES study (Den Hond et al., 2015). In the Restriction Report of ECHA (2016) risk characterisation ratios (RCRs) for the health of the general public were calculated based on DEMOCOPHES data revealing that in 13 out of 15 Member States of the EU RCRs for combined 95<sup>th</sup> percentile exposure for DEHP, DnBP, BBzP and DiBP are at or above 1 for children (ECHA, 2016). This stresses the fact, that cumulative risk assessment is crucial to accurately determine the hazards originating from phthalates exposure. Since endocrine active phthalates can act in a dose additive manner and humans simultaneously are exposed to multiple phthalates, cumulative exposure to phthalates might exceed health-based guidance values and therefore pose a risk to the public health.

Nonetheless, phthalate use in the industry and in the consumer environment has changed dramatically during the past decade due to regulatory restrictions. Recently, Koch et al., investigated the time trend of phthalates exposure using urinary samples from the German Environment Specimen Bans (ESB) regularly taken in the time frame of 1988 until 2015. They showed that the exposure to old, well-known and restricted phthalates (DEHP, DnBP, BBzP) has decreased. When comparing DEMOCOPHES data to older studies, a significant decline in exposure was also seen for Germany and Denmark (ECHA, 2017). Exposure to the metabolites of the substitutes Hexamoll® DINCH® has increased in Germany and in Sweden (Koch et al, 2017; Gyllenhammar et al., 2017). The population may also be significantly exposed to newer phthalates like DiNP and DPHP and one can assume that the European population will still be exposed to restricted phthalates in the future, e.g. due to long lifetimes of articles, recycled PVC and from remaining authorised uses or uses that are not restricted. Concerning occupational exposure there is only limited data on the exposure of workers to different phthalates in the plastic industry, but the same trends as for consumers are considered relevant.

### 1.1.3. Technical aspects

In the course of human biomonitoring of phthalates, the concentration of the degradation products (metabolites) are commonly analysed in urine due to its non-persistent nature, since urinary concentrations of the compounds and their metabolites are usually higher than in blood. After exposure, phthalates rapidly metabolised and are completely excreted within 24 hours (Wittasek, 2001). Therefore, it is important to have comprehensive knowledge on the metabolism of the respective compound. LMW phthalates are generally determined via their primary monoester metabolites, whereas HMW phthalates are determined via their oxidised metabolites. The longer the alkyl side chains are the stronger is the oxidative modification of the monoester. Therefore, the LMW phthalates are excreted mainly as their monoesters and to a lesser extent as their oxidative

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 5

metabolites. The HMW are excreted mainly as their oxidative metabolites and to a lesser extent as their simple monoesters. For some monoesters, e.g. MnBP, MiBP, MEHP and MiNP an internal and external contamination control is warranted. Due to the omnipresence of phthalates and usage in laboratory equipment external contamination of the sample with the parent compound or their monoester can occur. Biodegradation can lead to the contamination of the samples with monoesters, since they cannot be distinguished from the monoester that indicate the body burden. HMW phthalates as DiNP and DiDP are challenging due to their presence in different isomers. Separation of the isomers is difficult and experience is needed to identify the various isomers in the chromatogram.

For most of the phthalates discussed here, a solid mass spectrometry method exist. However, until today there is no method available that can distinguish between DPHP and DIDP metabolites since they have the same molecular mass and similar retention times in HPLC (high-performance liquid chromatography). DPHP metabolites can be determined separately using a GC-MS method. Hexamoll® DINCH® metabolites can be measured using a LC-MS/MS but an external quality assessment scheme is currently not available. No or insufficient methods exist for DiPeP, DMEP and DHNUP.

#### 1.1.4. Policy relevance

DEHP, DnBP, DiBP, BBzP, DnPeP, DiPeP, DHNUP, DnHP and DMEP are classified as reproductive toxicants category 1B under Annex VI to the Classification, Labelling and Packaging (CLP) regulation (EC 1272/2008). Due to their reprotoxic properties and for DEHP, BBzP, DnBP and DiBP since 2017 additionally due to their endocrine disrupting properties, these substances have been identified as substances of very high concern (SVHC) and therefore included in the candidate list for the inclusion in Annex XIV of the REACH regulation (Annex XIV of REACH EC 1907/2006). Four of the nine above mentioned phthalates are already subject to authorisation, namely DEHP, BBzP, DiBP and DnBP. Since February 2015 they must not be used within the European Union without authorisation. Applications for authorisation were submitted for DEHP and DnBP only. There are Commission decisions on some authorisations, others are currently under evaluation. However, imported goods do not come under the authorisation requirement. Since June 2017, three other phthalates are included in the Authorisation List: DiPeP, DMEP and DnPeP with a sunset date of July 2020.

The current restrictions under REACH also cover some phthalates to a certain extent. Reprotoxic substances, such as DEHP, BBzP, DnBP, DiBP, DnPeP, DiPeP, DCHP, DHNUP, DnHP and DMEP are generally not allowed to be placed on the market, in the EU as individual substances or in mixtures for supply to the general public when concentration limits are equal or exceed 0,3%. Furthermore, the use of DEHP, DnBP, DiBP and BBzP is restricted in plasticised materials of all toys and childcare articles with a concentration limit of 0.1% by entry 51 of Annex XVII to REACH. In addition, DiNP, di-*n*-octyl phthalate (DnOP), DiDP are restricted for all children's toys and childcare articles that can be placed in children's mouth with a concentration limit of 0.1% by entry 52 of Annex XVII to REACH. Current efforts for a further restriction of DEHP, DnBP, DiBP, and BBzP have been initiated by ECHA in the form of an Annex XV restriction dossier in April 2016 and is now up for decision by the Commission. If decided upon positively the restriction in articles will take effect probably 2020 or 2021.

For Hexamoll® DINCH® an analysis of the most appropriate risk management option (RMOA, January 2016) was conducted by the French Agency for food, environmental and occupational health & safety (ANSES). As a result the suspicion of reprotoxicity and endocrine disrupting properties could not be confirmed. The effect on the thyroid gland observed in rats after exposition of Hexamoll® DINCH® cannot be generally applied to humans due to the higher susceptibility of the

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 6

thyroid tissue to contaminants in rats and the relatively high doses used. The possible carcinogenicity in humans was negated. Furthermore, impairment of the environment was also negated, due to the production and use patterns. As a consequence, currently no further risk mitigation measures are necessary.

In addition to the REACH legislation, there is also a product-specific legislation which regulates certain phthalates, i.e. the Cosmetic Products' Regulation (EC/1223/2009) and the regulation on plastic materials and articles intended to come into contact with food (EC 1935/2004 and Directives 80/590/ECC & 89/109/ECC), more specific the Regulation for Plastics Implementation Measure (10/2011/EC). In the Cosmetic Products' Regulation, Article 15 outlines the prohibition of CMR substances in cosmetic products. Furthermore, Annex II lists the substances that are prohibited for use in cosmetics. These include the following: DEHP, DnBP, BBzP, DMEP, DnPeP, DiPeP and DHNUP. In Annex I (Union List) of the regulation on plastic materials and articles intended to come into contact with food, all substances are listed, which are authorised for the use as starting material, excipient or additive for plastic layers in plastic materials and articles. Each substance must not exceed its specific migration limit (SML). The following phthalates and phthalate substitutes are authorised for use as excipient or additive: DEHP with a SML of 1.5 mg/kg foodstuff, BBzP with an SML of 30 mg/kg foodstuff, DnBP with a SML of 0.3 mg/kg foodstuff and DiNP, DiDP and Hexamoll® DINCH®. Thereby apply different use restrictions. DnBP, BBzP, DEHP, DiNP and DiDP can only be used as plasticiser for articles which come in contact with fatless foodstuff and BBzP, DiNP and DiDP cannot be used in articles containing infant formulas. Furthermore, for DnBP, BBzP, DEHP, DiNP, DiDP and Hexamoll® DINCH® applies a group restriction, that is, the sum of these substances must not exceed an SML of 60 mg/kg foodstuff.

Annex I, Part II, Article 7.5 of the Medical Device Directive (93/42/EWG) states that medical devices containing phthalates classified as CMR must be labelled and if these are intended to be used for children, nursing mothers and pregnant women the manufacture must give a specific justification for this use.

DEHP, BBzP, DnBP and DiBP must not be contained in homogenous materials above the concentration of 0.1% from July 2019 on according to the Restriction of Hazardous Substances Directive in electrical and electronic equipment RoHS2 (2011/65/EC). For medical devices and *in-vitro* diagnostic products this restriction takes effect in July 2021.

For some of the phthalates human biomonitoring assessment values, namely Biomonitoring equivalents (BE) or HBM I values, have been derived – these are concentrations of biomarkers (metabolites) in urine, which reflect an acceptable chronic exposure, since the basic assumption is an equilibrium between external exposure and internal burden (Angerer et al. 2011, Apel et al. 2017). BE values have been derived for the Category A phthalates and HBM I values are available for DEHP, DPHP and Hexamoll® DINCH®. In the course of the work done within the HBM4EU project EU-wide health-based guidance values for the general population (HBM HBGV<sub>GenPop</sub>) could be derived for DEHP and Hexamoll® DINCH® and for workers (HBM HBGV<sub>workers</sub>) for DEHP (see HBM4EU Deliverable D5.2).

### 1.1.5. Societal Concern

Phthalates are a well-known group of plasticisers and are widely used since the 1920s. Due to the endocrine disrupting properties, some phthalates have been assigned with labelling requirements and use restrictions already in the late 1990s. Since then phthalates as a group are of great societal concern due to their toxicity to reproduction and omnipresence in the biological matrices of humans. Greenpeace conducted several studies addressing phthalates in consumer products and the potential health effects emerging from its endocrine disrupting effects (Greenpeace, 2006). Many

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 7

websites inform the public worldwide about consumer products free of phthalates. Furthermore, efforts have been made to reduce the phthalate uses in cosmetics and toys beyond the scope of European regulation as in the US, Japan and China. In addition, industry already substituted many of the endocrine disrupting phthalates with less potent or no endocrine disrupting substances, such as Hexamoll® DINCH®. All phthalates discussed here, except DPHP and the substitute Hexamoll® DINCH® are included in the SIN list.

## 1.2. Categorisation of substances

**Table 1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, D or E substances based on the Prioritisation Strategy and criteria elaborated under WP4, Year 1 (Deliverable D4.3)**

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Classification (CHL/Annex III entry)	Regulation
<b>A</b>	DEHP	Di(2-ethylhexyl) phthalate	117-81-7	CLH: Repr. 1B	REACH Annex XIV; Annex XVII, Entry 51
	BBzP	Butyl benzyl phthalate	85-68-7	CLH: Repr. 1B; Aquatic Acute1; Aquatic Chronic 1	REACH Annex XIV; Annex XVII, Entry 51
	DnBP	Di-n-butyl phthalate	84-74-2	CLH: Repr. 1B; Aquatic Acute 1	REACH Annex XIV; Annex XVII, Entry 51
	DiBP	Diisobutyl phthalate	84-69-5	CLH: Repr. 1B	REACH Annex XIV
	DEP	Diethyl phthalate	84-66-2	<i>Self classification:</i> Acute tox3; STOT RE 2; Eye Irrit.2; STOT SE 3; Skin Irrit. 2; Repr. 2; Aquatic Chronic 1	
	DiNP	Diisononyl phthalate	28553-12-0 / 68515-48-0		REACH Annex XVII, Entry 52; proposed for harmonised classification as Repr. 1B by DK
<b>B</b>	DnOP	Di-n-octyl phthalate	117-84-0	Entry on Annex III Inventory: Susp.carcinogen; Susp. hazardous to aquatic environment; Susp. skin sensitizer; Susp. bioaccumulative; Susp. toxic for reproduction	REACH Annex XVII, Entry 52

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 8

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Classification (CHL/Annex III entry)	Regulation
	DiDP	Diisodecyl phthalate	26761-40-0 / 68515-49-1	Entry on Annex III Inventory: Susp.carcinogen; Susp. hazardous to aquatic environment; Susp. persistent in the environment; Susp. skin sensitizer	REACH Annex XVII, Entry 52
	DMP	Dimethyl phthalate	131-11-3	<u>Self classification:</u> <i>Acute tox 3; Eye Irrit.2; STOT SE 3; Skin Irrit. 2; Repr. 2; Aquatic Acute 3; Aquatic Chronic 1</i>	
	DnPeP	Di-n-pentyl phthalate	131-18-0	CLH: Repr. 1B Aquatic Acute 1 Entry on Annex III Inventory: Susp.carcinogen; Susp. hazardous to aquatic environment; Susp. skin sensitizer; Susp. bioaccumulative; Susp. toxic for reproduction	REACH Annex XIV
	DCHP	Dicyclohexyl phthalate	84-61-7	CLH: Repr. 1B, Skin Sens.1	CoRAP list; currently under Substance Evaluation for potential ED properties
	DPHP	Di(2-propylheptyl) phthalate	53306-54-0		CoRAP list; currently under Substance Evaluation for potential ED properties
	Hexamoll®DINCH®	Diisononyl cyclohexane-1,2-dicarboxylate	166412-78-8	Entry on Annex III Inventory: Susp.carcinogen; Susp. hazardous to aquatic environment	
<b>C</b>	DiPeP	Di-isopentyl phthalate	605-50-5	CLH: Repr. 1B; Aquatic Acute1	REACH Annex XIV

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 9

Cat.	Abbrev./ Acronym	Systematic name	CAS No.	Classification (CHL/Annex III entry)	Regulation
	DHNUP	Di-C7-11-(linear and branched)-alkyl phthalate	68515-42-4	CLH: Repr. 1B; Entry on Annex III Inventory: Susp.carcinogen; Susp. hazardous to aquatic environment; Susp. skin sensitizer; Susp. toxic for reproduction	REACH Annex XIV
	DnHP	Di-n-hexyl phthalate	84-75-3	CLH: Repr. 1B Entry on Annex III Inventory: Susp. carcinogen; Susp.hazardous to the aquatic environment; Susp. mutagen; Susp.persistent in the environment; Susp. respiratory sensitizer; Susp. skin irritant; Susp. skin sensitizer	SVHC on the candidate list, recommended for inclusion on REACH Annex XIV
	DMEP	Di(methoxyethyl) phthalate	117-82-8	CLH: Repr. 1B Entry on Annex III Inventory: Susp. carcinogen; Susp. hazardous the the aquatic environment; Susp. mutagen	REACH Annex XIV

### 1.2.1. Categorisation according to the Prioritisation Strategy and criteria elaborated under WP4, Year 1 (Deliverable D4.3)

**Category A** is defined as “substances for which HBM data are sufficient to provide an overall picture of exposure levels across Europe, and interpretation of biomonitoring results in terms of health risks is possible. Risk management measures have been implemented at national or European level. Improvement of knowledge for these substances will therefore focus on policy-related research questions and evaluation of the effectiveness of existing regulatory measures.”

**Category B** is defined as “substances for which HBM data exists, but not sufficiently to have a clear picture across Europe. Also, knowledge on the extend of exposure, levels and impact on the human health should be improved, in order to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. Analytical method and capacities to monitor the substances across Europe might have to be improved.”

**Category C** is defined as “substances for which HBM data scarcely or doesn’t exists. Efforts to develop an analytical method to obtain relevant HBM results need to be done Hazardous properties of the substances are identified, yet greater knowledge on toxicological characteristics and effects

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 10

on the human health is needed. Interpretation of HBM data is not possible, due to the lack of HBM guidance values.”

**Category D** is defined as “substances for which a toxicological concern exists but HBM data are not available. HBM4EU research may be focused on the development of suspect screening approaches permitting to generate a first level of data enabling to document the reality of human exposure and better justify further investment in a full quantitative and validated method development.”

**Category E** is defined as “substances not yet identified as of toxicological concern and for which no HBM data are available. A bottom-up strategy will be applied, consisting to non-targeted screening approaches coupled to identification of unknowns capabilities for revealing, and further identifying, new (i.e. not yet known) markers of exposure related to chemicals of concern for HBM (parent compound or metabolite).”

### Justification of Grouping:

DEHP, BBzP, DnBP, DiBP, DEP and DiNP were categorised as Category A substances since HBM data is available for at least one country from one of the four geographical regions of the European Union defined by the UN. Furthermore, for all substances well-established analytical methods exist and all substances, except DEP are regulated. DEP and DiNP are the only ones in this category which are not classified as toxic for reproduction 1B. However, Denmark suggested to classify DiNP as toxic for reproduction 1B.

DiDP, DnOP, DMP, DnPeP, DCHP, DPHP, Hexamoll®/DINCH® were categorised as Category B substances since HBM data is available for some countries, but lacking for at least two of the four geographical regions of the European Union defined by the UN. For most of the substances established analytical methods are available, but might need to be quality assured and/or harmonised. Currently, the metabolites for DPHP and DiDP cannot be distinguished and improvement of analytical methods are needed. Three of these phthalates are regulated and two are currently under evaluation for ED properties.

DiPeP, DHNUP, DMEP and DnHP were categorised as Category C substances, since only little HBM data exists. Methods only exists to measure DHNUP and further research on metabolism and feasibility of method development are needed. However, all substances are classified as toxic to reproduction 1B and three of four are on the authorisation list, with DnHP being recommended for inclusion to this list.

#### 1.2.2. Additional information:

**DnOP** (category B): doesn't exist on the EU market. See page 14 of the ECHA review report: <https://echa.europa.eu/documents/10162/31b4067e-de40-4044-93e8-9c9ff1960715>. However, DnOP metabolites are detected in humans even though to a lesser extent than other phthalates (Frederiksen et al., 2015; Zeman et al., 2013). DnOP do seem to not have antiandrogenic effects, but indications for systemic toxic effects on liver, thyroid, immune system and kidney exist. Due to the scarce data basis, monitoring of the exposure and further research on toxicity is warranted.

**DHNUP** (category C): It is not registered under REACH. There is almost no information available about this phthalate which suggests that it is not on the market or only has a very marginal market. E.g. Health Canada 2015: stopped at screening assessment because lack of exposure. (<https://www.canada.ca/en/health-canada/services/chemical-substances/challenge/batch-6/dhnup.html>).

**DMEP** (category C): It is not REACH registered and it is unlikely that there is significant use in the EU.

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Leuret, Greet Schoeters	Page: 11

However, import of goods is not covered by the authorisation of substances under REACH and no restrictions are in effect for these substance. In addition, it has been demonstrated that exposure patterns differ between countries within the EU (Den Hond et al., 2015) and between EU and U.S. (Koch et al., 2017). Therefore, it is suggested to include these substances in the prioritisation list of phthalates to be able to monitor their possible occurrence in human matrices within the European population.

### 1.3. Objectives / Policy related questions

#### *Exposure characteristics*

1. Which are the most sensitive, reliable and cost effective methods and biomarkers to measure phthalates and Hexamoll® DINCH®?
2. What is the extent of the current exposure of the EU population to the 16 phthalates (Cat A, B and C) and their substitute Hexamoll® DINCH®?
3. Do the exposure levels differ significantly between the countries?
4. What are the main sources of exposure and the reasons for differences in exposure (different regulations in different countries) to phthalates and Hexamoll® DINCH®?
5. What are the high exposure groups? (Is there a statistical significant and toxicological relevant difference in mean concentration between adults and children? [...] between occupational exposed and non-exposed adults? [...] between male and female?)

#### *Monitoring the success of existing policy actions and assessing the needs for further regulation*

6. Are there different time trends for **unregulated** (DEP, DMP, DCHP, DPHP) and **regulated phthalates** (DEHP, BBzP, DnBP, DiBP, DinP, DnOP) and Hexamoll® DINCH®? (Starting with Cat. A substances for which methods can be standardized in AWP 2)
7. How effective have the different mitigation steps and regulations been for phthalates?
  - 7a)** Had the restriction under REACH the favourable impact, that is a reduction of GM/median concentrations of the already restricted phthalates (DEHP, BBzP, DnBP, DiNP, DiDP, DnOP), especially for children from 2007 until today (2018-2021)?
  - 7b)** Was the introduction of the Authorisation obligation under REACH effective enough to protect European citizen? Is there a sufficient decrease of the Cat. A substance levels subject to authorisation (GM/median) in the European population (general/children?) from year 2015 until today (2018-2021) (i.e. DEHP, DnBP, DiBP, BBzP)? Are there differences between countries?
  - 7c)** Had the identification as SVHC already an impact on the reduction of the phthalate exposure of the population (i.e. Did the exposure of a certain substance decline after the substance is identified as SVHC)?

#### *Impact on human health*

8. Is the exposure to phthalates and their substitutes of health-relevance for the general population and vulnerable groups (inter alia children and pregnant women)? What part of the population has exposure levels exceeding the HBM guidance values - if existing- or TDI)?
9. Does the health relevance depend on age and gender?
10. Can EU wide accepted HBM guidance values be derived for single substances and for the additively acting phthalates?
11. How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance? Are their additive effects relevant for regulation?

#### *Usage of HBM4EU results for policy making*

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 12

12. How can HBM4EU results feed into the regulatory decisions of ECHA and EFSA?
13. What is the economic impact of phthalates and substitute exposure?



**Table 2: Listing of research activities to be carried out to answer the policy questions concerning phthalates & Hexamoll® DINCH®**

Policy Question	Substances	Available knowledge related to policy question	Knowledge gaps / Activities needed to answer policy question
1. Which are the most sensitive, reliable and cost effective methods and biomarkers to measure phthalates and Hexamoll® DINCH®?	<b>Cat. A-C</b>	Methods available to measure the metabolites of all parental compounds, except: DiPeP, DMEP and DHNUP; method exists to measure 21 metabolites covering 11 parental compounds simultaneously but not quality assured- costs differ between countries/labs; not possible to distinguish DiDP and DPHP metabolites	<ul style="list-style-type: none"> <li>▶ Need to be investigated, for which of the substance a method is available and for which not (WP9, Y1); if quality assured or not &amp; if there is a need for new method development</li> <li>▶ if there is a need for generating biomonitoring data, cost-benefit-analysis has to be done for determination of phthalates to be measured in national studies (WP8)</li> </ul>
2. What is the extent of the current exposure of the EU population to the 16 phthalates (Cat A, B and C) and their substitute Hexamoll® DINCH®?	<b>Cat. A</b>	Cat. A substances are expected to be detected in most countries based on experience of DEMOCOPHES; In Year 1 an extensive review will be conducted by Task 7.1 to get an overview of recent studies in the European Union	<ul style="list-style-type: none"> <li>▶ The Statistical Analysis Group will determine if the existing exposure data are sufficient to derive valid and general statements for the exposure of the European Population and derive reference values, where possible (WP10, Y2)</li> <li>▶ Studies on metabolisation are needed, in order to develop a method for the following phthalates: DnHP (analogies to DnPeP likely), DHNUP (analogies to HMW (high molecular weight) phthalates such as DEHP DiNP and DiDP likely), DiPeP and DMEP (analogies to DnPeP likely) (WP9) <ul style="list-style-type: none"> <li>▶ Prior to method development, it should be determined, if there is a need for the monitoring of Cat. C phthalates in human matrices (Extrapolation of exposure data from other countries, e.g. US, Canada, Asia: WP5, Y2 or prioritisation exercise (WP4, Y2)</li> </ul> </li> <li>▶ Data will be generated in targeted studies and from biobanked samples if available for Cat. B and Cat. C substances (Y3, Y4 in WP8 with preparatory work conducted in WP7 (Y2-Y3)</li> </ul>
	<b>Cat. B</b>	Cat. B substances are likely to be increasingly detected in the European Population such as DINP, DPHP & Hexamoll® DINCH® due to its usage as substitutes for known endocrine disrupter phthalates	
	<b>Cat. C</b>	For Cat. C substances no data on exposure is available and for most no uses are registered within the EU, however exposure	

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sariqiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 14

		patterns differ between countries and authorisation under REACH does not cover import	
3. Do the exposure levels differ significantly between the countries?	<b>Cat. A</b>	Based on the DEMOCOPHES data (sampling year 2011-2012) differences in countries are expected (higher concentration of Cat. A substances in Eastern Europe), but also similar exposure patterns were observed for Germany, Netherlands, Denmark, Israel	<ul style="list-style-type: none"> <li>▶ The Statistical Analysis Group will determine if the existing exposure data are suitable for comparison between countries (WP10) and if so compare data sets and/ or reference values per country (Y2)</li> </ul>
	<b>Cat. B</b>	Human biomonitoring data is scarce (only available for some countries with different population groups measured, e.g. Germany, Sweden)	<ul style="list-style-type: none"> <li>▶ We need to answer Question 2 first to be able to recognise differences in exposure depending on geographical origin (Y2-Y3); if not possible to obtain results based on existing data (Statistical Analysis Group, WP10) targeted studies need to be conducted (WP8; Y3-Y5) or targeted analysis in existing biobanked samples should be conducted (WP9; Y2-3)</li> </ul>
	<b>Cat. C</b>	For Cat. C substances no data on exposure is available and for most no uses are registered within the EU	<ul style="list-style-type: none"> <li>▶ Should be determined, whether there is a need for the monitoring of Cat. C phthalates in human urine (Comparison of exposure data from other countries, e.g. US, Canada, Asia) (WP5; Y2)</li> </ul>
4. What are the main sources of exposure and the reasons for differences in exposure (different regulations in different countries) to phthalates and Hexamoll® DINCH®?	<b>Cat. A &amp; B</b>	Differences of exposure sources exist for HMW phthalates and LMW phthalates: for the first mainly food and indoor air & for the latter others than food; also specific exposure sources exist for DEHP, DiBP (medical devices, medications)	<ul style="list-style-type: none"> <li>▶ Exposure determinants for LMW phthalates will be investigated by the Statistical Analysis Group (WP10) to identify sources of exposure per single substance and substance group (Y2)</li> <li>▶ By means of reverse PBTK modelling identification of the contribution of different routes of exposure to the total exposure can be estimated (WP12; Y2-3)</li> </ul>

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 15

<p>5. What are the high exposure groups? (Is there a statistical significant and toxicological relevant difference in mean concentration between adults and children? [...] between occupational exposed and non-exposed adults? [...] between male and female?)</p>	<p><b>Cat. A &amp; B</b></p>	<p>Based on biomonitoring studies in Europe (DEMOCOPHES project and others) it can be observed that children are exposed to a higher extend than adults; only slight differences expected for male and female population; data on the exposure of workers is lacking, but a higher exposure to phthalates are assumed</p>	<ul style="list-style-type: none"> <li>▶ Need to be investigated whether there is a difference in the exposure levels of male and female population by comparing exposure levels based on existing data (Statistical Analysis Group, WP10; Y2)</li> <li>▶ Statistical Analysis Group will also determine different exposure levels of different age groups depending on the data available (WP10; Y2)</li> <li>▶ Need to be determined whether data on occupational population is existing (WP7; Task 7.1; Y1); if so Statistical Analysis Group will also determine different exposure levels of occupational population in comparison with general population (WP10; Y2)</li> <li>▶ Targeted occupational studies for phthalate exposure (e.g. in plastic and construction sectors) will be planned (WP8; Y2)</li> <li>▶ Occupational exposure will be estimated (WP12, Y4)</li> </ul>
<p>6. Are there different time trends for unregulated (DEP, DMP, DCHP, DPHP) and regulated phthalates (DEHP, BBzP, DnBP, DiBP, DinP, DnOP) and Hexamoll® DINCH®? 7. How effective have the different mitigation steps and regulations been for phthalates?</p>	<p><b>Cat. A &amp; B</b></p>	<p>Time trend analysis in Germany, Sweden, Flanders suggest a decline of regulated phthalates (e.g. DEHP, DiBP; BBzP, DnBP), whereas DiNP &amp; DPHP &amp; the substitute Hexamoll® DINCH®? show an increasing trend</p>	<ul style="list-style-type: none"> <li>▶ Does this apply to other countries as well? Are time trends available for other countries? To answer these questions gap analysis need to be performed (WP7; Y1) and comparability of data available need to be evaluated and analysed (WP10; Y2)</li> <li>▶ Do the different regulation steps (Identification as SVHC; Restriction, Authorisation) have a direct impact on the phthalates exposure patterns in the EU population? (WP10)</li> <li>▶ Does the authorisation process stimulates substitution? (WP10)</li> <li>▶ Is the current regulation system effective enough to reduce exposure to phthalates? How affect the different regulation steps the exposure patterns? Are there differences? Do we need further regulation to reduce the health-risk? (WP10, WP5)</li> </ul>
<p>8. Is the exposure to</p>	<p><b>Cat. A &amp; B</b></p>	<p>German HBM values are available for the sum of DEHP metabolites, Hexamoll®</p>	<ul style="list-style-type: none"> <li>▶ Compare current exposure data (reference values) with EU health-based guidance values, if available (derived in WP5→ Hexamoll®</li> </ul>

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 16

phthalates and their substitutes of health-relevance for the general population and vulnerable groups (inter alia children and pregnant women)? What part of the population has exposure levels exceeding the HBM guidance values - if existing- or TDI)?		DINCH® metabolites, DPHP metabolites; BE values exist for sum of DEHP metabolites	DINCH®, DEHP: Y1; DPHP, DiBP, BBzP, DnBP: Y2; ) or if not available other as German HBM values and BE values <ul style="list-style-type: none"> <li>▶ Exposure and specific determinants will be assessed and compared to toxicological threshold values and vulnerable groups and geographical hot spots where policy actions are required can be identified using PBTK modelling (WP12, Y2-3)</li> </ul>
9. Does the health relevance depend on age and gender?	<b>Cat. A</b>	Sensitive groups for health effects resulting from phthalates exposure are pregnant women and their foetuses based on the endocrine disrupting effects on the male reproductive tract development and effects on neurodevelopment (both male and female infants and young children); phthalates exposure is also associated with obesity in older women	<ul style="list-style-type: none"> <li>▶ Epidemiological studies investigating effects on neurodevelopment in infants and children/male reproductive tract development should be compared and statistically analysed (meta-analysis) to strengthen the correlation of age, gender and other determinants with single/cumulative substance exposure (WP11, WP10)</li> <li>▶ Use of AOPs to establish associations of health outcomes and exposure (WP13; Y3-4)</li> <li>▶ Estimation of the burden of disease of phthalates and EDCs in general for EU population (WP5)</li> </ul>
	<b>Cat. B/C</b>		<ul style="list-style-type: none"> <li>▶ Same can be assumed for Cat.B&amp;C substances, if reprotoxic potential is given; for Hexamoll® DINCH® and other phthalates thought to be no endocrine disrupting chemicals health-relevant determinants should be investigated (WP10, WP11, WP13)</li> </ul>
10. Can EU wide accepted HBM guidance values be derived for single	<b>Cat. A &amp; B</b>	For some single substances German HBM values exist and within 1 year, it can be determined whether EU wide health-based guidance values can be derived	<ul style="list-style-type: none"> <li>▶ WP5 will develop a concept to derive EU wide health-based guidance values (Y1) and will determine for which single substances it is possible and develop a time frame for the derivation of EU wide health-based guidance values (Y1)</li> </ul>

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 17

substances and for the additively acting phthalates?			<ul style="list-style-type: none"> <li>▶ In Y2-Y3 WP5 will examine the possibility of an aggregated (EU-wide) health-based guidance value for phthalates in close collaboration with WP15</li> <li>▶ WP15 will further develop on the scientific basis for a cumulative risk assessment</li> </ul>
	<b>Cat. C</b>	For those substances, exposure data is scarce, if available at all. No BE or German HBM values exist.	<ul style="list-style-type: none"> <li>▶ Lack of exposure data makes it difficult to derive health-based guidance values → need to be determined, whether it is suitable and useful to derive values for Cat. C substances (WP5; Y2-Y5) based on gap analysis (WP7, task 7.1; Y1)</li> </ul>
11. How can cumulative risks of phthalates and other anti-androgenic substances be assessed for their health relevance? Are their additive effects relevant for regulation?	<b>Cat. A-C</b>	Since many relevant phthalates have similar toxicological profiles, a cumulative assessment is important in order to not underestimate risks. A decision is needed on which substances of the phthalate group should be included in such an additive approach. Basis for this should be similar adverse effects (function that is disrupted) and not only the mode of action.	<ul style="list-style-type: none"> <li>▶ Basis for a cumulative risk assessment should be similar adverse effects (function that is disrupted, here anti-androgenic effects) and not only the mode of action. (WP15)</li> <li>▶ WP5 will in close collaboration with WP15 assess the feasibility of deriving an HBM health-based guidance value for combined phthalate exposure (Y2-Y3) and explore health risk assessment (HRA) and health impact assessment (HIA) of combined exposure for phthalates</li> </ul>
12. How can HBM4EU results feed into the regulatory decisions of ECHA and EFSA?	<b>Cat A &amp; B</b>		<ul style="list-style-type: none"> <li>▶ EU-wide health-based guidance values will be derived for phthalates (WP5, Y1-2), which are a useful tool to determine if a concern to human health exist for the exposure to phthalates and therefore measures need to be taken</li> <li>▶ In WP5 the improved use of HBM in health risk assessment (HRA) and in health impact assessment (HIA) for phthalates will be explored (Y1) and case studies will be performed on the integration of HBM information in HRA and HIA for phthalate substitutes as DPHP and Hexamoll® DINCH® including the EU-wide health based guidance values and reference values (WP10) in Y2</li> <li>▶ Method for HBM-based indicators will be developed (WP5; Y1) and applied on single substances and the use of substance groups (as phthalates) will be addressed (WP5; Y2)</li> </ul>

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 18

			<ul style="list-style-type: none"> <li>▶ Instruments to link health and exposure (WP13; WP14) and to better estimate risks from exposure (WP12) will be explored and their suitability in risk assessment and management will be evaluated (e.g. cumulative risk assessment; WP15)</li> </ul>
13. What is the economic impact of phthalates and substitute exposure?	<b>Cat A</b>	<p>Legler et al., 2015 estimated obesity, diabetes and associated costs attributed to EDCs including phthalates in the EU. According to their calculations exposures to phthalates contribute substantially to obesity in older women, with a moderate probability of €15 billion costs per year</p>	<ul style="list-style-type: none"> <li>▶ In WP5 health impact assessment (HIA) for phthalates (single substances and cumulative) will be explored: it should be discussed whether the cost estimation should be included together with the burden of disease estimates and how this can feed into the HIA</li> </ul>

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 19

### 1.3.1. Additional Comments:

- a) Surveyed data to be analyzed or published (in English)
  - ▶ Spain: Adult working population, 18-65 years, n = 1880. Nation-wide representativeness. March 2009-July 2010
  - ▶ Sweden: DEHP, DnBP, BBzP and DEP: Time series on children and population based study from 2010-2011 (Bjerme et al., report in Swedish)
  - ▶ Belgium: FLEHS3: Data surveyed for DiBP and DEP
- b) Data (representative for population) expectable from:
  - ▶ France: Esteban (running since 2nd half of 2016): DEHP, DnBP, BBzP, DEP, DiNP, DnOP, DMP, DCHP
  - ▶ Finland: FinHealth from 2017 on. 6000 samples planned: all Cat A substances and DiNP, DiDP, DnOP, DCHP, DPHP
  - ▶ Germany: GerES V (children): 2015-2017, all Cat A and B substances
- c) Information for Pillar 3:
  - ▶ Like it was mentioned in the Background Information some phthalates (3 to 8 carbon atoms in the backbone of the side chain) have or are suspected to have anti-androgenic properties and as such induce developmental and reproductive malfunctions in rodent studies (phthalate syndrome). Those disturbances include malformations of the epididymis, vas deferens, seminal vesicles, prostate, external genitalia (hypospadias), and cryptorchidism (undescended testes) as well as retention of nipples/areolae (sexually dimorphic structures in rodents) and demasculinization of the perineum, resulting in reduced anogenital distance (AGD). Those effects can be ascribed to a disturbance of fetal testicular Leydig function, which results in significant reduction of testosterone levels.[2] Also the production of insulin like factor 3 in Leydig cells is disturbed by phthalates, which also causes anti-androgenic effects.  
Those effects are similar to the ones subsumed under the human testicular dysgenesis syndrome. However, there are no resilient data on humans, which is why epidemiological studies should try to prove the associations between a phthalate burden and adverse health effects. Data from birth cohorts would probably meet some of the requirements, since the discussion on whether the health impacts can be traced back to in utero exposure or to exposure during childhood could be furthered. Among other endocrine effects in adults (differing for male and female individuals), phthalates are furthermore associated with respiratory problems and effects on blood pressure. For Category C phthalates a first step should be an assessment concerning the relevancy (are the people in Europe exposed or not?), before starting research activities in pillar 3 on those substances.

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 20

## 1.4. References

1. Angerer, J., L. L. Aylward, S. M. Hays, B. Heinzow and M. Wilhelm (2011). "Human biomonitoring assessment values: approaches and data requirements." *Int J Hyg Environ Health* **214**(5): 348-360 <https://www.ncbi.nlm.nih.gov/pubmed/21764371>.
2. Apel, P., J. Angerer, M. Wilhelm and M. Kolossa-Gehring (2017). "New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission." *Int J Hyg Environ Health* **220**(2 Pt A): 152-166 <https://www.ncbi.nlm.nih.gov/pubmed/27914867>.
3. Apel, P., E. Ougier (2017) Deliverable Report D 5.2 - 1st substance-group specific derivation of EU-wide health-based guidance values.
4. Becker, K., T. Goen, M. Seiwert, A. Conrad, H. Pick-Fuss, J. Muller, M. Wittassek, C. Schulz and M. Kolossa-Gehring (2009). "GerES IV: phthalate metabolites and bisphenol A in urine of German children." *Int J Hyg Environ Health* **212**(6): 685-692 <http://www.ncbi.nlm.nih.gov/pubmed/19729343>.
5. Berman, T., R. Goldsmith, T. Goen, J. Spungen, L. Novack, H. Levine, Y. Amitai, T. Shohat and I. Grotto (2013). "Urinary concentrations of environmental contaminants and phytoestrogens in adults in Israel." *Environ Int* **59**: 478-484 <https://www.ncbi.nlm.nih.gov/pubmed/23962452>.
6. Bizzari, S. N., M. Blagoev and A. Kishi (2009). CEH Marketing Research Report Plasticizers. *Chemical Economics Handbook*. S. Consulting.
7. Casas, M., C. Chevrier, E. D. Hond, M. F. Fernandez, F. Pierik, C. Philippat, R. Slama, G. Toft, S. Vandentorren, M. Wilhelm and M. Vrijheid (2013). "Exposure to brominated flame retardants, perfluorinated compounds, phthalates and phenols in European birth cohorts: ENRIECO evaluation, first human biomonitoring results, and recommendations." *Int J Hyg Environ Health* **216**(3): 230-242 <http://www.ncbi.nlm.nih.gov/pubmed/22795704>
8. [http://ac.els-cdn.com/S1438463912000831/1-s2.0-S1438463912000831-main.pdf?\\_tid=969f79ce-1145-11e3-9484-00000aacb35f&acdnat=1377847812\\_35b54b831a18d37cfe580f4a8037465c](http://ac.els-cdn.com/S1438463912000831/1-s2.0-S1438463912000831-main.pdf?_tid=969f79ce-1145-11e3-9484-00000aacb35f&acdnat=1377847812_35b54b831a18d37cfe580f4a8037465c).
9. Cerna, M., M. Maly, P. Rudnai, S. Kozepesy, M. Naray, K. Halzlova, M. Jajcaj, A. Grafnetterova, A. Krskova, D. Antosova, K. Forysova, E. Den Hond, G. Schoeters, R. Joas, L. Casteleyn, A. Joas, P. Biot, D. Aerts, J. Angerer, L. Bloemen, A. Castano, M. Esteban, H. M. Koch, M. Kolossa-Gehring, A. C. Gutleb, J. Pavlouskova and K. Vrbik (2015). "Case study: Possible differences in phthalates exposure among the Czech, Hungarian, and Slovak populations identified based on the DEMOCOPHES pilot study results." *Environ Res* **141**: 118-124 <https://www.ncbi.nlm.nih.gov/pubmed/25532669>.
10. Correia-Sa, L., A. Schütze, S. Norberto, C. Calhau, V. F. Domingues and H. M. Koch (2017). "Exposure of Portuguese children to the novel non-phthalate plasticizer di-(iso-nonyl)-cyclohexane-1,2-dicarboxylate (DINCH)." *Environ Int* <https://www.ncbi.nlm.nih.gov/pubmed/28188053>.
11. Cutanda, F., H. M. Koch, M. Esteban, J. Sanchez, J. Angerer and A. Castano (2015). "Urinary levels of eight phthalate metabolites and bisphenol A in mother-child pairs from two Spanish locations." *Int J Hyg Environ Health* **218**(1): 47-57 <https://www.ncbi.nlm.nih.gov/pubmed/25159680>.
12. Den Hond, E., E. Govarts, H. Willems, R. Smolders, L. Casteleyn, M. Kolossa-Gehring, G. Schwedler, M. Seiwert, U. Fiddicke, A. Castano, M. Esteban, J. Angerer, H. M. Koch, B. K. Schindler, O. Sepai, K. Exley, L. Bloemen, M. Horvat, L. E. Knudsen, A. Joas, R. Joas, P. Biot, D. Aerts, G. Koppen, A. Katsonouri, A. Hadjipanayis, A. Krskova, M. Maly, T. A. Morck, P. Rudnai, S. Kozepesy, M. Mulcahy, R. Mannion, A. C. Gutleb, M. E. Fischer, D. Ligocka, M. Jakubowski, M. F. Reis, S. Namorado, A. E. Gurzau, I. R. Lupsa, K. Halzlova, M. Jajcaj, D. Mazej, J. S. Tratnik, A. Lopez, E. Lopez, M. Berglund, K. Larsson, A. Lehmann, P. Crettaz and G. Schoeters (2015). "First

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 21

- steps toward harmonized human biomonitoring in Europe: demonstration project to perform human biomonitoring on a European scale." *Environ Health Perspect* **123**(3): 255-263 <https://www.ncbi.nlm.nih.gov/pubmed/25493439>.
13. Dereumeaux, C., C. Fillol, M. A. Charles and S. Denys (2017). "The French human biomonitoring program: First lessons from the perinatal component and future needs." *Int J Hyg Environ Health* **220**(2 Pt A): 64-70 <https://www.ncbi.nlm.nih.gov/pubmed/27919640>.
  14. Dereumeaux, C., A. Saoudi, M. Pecheux, B. Berat, P. de Crouy-Chanel, C. Zaros, S. Brunel, C. Delamaire, A. le Tertre, A. Lefranc, S. Vandentorren and L. Guldner (2016). "Biomarkers of exposure to environmental contaminants in French pregnant women from the Elfe cohort in 2011." *Environ Int* **97**: 56-67 <https://www.ncbi.nlm.nih.gov/pubmed/27788374>.
  15. EFSA (2006). Opinion of the Scientific Panel on food additives, flavorings, processing aids and materials in contact with food (AFC) on a request related to a 12th list of substances for food contact materials. EFSA J 395-401, 1-21. [http://www.efsa.europa.eu/sites/default/files/scientific\\_output/files/main\\_documents/395.pdf](http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/395.pdf)
  16. Engel, S.M., Miodovnik, A., Canfield, R.L. et al. (2010). "Prenatal Phthalate Exposure is Associated with Childhood Behavior and Executive Functioning". *Environ Health Perspect* **118**: 565-571.
  17. Exley, K., D. Aerts, P. Biot, L. Casteleyn, M. Kolossa-Gehring, G. Schwedler, A. Castano, J. Angerer, H. M. Koch, M. Esteban, B. K. Schindler, G. Schoeters, E. Den Hond, M. Horvat, L. Bloemen, L. E. Knudsen, R. Joas, A. Joas and O. Sepai (2015). "Pilot study testing a European human biomonitoring framework for biomarkers of chemical exposure in children and their mothers: experiences in the UK." *Environ Sci Pollut Res Int* **22**(20): 15821-15834 <https://www.ncbi.nlm.nih.gov/pubmed/26036586>.
  18. Franken, C., N. Lambrechts, E. Govarts, G. Koppen, E. Den Hond, D. Ooms, S. Voorspoels, L. Bruckers, I. Loots, V. Nelen, I. Sioen, T.S. Nawrot, W. Baeyens, N. Van Larebeke, G. Schoeters. (2017). Phthalate-induced oxidative stress and association with asthma-related airway inflammation in adolescents. *Int J Hyg Environ Health* **220**:468-77.
  19. Frederiksen, H., T. K. Jensen, N. Jorgensen, H. B. Kyhl, S. Husby, N. E. Skakkebaek, K. M. Main, A. Juul and A. M. Andersson (2014). "Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012." *Reproduction* **147**(4): 555-565 <https://www.ncbi.nlm.nih.gov/pubmed/24395915>.
  20. Frederiksen, H., J. K. Nielsen, T. A. Morck, P. W. Hansen, J. F. Jensen, O. Nielsen, A. M. Andersson and L. E. Knudsen (2013). "Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs." *Int J Hyg Environ Health* **216**(6): 772-783 <http://www.ncbi.nlm.nih.gov/pubmed/23528233>.
  21. Fromme, H., A. Schütze, T. Lahrz, M. Kraft, L. Fembacher, S. Siewering, R. Burkardt, S. Dietrich, H. M. Koch and W. Völkel (2016). "Non-phthalate plasticizers in German daycare centers and human biomonitoring of DINCH metabolites in children attending the centers (LUPE 3)." *International Journal of Hygiene and Environmental Health* **219**(1): 33-39 <http://www.sciencedirect.com/science/article/pii/S1438463915001030>.
  22. Geens, T., L. Bruckers, A. Covaci, G. Schoeters, T. Fierens, I. Sioen, G. Vanermen, W. Baeyens, B. Morrens, I. Loots, V. Nelen, B. N. de Belleaux, N. V. Larebeke and E. D. Hond (2014). "Determinants of bisphenol A and phthalate metabolites in urine of Flemish adolescents." *Environ Res* **134**: 110-117 <https://www.ncbi.nlm.nih.gov/pubmed/25127521>.
  23. Gennings, C., R. Hauser, H. M. Koch, A. Kortenkamp, P. J. Lioy, P. E. Mirkes and B. A. Schwetz (2014). Report by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives, U.S. Consumer Product Safety Commission.
  24. Giovanoulis, G., A. Alves, E. Papadopoulou, A. P. Cousins, A. Schutze, H. M. Koch, L. S. Haug, A. Covaci, J. Magner and S. Voorspoels (2016). "Evaluation of exposure to phthalate esters and

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 22

- DINCH in urine and nails from a Norwegian study population." *Environ Res* **151**: 80-90  
<https://www.ncbi.nlm.nih.gov/pubmed/27466754>.
25. Goen, T., L. Dobler, J. Koschorreck, J. Muller, G. A. Wiesmuller, H. Drexler and M. Kolossa-Gehring (2011). "Trends of the internal phthalate exposure of young adults in Germany--follow-up of a retrospective human biomonitoring study." *Int J Hyg Environ Health* **215**(1): 36-45  
<http://www.ncbi.nlm.nih.gov/pubmed/21889907>
  26. Gray, L.E., Wilson, V.S., Stoker, T. et al. (2006). "Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals." *Int J Androl* **29**:96-104.
  27. Gries, W., D. Ellrich, K. Kupper, B. Ladermann and G. Leng (2012). "Analytical method for the sensitive determination of major di-(2-propylheptyl)-phthalate metabolites in human urine." *J Chromatogr B Analyt Technol Biomed Life Sci* **908**: 128-136  
<http://www.ncbi.nlm.nih.gov/pubmed/23040987>; [http://ac.els-cdn.com/S1570023212005399/1-s2.0-S1570023212005399-main.pdf?\\_tid=3f645e7c-0ee3-11e3-8e01-00000aacb35e&acdnat=1377585673\\_7a2d7e4a84e2ed72c335ec9dd5109873](http://ac.els-cdn.com/S1570023212005399/1-s2.0-S1570023212005399-main.pdf?_tid=3f645e7c-0ee3-11e3-8e01-00000aacb35e&acdnat=1377585673_7a2d7e4a84e2ed72c335ec9dd5109873).
  28. Hatch, E.E., Nelson, J.W., Stahlhut, R.W., Webster, T.F. (2010). "Association of endocrine disruptors and obesity: perspectives from epidemiological studies, *Int J Androl* **32**: 324-269.
  29. Hartmann, C., M. Uhl, S. Weiss, H. M. Koch, S. Scharf and J. König (2015). "Human biomonitoring of phthalate exposure in Austrian children and adults and cumulative risk assessment." *International Journal of Hygiene and Environmental Health* **218**(5): 489-499  
<http://www.sciencedirect.com/science/article/pii/S1438463915000504>.
  30. HBM (Human Biomonitoring) Commission, 2011. "Stoffmonographie für Phthalate - Neue und aktualisierte Referenzwerte für Monoester und oxidierte Metabolite im Urin von Kindern und Erwachsenen. *Bundesgesundheitsbl. Gesundheitsforsch. Gesundheitsschutz* **54**:770-785.
  31. Heudorf, U., V. Mersch-Sundermann and J. Angerer (2007). "Phthalates: toxicology and exposure." *Int J Hyg Environ Health* **210**(5): 623-634  
<http://www.ncbi.nlm.nih.gov/pubmed/17889607>.
  32. Howdeshell, K. L., A. K. Hotchkiss and L. E. Gray, Jr. (2017). "Cumulative effects of antiandrogenic chemical mixtures and their relevance to human health risk assessment." *Int J Hyg Environ Health* **220**(2 Pt A): 179-188 <https://www.ncbi.nlm.nih.gov/pubmed/27923611>.
  33. Katsikantami, I., S. Sifakis, M. N. Tzatzarakis, E. Vakonaki, O.-I. Kalantzi, A. M. Tsatsakis and A. K. Rizos (2016). "A global assessment of phthalates burden and related links to health effects." *Environment International* **97**: 212-236  
<http://www.sciencedirect.com/science/article/pii/S0160412016304147>.
  34. Koch, H. M. and J. Angerer (2012). Phthalates: Biomarkers and Human Biomonitoring. *Biomarkers and Human Biomonitoring* L. E. Knudsen and D. F. Merlo, RSC Publishing. **1**: 179-233.
  35. Koch, H. M. and A. M. Calafat (2009). "Human body burdens of chemicals used in plastic manufacture." *Philos Trans R Soc Lond B Biol Sci* **364**(1526): 2063-2078  
<http://www.ncbi.nlm.nih.gov/pubmed/19528056>
  36. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873011/pdf/rstb20080208.pdf>.
  37. Koch, H. M., A. Haller, T. Weiss, H. U. Kafferlein, J. Stork and T. Bruning (2012). "Phthalate exposure during cold plastisol application--a human biomonitoring study." *Toxicol Lett* **213**(1): 100-106 <http://www.ncbi.nlm.nih.gov/pubmed/21704685>; [http://ac.els-cdn.com/S0378427411012744/1-s2.0-S0378427411012744-main.pdf?\\_tid=bd4868c4-1145-11e3-820f-00000aacb360&acdnat=1377847877\\_7707cf4717c65961e0e2d88ef64edba9](http://ac.els-cdn.com/S0378427411012744/1-s2.0-S0378427411012744-main.pdf?_tid=bd4868c4-1145-11e3-820f-00000aacb360&acdnat=1377847877_7707cf4717c65961e0e2d88ef64edba9).
  38. Koch, H. M., M. Rütther, A. Schütze, A. Conrad, C. Pälmeke, P. Apel, T. Brüning and M. Kolossa-Gehring (2016). "Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012." *Int J Hyg Environ Health* <https://www.ncbi.nlm.nih.gov/pubmed/27863804>.

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 23

39. Larsson, K., C. H. Lindh, B. A. Jonsson, G. Giovanoulis, M. Bibi, M. Bottai, A. Bergstrom and M. Berglund (2017). "Phthalates, non-phthalate plasticizers and bisphenols in Swedish preschool dust in relation to children's exposure." *Environ Int* <https://www.ncbi.nlm.nih.gov/pubmed/28274486>.
40. Larsson, K., K. Ljung Bjorklund, B. Palm, M. Wennberg, L. Kaj, C. H. Lindh, B. A. Jonsson and M. Berglund (2014). "Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children." *Environ Int* **73**: 323-333 <https://www.ncbi.nlm.nih.gov/pubmed/25216151>.
41. Mariana, M., J. Feiteiro, I. Verde and E. Cairrao (2016). "The effects of phthalates in the cardiovascular and reproductive systems: A review." *Environ Int* **94**: 758-776 <https://www.ncbi.nlm.nih.gov/pubmed/27424259>.
42. Mínguez-Alarcón L., I. Souter, Y.H. Chiu, P.L. Williams, J.B. Ford, X. Ye, A.M. Calafat, R. Hauser, Earth Study Team (2016). Urinary concentrations of cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester, a metabolite of the non-phthalate plasticiser di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), and markers of ovarian response among women attending a fertility center. *Environ Res* **151**:595-600.
43. Myridakis, A., E. Fthenou, E. Balaska, M. Vakinti, M. Kogevinas and E. G. Stephanou (2015). "Phthalate esters, parabens and bisphenol-A exposure among mothers and their children in Greece (Rhea cohort)." *Environ Int* **83**: 1-10 <https://www.ncbi.nlm.nih.gov/pubmed/26072145>.
44. Petrovicova, I., B. Kolena, M. Sidlovska, T. Pilka, S. Wimmerova and T. Trnovec (2016). "Occupational exposure to phthalates in relation to gender, consumer practices and body composition." *Environ Sci Pollut Res Int* **23**(23): 24125-24134 <https://www.ncbi.nlm.nih.gov/pubmed/27640056>.
45. Riders, C.V., Furr, J.R., Wilson, V.S., Gray, L.E., Jr (2010). "Cumulative effects of in utero administration of mixtures of reproductive toxicants that disrupt common target tissues via diverse mechanisms of toxicity." *Int J Androl* **33**:443-462.
46. Schoeters, G., E. Govarts, L. Bruckers, E. Den Hond, V. Nelen, S. De Henauw, I. Sioen, T. S. Nawrot, M. Plusquin, A. Vriens, A. Covaci, I. Loots, B. Morrens, D. Coertjens, N. Van Larebeke, S. De Craemer, K. Croes, N. Lambrechts, A. Colles and W. Baeyens (2017). "Three cycles of human biomonitoring in Flanders - Time trends observed in the Flemish Environment and Health Study." *Int J Hyg Environ Health* **220**(2 Pt A): 36-45 <https://www.ncbi.nlm.nih.gov/pubmed/28160993>.
47. Schütze, A., W. Gries, M. Kolossa-Gehring, P. Apel, C. Schröter-Kermani, U. Fiddicke, G. Leng, T. Brüning and H. M. Koch (2015). "Bis-(2-propylheptyl)phthalate (DPHP) metabolites emerging in 24 h urine samples from the German Environmental Specimen Bank (1999–2012)." *International Journal of Hygiene and Environmental Health* **218**(6): 559-563 <http://www.sciencedirect.com/science/article/pii/S1438463915000796>.
48. Schütze, A., M. Kolossa-Gehring, P. Apel, T. Brüning and H. M. Koch (2014). "Entering markets and bodies: Increasing levels of the novel plasticizer Hexamoll® DINCH® in 24 h urine samples from the German Environmental Specimen Bank." *International Journal of Hygiene and Environmental Health* **217**(2–3): 421-426 <http://www.sciencedirect.com/science/article/pii/S1438463913001168>.
49. Schütze, A., R. Otter, H. Modick, A. Langsch, T. Brüning and H. M. Koch (2017). "Additional oxidized and alkyl chain breakdown metabolites of the plasticizer DINCH in urine after oral dosage to human volunteers." *Arch Toxicol* **91**(1): 179-188 <https://www.ncbi.nlm.nih.gov/pubmed/26976210>.
50. Schütze, A., C. Pälme, J. Angerer, T. Weiss, T. Brüning and H. M. Koch (2012). "Quantification of biomarkers of environmental exposure to di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH) in urine via HPLC-MS/MS." *J Chromatogr B Analyt Technol Biomed Life Sci* **895-896**: 123-130 <http://www.ncbi.nlm.nih.gov/pubmed/22503746>; <http://ac.els-cdn.com/S1570023212001900/1->

D 4.2 Scoping Documents for 2018	Security: Public
WP 4 - Prioritisation and input to the Annual Work Plan	Version: 3.1
Authors: Carolin Tschersich, Robert Barouki, Maria Uhl, Jana Klánová, Milena Horvat, Alessandro Alimonti, Denis Sarigiannis, Tiina Santonen, Erik Lebret, Greet Schoeters	Page: 24

[s2.0-S1570023212001900-main.pdf? tid=42b80448-0ee3-11e3-bd65-00000aab0f01&acdnat=1377585679\\_b6f0861bb1c865442d4bcb0e580bfab2.](#)

51. Schwedler, G., M. Seiwert, U. Fiddicke, S. Issleb, J. Holzer, J. Nendza, M. Wilhelm, J. Wittsiepe, H. M. Koch, B. K. Schindler, T. Goen, J. Hildebrand, R. Joas, A. Joas, L. Casteleyn, J. Angerer, A. Castano, M. Esteban, G. Schoeters, E. Den Hond, O. Sepai, K. Exley, L. Bloemen, L. E. Knudsen and M. Kolossa-Gehring (2017). "Human biomonitoring pilot study DEMOCOPHES in Germany: Contribution to a harmonized European approach." *Int J Hyg Environ Health* <https://www.ncbi.nlm.nih.gov/pubmed/28254163>.
52. Wang, I.J., W.J. Karmaus, S.L. Chen, J.W. Holloway, S. Ewart. (2015). Effects of phthalate exposure on asthma may be mediated through alterations in DANN methylation. *Clin Epigenetics* **7**:27.
53. Wittassek, M., H. M. Koch, J. Angerer and T. Bruning (2011). "Assessing exposure to phthalates - the human biomonitoring approach." *Mol Nutr Food Res* **55**(1): 7-31 <http://www.ncbi.nlm.nih.gov/pubmed/20564479>.
54. Wittassek, M., G. A. Wiesmüller, H. M. Koch, R. Eckard, L. Dobler, J. Müller, J. Angerer and C. Schlüter (2007). "Internal phthalate exposure over the last two decades--a retrospective human biomonitoring study." *Int J Hyg Environ Health* **210**(3-4): 319-333 <http://www.ncbi.nlm.nih.gov/pubmed/17400024>.