DRAFT SCIENTIFIC OPINION

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Draft update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and di-isodecylphthalate (DIDP) for use in food contact materials

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Abstract

The EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP Panel) was asked by the European Commission to update its 2005 risk assessments of DBP, BBP, DEHP, DINP and DIDP which are authorised for use in plastic FCM, by using the same database as ECHA for its 2017 assessment of certain phthalates. Dietary exposure estimates (mean and high (P95)) were obtained by combining literature occurrence data with consumption data from the EFSA Comprehensive Database. The highest exposure was found for DINP, ranging from 0.2-4.3 and from 0.4-7.0 µg/kg bw per day for mean and high consumers, respectively. There was not enough information to draw conclusions on how much migration from plastic FCM contributes to dietary exposure to phthalates. The review of the toxicological data focused mainly on reproductive effects. The CEP Panel re-confirmed the same critical effects and individual TDIs (mg/kg bw per day) derived in 2005 for all the phthalates, i.e. reproductive effects for DBP (0.01), BBP (0.5), DEHP (0.05), and liver effects for DINP and DIDP (0.15 each). Based on a plausible common mode of action (i.e. reduction in fetal testosterone) underlying the reproductive effects of DEHP, DBP and BBP, the Panel considered it appropriate to establish a group-TDI for these phthalates, taking DEHP as index compound as a basis for introducing relative potency factors. The Panel noted that DINP also affected fetal testosterone levels at doses around three-fold higher than liver effects and therefore considered it prudent to include it within the group-TDI which was established to be 50 µg/kg bw per day, expressed as DEHP equivalents. The aggregated dietary exposure for DBP, BBP, DEHP and DINP was estimated to be 0.9-7.2 and 1.6-11.7 µg/kg bw per day for mean and high consumers, respectively, thus contributing up to 23% of the group-TDI in the worst case scenario. For DIDP, not included in the group-TDI, dietary exposure was estimated to be always below 0.1 µg/kg bw per day and therefore far below the TDI of 150 µg/kg bw per day. This assessment covers European consumers of any age, including the most sensitive groups.

Keywords: phthalates, food contact materials, DBP, BBP, DEHP, DINP, DIDP, safety assessment

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Summary

The European Commission (EC) asked the European Food Safety Authority (EFSA) in accordance with Article 12(3) of Regulation (EC) No 1935/2004, to update its opinions published in 2005 on certain phthalates (DBP, BBP, DEHP, DINP and DIDP) authorised for use as plasticisers and technical support agents in plastic Food Contact Materials (FCM), and to evaluate whether the authorisation under Regulation (EU) No 10/2011 is still in accordance with the FCM Regulation. According to the Terms of Reference (ToR), the EFSA evaluation should aim at assessing the contribution of the exposure from plastic FCM to the individual tolerable daily intake (TDI) for each of these authorised phthalates, and pronounce itself on the potential health risks resulting from the combined exposure of consumers to these phthalates from plastic FCM.

In compliance with what requested by the EC mandate, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP Panel) used the information that was available to the ECHA RAC for its evaluation of DBP, BBP and DEHP (ECHA, 2017a) in the context of its assessment of the restriction proposal submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation proposing restrictions on these phthalates. In addition, recent exposure and toxicity data on DINP and DIDP, focusing on reproductive effects as these were the basis on which ECHA established a Derived No Effect Level (DNEL) for DEHP, DBP and BBP, were considered.

Consequently, the CEP Panel's assessment is mainly centred on phthalate-induced reproductive toxicity. With regards to the data used for assessing the reproductive toxicity of DINP and DIDP, also the ECHA assessment of DINP and DIDP (ECHA, 2013) as well as the more recent opinion on harmonised classification of DINP (ECHA, 2018) were considered.

The CEP Panel is fully aware of the intrinsic limitations of this approach, and considers that all the potential toxicological endpoints should be examined with the same degree of rigour. However, due to the limited time for the completion of the opinion and the amount of new evidence available since the 2005 publication of the EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) assessments of DBP, BBP, DEHP, DINP and DIDP, the Panel considered it unfeasible to perform a comprehensive review of all the new data on these phthalates.

For this reason, the CEP Panel decided to:

(i) undertake the review of the toxicological data used by ECHA on DBP, BBP and DEHP mainly dealing with reproductive toxicity;

(ii) additionally review the toxicological data for reproductive effects of DINP and DIDP (published after EFSA's previous assessment of phthalates in 2005);

(iii) analyse the possibility of setting a group-health based guidance value for these substances;

(iv) refine the assessment of dietary consumer exposure to these substances which are all authorised in plastic FCMs;

(v) carry out a risk characterisation on this basis.

The Panel highlights that other possible effects (as pointed out by the 2017 ECHA RAC assessment) e.g. on the immune and metabolic systems and/or on neurodevelopment, are evaluated less in-depth and these are taken into account in the uncertainty analysis and in the recommendations of this opinion.

<u>Exposure</u>

Data on the levels of phthalates in food were extracted from the EFSA Chemical Occurrence database (EFSA database). After data cleaning and validation, there was a total of 1,776 results for the five phthalates of interest here, submitted by institutions from five different EU countries. Reported levels of quantification (LOQs) were relatively high, most likely because the analytical methods used were to enforce legislative limits rather than to achieve high sensitivity. The reported samples were 100% left-censored for DIDP and above 95% for DBP, BBP and DINP. For DEHP, the quantified results were still only about 20% of the total, with 24 out of 49 food categories still fully left-censored. Considering

these significant limitations, it was decided to gather occurrence data on phthalates in food from the literature to perform an alternative assessment of dietary exposure.

Papers referenced in the ECHA opinion (2017a) on DBP, BBP, DEHP and DIBP were considered and complemented with additional literature on DINP and DIDP and on specific foods not covered in the literature from ECHA. In most of the studies, only summary statistics were presented for aggregated food groups. Not all papers reported the specific LOQs associated with each of the food categories. Therefore, all the categories reported as left-censored were substituted by 0 (lower bound (LB) approach). In order to match the occurrence data gathered from literature with the consumption data from the EFSA Comprehensive Database, a FoodEx code was assigned to each food descriptor reported in the studies. When more than one chemical occurrence mean/median value was available from different studies for the same FoodEx code, the highest value was used in the assessment of exposure.

The resulting estimates of dietary exposure (ranges of the min-max estimates for all ages, all surveys and all countries) were as follows:

- DBP mean of (0.042 - 0.769) and P95 of (0.099 - 1.503), µg/kg bw per day
- BBP mean of (0.009 - 0.207) and P95 of (0.021 - 0.442), µg/kg bw per day
- DEHP mean of (0.446 - 3.459) and P95 of (0.902 - 6.148), µg/kg bw per day
- DINP mean of (0.232 - 4.270) and P95 of (0.446 - 7.071), µg/kg bw per day
- DIDP mean of (0.001 – 0.057) and P95 of (0.008 – 0.095), µg/kg bw per day)

Taken as a whole, these estimates compared well with, and tend to be slightly higher than, estimates for dietary exposure to these phthalates as reported in three Total Diet Studies (TDS) for the UK, Ireland and France, with samples purchased in 2007, 2012 and 2011-12, respectively.

Hazard characterisation

The review of the literature focused mainly on the reproductive effects of DBP, BBP, DEHP, DINP and DIDP. The critical effects of each of the phthalates were selected and the TDIs were calculated as follows:

- For DBP, a Lower Observed Adverse Effect (LOAEL) of 2 mg DBP/kg bw per day for reduced spermatocyte development and effects on the mammary gland was identified from a developmental toxicity study in rats. The CEP Panel proposes to apply to this Point of Departure (PoD) an uncertainty factor of 200[1] (an extra factor of 2 because of the use of the LOAEL instead of the No Observed Adverse Effect (NOAEL)) for deriving a HBGV.
- For BBP, a NOAEL of 50 mg BBP/kg bw per day was identified from a multi-generation study in rats, based on reduced anogenital distance (AGD) in F1- and F2- males at birth in the 250 mg BBP/kg bw per day group. The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.
- For DEHP, a NOAEL of 4.8 mg DEHP/kg bw per day based on effects on the testis in F1-animals was identified from a three-generation reproductive toxicity study in rats. The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.
- For DINP and DIDP, EFSA set individual TDIs in its evaluations of 2005 based on liver effects:
    - For DINP, a NOAEL of 15 mg DINP/kg bw per day for non-peroxisomal proliferation-related chronic hepatic and renal effects in rats was identified. An uncertainty factor of 100 was applied for deriving the TDI of 0.15 mg/kg bw per day for DINP.
    - For DIDP, a NOAEL of 15 mg DIDP/kg bw per day for liver effects in dogs was identified. An uncertainty factor of 100 was applied for deriving the TDI of 0.15 mg/kg bw per day for DIDP.

[1] ECHA (2017a) used a factor of 3 (total UF 300) for the extrapolation from LOAEL to NAEL.

The CEP Panel concludes that the effect on the liver is still the most sensitive endpoint for these two phthalates. However, the possibility to establish HBGVs for reproductive effects for DINP and DIDP was explored, in order to evaluate whether a grouping (based on reproductive effects) with the other three phthalates was appropriate.

With regards to the grouping of these phthalates due to similar effects, the CEP Panel considered the reduction of the fetal testosterone production in rats induced by DBP, BBP and DEHP as a critical step in the reproductive toxicity of the phthalates. This anti-androgenic effect provided the basis for grouping together these phthalates, there being a plausible mode of action indicating that their reproductive effects occur through a common mechanism. Regarding the anti-androgenic potential of DINP and DIDP, the Panel concluded that DINP shows anti-androgenic effects, i.e. decreased fetal testosterone production, whereas DIDP showed reproductive effects not associated with anti-androgenicity (i.e decreased survival rate in F2).

Therefore, the CEP Panel decided to group DBP, BBP, DEHP and DINP into a group-TDI on the basis of similar anti-androgenic reproductive effects. Nonetheless, the most sensitive endpoint for DINP was still considered to be liver effects. In consequence, the HBGV for reproductive effects of DINP was adjusted by means of an additional assessment factor of 3.3 to account for the differences in potency between the effects on liver and reproduction.

DEHP was identified as index compound since it has the most robust underlying toxicological dataset. Consequently, the group-TDI was established to be 0.05 mg/kg bw per day, expressed as DEHP equivalents, and the relative potency factors for the other phthalates were calculated by comparing the respective HBGVs. DIDP maintained its individual TDI for liver effects of 0.15 mg/kg bw per day.

<u>Risk characterisation</u>

Having decided to group DBP, BBP, DEHP and DINP into a common assessment group and to allocate potency factors relative to DEHP as the reference substance to derive a group-TDI, an aggregated dietary exposure assessment to these phthalates was carried out. The following equation was applied at the level of chemical occurrence (concentration) data for each food category:

GroupPhthalates concentration expressed as DEHP Equivalents ([GPDEq], µg/kg food) = DEHP*1 + DBP*5 + BBP*0.1 + DINP*0.3.

The highest estimated exposure for GroupPhthalates was in the range of 0.9-7.2 for the mean consumer and 1.6-11.7 µg/kg bw per day for the high (P95) consumers.

Comparing the GroupPhthalates exposure estimates for the mean consumer with the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents), it can be concluded that this exposure contributes for 1.8 to 14% of the group-TDI.

As regards the high (P95) consumers, it can be concluded that the exposure amounts for 3 to 23% of the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents).

These conclusions cover all European population groups (all countries, all surveys, all age groups), including children and women of child-bearing age.

As regards DIDP, not being included in the group-TDI due to its lack of anti-androgenic effects, a separate risk analysis was conducted. According to the exposure estimates, covering all population groups (all countries, all surveys, all age groups), the mean exposure level was 0.001-0.057 µg/kg bw per day, and the P95 exposure level was 0.008-0.095 µg/kg bw per day. These estimates are far below the TDI for DIDP of 150 µg/kg bw per day, which is based on liver effects.

<u>Contribution from plastic FCM</u>

The above estimates concern exposure from food containing phthalates from all sources (e.g. FCM, environment, etc.). The Panel addressed the question of the contribution of the exposure from specifically plastic FCM to the group-TDI for these authorised phthalates. Clearly, the contribution of plastics, or even FCM more generally, cannot exceed the total estimates from food, being 3 to 23% of the group-TDI for the high consumers. The CEP Panel examined several papers with the aim to derive the contribution from plastic FCM. However, the CEP Panel noted that in general there is not enough information available to make firm conclusions on the contribution from plastic FCM.

Uncertainties

A qualitative approach was chosen for the uncertainty analysis. In addition to several other sources of uncertainty, for the hazard identification and characterisation, the main impacts on risk assessment were attributed to the following issues:

- Due to the limited time for the completion of the evaluation and the large amount of new evidence available since the EFSA AFC Panel's assessments of DBP, BBP, DEHP, DINP and DIDP in 2005, the CEP Panel considered it unfeasible to perform a comprehensive review of all the new data on these phthalates. In agreement with ECHA's assessment of 2017, the Panel concluded that effects not evaluated in depth in this opinion, in particular potential effects on neurodevelopment, the immune and/or the metabolic systems, could be more sensitive endpoints compared to the reproductive toxicity. This could lead to an underestimation of the risk based on the currently proposed group approach focusing on the reprotoxic/anti-androgenic effects.
- In addition, the CEP Panel is aware that other phthalates than those under evaluation in this opinion, such as DIBP, may have reproductive toxic/anti-androgenic (and potentially other relevant) effects. DIBP is not authorised for use in plastic food contact materials, and therefore not within the scope of this assessment. However, noting the similar i) potency with regards to reprotoxic effects and ii) intake estimates compared to DBP (as outlined in the ECHA RAC assessment of 2017), the CEP Panel considers that DIBP substantially adds to the overall exposure of consumers to phthalates, from food and from other sources.

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1. Introduction

1.1. Background and Terms of Reference as provided by the European Commission

"The Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) published in March 2017 an opinion on DBP, BBP, DEHP and DIBP in the context of a restriction dossier under Annex XV of the REACH Regulation. This opinion is expected to lead to a proposal for an amendment of Annex XVII to REACH.

In 2005, EFSA published opinions on three of these phthalate esters (di-butylphthalate (DBP, FCM No 157), butyl-benzyl-phthalate (BBP, FCM No 159), and Bis(2-ethylhexyl)phthalate (DEHP, FCM No 283), which have since been authorised for use as plasticisers and technical support agents in plastic Food Contact Materials (FCM).

In its 2017 evaluation, the ECHA RAC made use of scientific information which was largely available only after the 2005 EFSA assessments of these phthalates. This new information should therefore be considered to determine whether the 2005 EFSA opinions on these three phthalate esters in the context of food contact materials are still valid.

Therefore, on the basis of Article 12(3) of Regulation (EC) No 1935/2004 ('the FCM Regulation'), the Commission hereby requests EFSA to evaluate whether the opinion and the authorisation under Regulation (EU) No 10/2011 are still in accordance with the FCM Regulation. When on the basis of the new scientific information the CEF Panel concludes in its opinion that this is not the case, the conditions under which the use of these three substances can be considered safe shall be characterised in order to allow the Commission to update its risk management Decision accordingly.

This review of the 2005 EFSA opinions for these phthalates should be conducted on the basis of the data package used by the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) to establish the opinion it published in March 2017. To this end, EFSA should use all the information available to ECHA which was submitted in support of the restriction dossier and was used by the RAC in its assessment of these phthalates, including the information on exposure.

We would be grateful if EFSA would deliver the updated opinions by November 2018. However, given these substances are SVHC and authorised at a relatively high use in some FCM, the EFSA should notify the Commission without delay if during the assessment the Panel identifies significant health risks, to allow the Commission to consider a potential temporary measure to address these risks.

Terms of Reference

In accordance with Article 12(3) of Regulation (EC) No 1935/2004[2], the European Commission asks EFSA to update its 2005 opinions on the safety assessment of di-butylphthalate (DBP, FCM No 157), butyl-benzyl-phthalate (BBP, FCM No 159), Bis(2-ethylhexyl)phthalate (DEHP, FCM No 283), which have been authorised for use as plasticisers and technical support agents in plastic Food Contact Materials (FCM).

In doing so, the CEF Panel should use all the information available to the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) on DBP, BBP and DEHP in the context of the dossier under Annex XV of the REACH Regulation[3] proposing restrictions on these three phthalates.

Using the ECHA RAC exposure assessment, the updated opinions should seek to assess the contribution of FCM to the individual TDI for each of these three phthalates, and pronounce themselves on the potential health risks resulting from the exposure of consumers to these three phthalates from food contact materials.

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[2] OJ L 338, 13.11.2004, p. 4.

[3] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000 21 EC (0.1 I. 396 30.12.2006. p.l.).

Given these substances are to be added to the REACH list of Substances of Very High Concern (SVHC), and authorised at a relatively high use in some FCM, EFSA should notify the Commission without delay if during the assessment the Panel identifies significant health risks, to allow the Commission to consider a potential temporary measure to address these risks."

To address this mandate, the EFSA CEF Panel set up an ad hoc Working Group (WG) on phthalates. During their first meeting, the WG members noted that the three phthalates mentioned in the mandate (especially DEHP) are being replaced by other phthalates such as DINP, which are also authorised for use in plastic FCM according to Regulation (EU) No 10/2011. This may have a considerable impact on the current exposure pattern of the general population as well as on the assessment of the combined exposure to several phthalates that might have similar toxicological properties. These observations were formally expressed in the minutes of the first WG meeting[4] and as a result the EC sent EFSA an updated mandate whose Terms of Reference (ToR) is reported below. Concomitantly, the deadline for delivery of the opinion was extended to December 2018.

Terms of Reference as provided in the updated mandate

"In accordance with Article 12(3) of Regulation (EC) No 1935/2004[5], the European Commission asks EFSA to update its 2005 opinions on the safety assessment of di-butylphthalate (DBP, FCM No 157), butyl-benzyl-phthalate (BBP, FCM No 159), and Bis(2-ethylhexyl)phthalate (DEHP, FCM No 283), which have been authorised for use as plasticisers and technical support agents in plastic Food Contact Materials (FCM).

In doing so, the EFSA should make use of the data and information on DBP, BBP and DEHP used by the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC) in the context of the dossier under Annex XV of the REACH Regulation[6] proposing restrictions on these three phthalates. In addition, in elaborating its views, the EFSA should also consider recent exposure and toxicity data on two other phthalates authorised for use in plastic FCM, namely DINP and DIDP, focusing on reproductive effects as these were the basis on which ECHA established a Derived No Effect Level (DNEL) for DEHP, DBP and BBP.

The opinion should aim to assess the contribution of the exposure from plastic FCM to the individual TDI for each of these authorised phthalates, and pronounce itself on the potential health risks resulting from the combined exposure of consumers to these phthalates from plastic FCM.

Given these substances are SVHC and authorised at a relatively high use in some plastic FCM, the EFSA should notify the Commission without delay if during the assessment the Panel identifies significant health risks, to allow the Commission to consider a potential temporary measure to address these risks."

1.2. Interpretation of the Terms of Reference

The EC asked EFSA to elaborate its views by making use of the data and information on DBP, BBP and DEHP that were used by the ECHA RAC in the context of its assessment of the restriction proposal submitted under the REACH Regulation proposing restrictions on these phthalates. In addition, EFSA should also consider recent exposure and toxicity data on DINP and DIDP, focusing on reproductive effects as these were the basis on which ECHA established a Derived No Effect Level (DNEL) for DEHP, DBP and BBP.

[4] https://www.efsa.europa.eu/sites/default/files/wgs/food-ingredients-and-packaging/minutes_phthalateswg.pdf.

[5] OJ L 338, 13.11.2004, p. 4.

[6] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21 /EC (OJ L 396 30.12.2006, p. 1.).

The toxicological information on DBP, BBP and DEHP used by the ECHA RAC was focused on reproductive toxicity as this was the effect with the underlying most robust dataset. Other potential effects, e.g. on the immune and metabolic systems and/or on neurodevelopment, were concisely discussed in this ECHA RAC opinion, even though the RAC itself recognised that there were (qualitative) indications that they could possibly be equally or more sensitive (e.g. effects on the immune system) than reproductive toxicity. While performing this risk assessment, a new opinion of the ECHA became available on DINP (ECHA, 2018): this opinion concluded that no harmonised classification (CLH) for Reproductive toxicity under the CLP Regulation was required for DINP based on the lack of any significant adverse reproductive effects on sexual function and fertility, or on development in animal studies.

In compliance with the EC mandate referring to the predefined dataset underlying the 2017 ECHA's proposal to restrict the use of DBP, BBP, DEHP and DIBP under the REACH Regulation, also this CEP Panel's assessment is mainly centred on phthalate-induced reproductive toxicity.

The CEP Panel is aware of the intrinsic limitations of this approach, and considers that all the potential toxicological endpoints should be examined with the same degree of rigour. However, due to the limited time for completion of the opinion and the amount of new evidence available since the 2005 publication of the EFSA AFC Panel's assessments of DBP, BBP, DEHP, DINP and DIDP (EFSA, 2005a, b, c, d, e), the Panel considered it unfeasible to perform a comprehensive review of all the new data on these phthalates.

For this reason, the CEP Panel decided to:

(i) undertake the review of the toxicological data used by ECHA on DBP, BBP and DEHP mainly dealing with reproductive toxicity;

(ii) additionally review the toxicological data for reproductive effects of DINP and DIDP (published after EFSA's previous assessment of phthalates in 2005), including also the ECHA RAC assessment of DINP and DIDP (2013) and the ECHA RAC opinion on a proposal for harmonised classification and labelling of DINP (2018);

(iii) analyse the possibility of setting a group-health based guidance value for these substances;

(iv) refine the assessment of dietary consumer exposure to these substances which are all authorised in plastic FCMs;

(v) carry out a risk characterisation on this basis.

The Panel highlights that other possible effects e.g. on the immune and metabolic systems and/or on neurodevelopment, are evaluated less in-depth and these are taken into account in the uncertainty analysis and considered in the recommendations of this opinion.

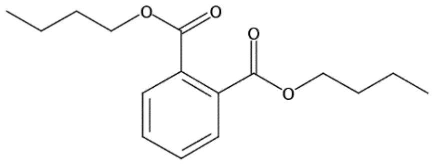
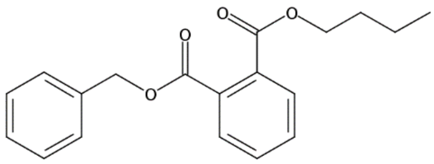
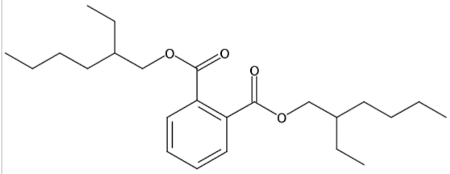
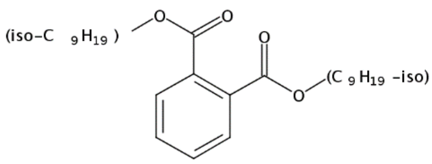
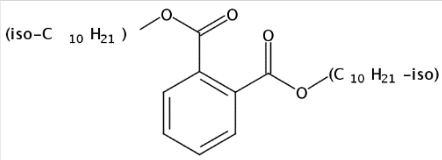
Overall, the Panel noted the high complexity and challenges posed by the assessment of the toxicology of- and of the exposure to- five different phthalates, when assessed either alone or in combination. Therefore, the need for a public consultation on the draft opinion was put forward to take into due consideration the high sensitivity of the topic and ensure openness and transparency in the process, as well as the engagement of all interested parties.

1.3. Additional information

1.3.1. Background

Phthalates or phthalic acid esters are dialkyl or alkyl aryl esters of phthalic acid commonly used as additives to increase the flexibility and other properties of plastic materials. They can have other functions too, as technical support agents in plastic FCM production, for example as solvents or carrier media. Phthalates can migrate into food from plastic FCM, therefore EFSA set in 2005 Tolerable Daily Intake values (TDIs) for several phthalates, namely for di-butylphthalate (DBP, 0.01 mg/kg bw per day), butylbenzylphthalate (BBP, 0.5 mg/kg bw per day), bis(2-ethylhexyl)phthalate (DEHP, 0.05 mg/kg bw per day), di-isononylphthalate (DINP, 0.15 mg/kg bw per day) and di-isodecylphthalate (DIDP, 0.15 mg/kg bw per day). The phthalates included in this opinion are listed in Table 1, together with the abbreviation used throughout the document and their identifier numbers.

Table 1: Description of the phthalates included in the mandate

Name	Acronym	CAS number(a)	FCM substance number(b)	Molecular weight (g/mol)	Chemical Structure(c)
Dibutyl-phthalate	DBP	84-74-2	157	278.34	
Butylbenzyl-phthalate	BBP	85-68-7	159	312.36	
Bis(2-ethylhexyl) phthalate (also known as Bis(2-ethylhexyl)phthalate)	DEHP	117-81-7	283	390.56	
Di-isononyl-phthalate	DINP	68515-48-0 28553-12-0	729	420.6 (average)	
Di-isodecyl-phthalate	DIDP	68515-49-1 26761-40-0	728	446.68 (assuming the molecular formula / structure shown)	

(a): DIDP and DINP have each two different CAS numbers, this is due to two different production processes with differences in isomeric distribution curves
(b): According to Regulation (EU) No 10/2011
(c): Images from Scifinder

1.3.2. Previous EFSA assessments

The former EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) was asked to re-evaluate DBP, BBP, DEHP, DIDP and DINP for use in the manufacture of plastic FCMs, and as a result it issued five separate opinions in 2005 (EFSA, 2005a, b, c, d, e). In addition, the AFC Panel published a statement regarding the possibility of allocating a group-TDI for those five phthalates (EFSA, 2005f).

DBP (EFSA, 2005a)

The AFC Panel focused on the most sensitive toxicological endpoints for DBP, namely reproduction and developmental toxicity. The Point of Departure (PoD) for the TDI was identified in a rat developmental toxicity study showing loss of germ cell development and mammary gland changes at the lowest dose given via the diet, i.e. 20 mg/kg diet (Lee et al., 2004). This dose corresponded to 1.5-3 mg DBP/kg bw per day and therefore, a NOAEL could not be established. The AFC Panel set the TDI for DBP to 0.01 mg/kg bw per day, based on a LOAEL of 2 mg/kg bw per day and making use of an uncertainty factor of 200 to account for the PoD derivation from a LOAEL. Using the limited exposure data available, the AFC Panel noted that the exposure to DBP from food consumption was in the range of the TDI.

BBP (EFSA, 2005b)

The AFC Panel identified reproductive and developmental toxicity as the most sensitive toxicological endpoint for BBP. After reviewing the literature, a NOAEL of 50 mg BBP/kg bw per day was identified in a rat multi-generation study (Tyl et al., 2001, 2004) based on testicular toxicity and reduced anogenital distance (AGD) at birth in F1 and F2 generations. The AFC Panel applied an uncertainty factor of 100 to the selected NOAEL and set the TDI to 0.5 mg/kg bw per day. Using the limited exposure data available, the AFC Panel noted that the dietary exposure to BBP (derived from packaging and other sources) could contribute up to about 1% of the TDI value.

DEHP (EFSA, 2005c)

The data available in 2005demonstrated that exposure to DEHP affects both fertility and reproduction in rodents of both sexes and also produces developmental effects in the offspring. A NOAEL of 5 mg/kg bw per day for testicular toxicity and developmental toxicity was identified from the study by Wolfe and Layton (2003). The AFC Panel applied an uncertainty factor of 100 to the selected NOAEL and set the TDI to 0.05 mg/kg bw per day. Using the limited exposure data available, the AFC Panel noted that the exposure to DEHP from food consumption was in the range of the TDI.

DINP (EFSA, 2005d)

Hepatic changes that were seen in various studies were taken as the key toxicological effects for DINP. In a two-year chronic toxicity study in rats (Exxon, 1986; also cited as Lington et al., 1997), there was an increased incidence of spongiosis hepatis, accompanied by increases in serum levels of liver enzymes and in absolute and relative liver and kidney weights in both sexes. The AFC Panel identified a NOAEL of 15 mg/kg bw per day for non-peroxisomal proliferation-related chronic hepatic and renal effects. The AFC Panel applied an uncertainty factor of 100 to the selected NOAEL and set the TDI of 0.15 mg/kg bw per day. The AFC Panel noted that the estimated exposure via the diet (around 10 µg/kg bw per day) was below the TDI. However, it also recommended to update the dietary exposure estimates.

DIDP (EFSA, 2005e)

From the several toxicological studies available on DIDP that were reviewed in 2005, the AFC Panel concluded that effects on liver, reproduction and development were the most relevant for risk assessment purposes. Based on the liver effects seen in dogs (a species considered as a non-sensitive species to peroxisome proliferation) in a 13-week oral study with DIDP (Hazleton, 1968), a NOAEL of 15 mg/kg bw per day was identified. The AFC Panel applied an uncertainty factor of 100 to the selected NOAEL and set the TDI of 0.15 mg/kg bw per day. The AFC Panel noted that the estimated exposure via the diet (around 7 µg/kg bw per day) was below the TDI. However, it also recommended to update the dietary exposure estimates.

While evaluating DINP and DIDP, the AFC Panel proposed that a group restriction for migration of these two phthalates from plastic food contact materials should be established, based on the fact that these phthalates are isomeric mixtures that overlap chemically with each other and cannot be analytically distinguished if present in a mixture.

Statement of the AFC Panel on the possibility of allocating a group-TDI for five phthalates (EFSA, 2005f)

The possibility of allocating DBP, BBP, DEHP, DIDP and DINP in a group-TDI was considered by the AFC Panel in 2005 after having reviewed these phthalates individually. The evidence then available supported that DBP and DEHP exerted pivotal effects on germ cell development/depletion, BBP on epididymal spermatozoa concentration and DINP and DIDP on the liver. While the three phthalates DBP, DEHP and BBP seemed to act on the same target organ (the testis), the profile of their effects at the hormonal and cellular level was not identical and their individual modes of action (MoA) had yet to be demonstrated. The AFC Panel then concluded in 2005 that a group-TDI could not be allocated to these five phthalates in consideration of their different pivotal effects.

1.3.3. ECHA RAC Opinion on DEHP, BBP, DBP and DIBP

ECHA published an opinion on an Annex XV dossier proposing restrictions on DBP, di-isobutylphthalate (DIBP), DEHP and BBP in 2017. That ECHA RAC opinion (ECHA, 2017a) made use of scientific information which was largely available after the 2005 EFSA assessments of DBP, BBP and DEHP. This is the new information that EFSA, according to the ToR of the mandate, should consider to update its 2005 EFSA opinions on these three phthalates in the context of FCM.

The hazard characterisation in the ECHA opinion covers an extensive review of the literature focusing on the reproductive toxicity of phthalates which is the endpoint with the most robust dataset for the risk assessment of these four phthalates. As described in the ECHA opinion, all four phthalates adversely affect the male reproductive organs and sexual differentiation during fetal development due to their common anti-androgenic effects. Based on these effects, these four phthalates are classified as reproductive toxicants class 1B.

The critical effects and relative PoDs selected by ECHA for calculating the DNELs for DBP, BBP and DEHP, are the following:

- DBP-induced reduction in spermatocyte development and mammary gland changes in adult male offspring, with a LOAEL of 2 mg/kg bw per day (being the lowest dose tested in the study by Lee et al. (2004));
- BBP-induced reduction in AGD, with a NOAEL of 50 mg/kg bw per day (Nagao et al., 2000; Tyl et al., 2004; Aso et al., 2005);
- DEHP-induced small reproductive organs (testes and prostate) and testis atrophy with a NOAEL of 4.8 mg/kg bw per day (Wolfe and Layton, 2003).

Endpoints other than reproductive toxicity were covered less extensively in the ECHA opinion (ECHA, 2017a) and the background document to that opinion (ECHA, 2017b).

As stated in the opinion, "RAC supports the primary focus on the effects known as phthalate syndrome, but also recognises there are (qualitative) indications for other effects that could possibly be equally or more sensitive (e.g. effects on the immune system)". In particular some recent studies indicate that there could be other effects associated with exposure to phthalates (and particularly to DEHP), such as effects on the immune system, metabolism and neurodevelopment.

The conclusions on human health hazard assessment highlight that even though reproductive toxicity was selected as the most relevant effect, there are indications that phthalate exposure could lead to immunological disorders (allergy, asthma and eczema) possibly at levels lower than reproductive toxicity. The effects on other endpoints such as metabolism and neurodevelopment have not been elucidated yet.

The exposure assessment of ECHA RAC principally relied on urinary biomonitoring, in particular on mother-child pairs' urinary biomonitoring data generated in the EU-wide DEMOCOPHES project (FPS, 2013) and the study by Myridakis et al. (2015). Studies that combined the duplicate diet method or changes in the diet (fasting or low-phthalate diet) with biomonitoring were used to estimate the fraction of exposure that can be attributed to exposure via food. On the basis of these studies, ECHA RAC assumed that 75% of the intake of DEHP is attributable to food (incl. drinks), while for DBP, BBP and DIBP the assumed contribution from food is lower (25%) (ECHA, 2017a).

In addition, exposure modelling was performed, mainly to characterise the relative contributions of the different exposure sources. The exposure to the four phthalates was modelled for the indoor environment, for ingestion of food and for contact with articles. By correcting for absorption, the exposure estimates were converted into internal dose estimates (µg/kg bw per day). Two scenarios were made: a typical (median, average) scenario for average consumers and a reasonable worst case (95th percentile, average) scenario for highly exposed consumers. Comparing the so derived exposure values from different sources, it was suggested that for DEHP the contribution from food is only 38%, 51% and 36% in infants, children and adults respectively. Lower contributions from exposure via food result for DBP and BBP (DBP: 32%, 19% and 10% in infants, children and adults respectively; BBP: 0% (no recent data available), 34% and 22% in infants, children and adults respectively) (for DIBP: 44%, 35% and 18% in infants, children and adults respectively).

Risk characterisation was only performed for the health of the general public. Risk was expressed by the so-called Risk Characterisation Ratio (RCR), obtained by calculating for each phthalate the ratio between the estimated (internal) exposure level and the DNEL (internal dose). If the RCR exceeds 1, i.e. when the exposure to a substance exceeds its DNEL, it can be concluded that the risk is not adequately controlled. Total risk from combined phthalate exposure was calculated by summing up the RCRs of the individual phthalates based on the dose addition principle.

RCRs were calculated for exposure to the four phthalates as estimated from median and 95th percentile urinary biomonitoring exposure levels. When considering the DEMOCOPHES data (FPS, 2013) in combination with the Myridakis et al. (2015) data, the ECHA RAC noted that there is an EU-wide risk for the reasonable worst case (P95) scenario for both children and mothers.

The RCRs were also calculated for the modelled exposure estimates for exposure via indoor environment, food and contact with articles. These appeared to be in reasonably good agreement with the biomonitoring RCRs. The RAC concluded that the existing regulatory risk management instruments are not sufficient to manage the risks from these four phthalates.

1.3.4. ECHA RAC opinion on DINP

In March 2018, ECHA RAC adopted an opinion on a proposal for harmonised classification and labelling at EU level of DINP (ECHA, 2018).

The dossier submitter (Denmark) had initially proposed a classification of DINP in the hazard class "Reproductive toxicity" Category 1B (hazard statement code H360Df: 'May damage the unborn child. Suspected of damaging fertility.'), considering adverse effects on sexual function and fertility and on development (both in human and non-human studies). Comparing relevant endpoints (nipple retention, AGD, hypospadias, testosterone production/content) with the effects on developmental toxicity of other phthalates, such as DBP, BBP and DEHP, for which a harmonised classification as Repr. 1B is already applicable, the dossier submitter identified a similar pattern of adverse effects and of MoA for DINP. Therefore, the dossier submitter concluded that a classification of DINP was supported.

However, assessing the available data and comparing the results with the classification criteria, the ECHA RAC concluded:

"DINP does not induce irreversible gross-structural malformations such as hypospadias and cryptorchidism in rats, nor permanent decreases of AGD or permanent nipple retention. Reversible histological changes in foetal testes and effects on testosterone production alone are not considered to justify classification. Therefore, RAC concluded that DINP warrants no classification for developmental toxicity. Overall, RAC concluded that no classification for DINP for either effects on sexual function and fertility, or for developmental toxicity is warranted."

1.3.5. Legislation

Use authorised in plastic FCM

The phthalates DBP, BBP, DEHP, DINP and DIDP are listed and authorised in the positive list in Annex I (Table 1) of Regulation (EC) No 10/2011[7] on plastic materials and articles intended to come into contact with food. They are authorised under a set of restrictions and specifications, as follows:

- Phthalic acid, dibutyl ester (DBP, FCM substance no 157; ref. no. 74880; CAS no. 000084-74-2) to be used only as:
  (a) plasticiser in repeated use materials and articles contacting non-fatty foods;
  (b) technical support agent in polyolefins in concentrations up to 0.05% in the final product.
  With a Specific Migration Limit (SML) = 0.3 mg/kg food simulant (including an allocation factor of 2).
- Phthalic acid, benzyl butyl ester (BBP, FCM substance no 159; ref. no. 74560; CAS no. 000085-68-7) to be used only as:
  (a) plasticiser in repeated use materials and articles;
  (b) plasticiser in single-use materials and articles contacting non-fatty foods except for infant formulae and follow-on formulae as defined by Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC;
  (c) technical support agent in concentrations up to 0.1% in the final product.
  With a SML = 30 mg/kg food simulant.
- Phthalic acid, bis (2-ethylhexyl) ester (DEHP, FCM substance no 283; ref. no. 74640; CAS no. 000117-81-7) to be used only as:
  (a) plasticiser in repeated use materials and articles contacting non-fatty foods;
  (b) technical support agent in concentrations up to 0.1% in the final product.
  With a SML = 1.5 mg/kg food simulant (including an allocation factor of 2).
- Phthalic acid, diesters with primary, saturated C8-C10 branched alcohols, more than 60% C9 (DINP, FCM substance no 728; ref. no. 75100; CAS no. 068515-48-0 and 028553-12-0) to be used only as:
  (a) plasticiser in repeated use materials and articles;
  (b) plasticiser in single-use materials and articles contacting non-fatty foods except for infant formulae and follow-on formulae as defined by Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC;
  (c) technical support agent in concentrations up to 0.1% in the final product.
  With a Total specific migration limit (SML(T)) = 9 mg/kg food simulant (sum of FCM substance no. 728 and 729).
- Phthalic acid, diesters with primary, saturated C9-C11 alcohols more than 90% C10 (DIDP, FCM substance no 729; ref no. 75105; CAS no. 068515-49-1 and 026761-40-0) to be used only as:
  (a) plasticiser in repeated use materials and articles;
  (b) plasticiser in single-use materials and articles contacting non-fatty foods except for infant formulae and follow-on formulae as defined by Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC;
  (c) technical support agent in concentrations up to 0.1% in the final product.
  With a SML(T) = 9 mg/kg food simulant (sum of FCM substance no. 728 and 729).

[7] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. Available online: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32011R0010&from=EN

As stated above, DBP, BBP and DEHP are authorised with individual specific migration limits, while DINP and DIDP are authorised under a group restriction (Group Restriction No. 26) where the sum of the substances cannot exceed the SML(T).

These 5 phthalates along with a number of other (dissimilar) substances (ca. 20 in total, including the phthalates) are also covered in the Regulation by Group Restriction No. 32, whereby a group total migration limit (SML (T)) of 60 mg/kg is established for that group. The value of 60 mg/kg stems from technical rather than toxicological considerations and is equal to the Overall Migration Limit for plastic FCM.

A summary of the restriction parameters for the 5 phthalates as set out in Regulation (EC) No 10/2011 is provided in Table 2 (adapted from Hoekstra et al., 2011).

Table 2: Restriction parameters for the 5 phthalates as set out in Regulation (EC) No 10/2011

<table>
<tr><th>FCM no.

Ref. no.</th><th>Substance</th><th>Use</th><th>SML</th><th>QM</th><th colspan="3">Parameter to control in single use Food Contact Material *</th><th colspan="3">Parameter to control in repeated use Food Contact Material</th></tr>
<tr><td></td><td></td><td></td><td>mg/kg food</td><td>w/w % in plastic</td><td>Fatty food</td><td>Infant food@</td><td>Non-fatty food</td><td>Fatty food</td><td>Non-fatty food</td><td>Infant food (non-fatty)</td></tr>
<tr><td rowspan="2">159

74560</td><td rowspan="2">BBP</td><td>Plasticiser</td><td>30</td><td>n.r.</td><td colspan="2">n.a.</td><td rowspan="2">SML</td><td rowspan="2" colspan="3">SML</td></tr>
<tr><td>TSA</td><td>30</td><td>0.1</td><td colspan="2">QM(+SML)&</td></tr>
<tr><td rowspan="2">283

74640</td><td rowspan="2">DEHP</td><td>Plasticiser</td><td>1.5</td><td>n.r.</td><td colspan="3">n.a.</td><td>n.a.</td><td rowspan="2" colspan="2">SML</td></tr>
<tr><td>TSA</td><td>1.5</td><td>0.1</td><td colspan="3">QM(+SML)&</td><td>QM(+SML)&</td></tr>
<tr><td rowspan="2">157

74880</td><td rowspan="2">DBP</td><td>Plasticiser</td><td>0.3</td><td>n.r.</td><td colspan="3">n.a.</td><td>n.a.</td><td rowspan="2" colspan="2">SML</td></tr>
<tr><td>TSA</td><td>0.3</td><td>0.05 #</td><td colspan="3">QM(+SML)&</td><td>QM(+SML)&</td></tr>
<tr><td rowspan="2">728

75100</td><td rowspan="2">DINP</td><td>Plasticiser</td><td>9 $</td><td>n.r.</td><td colspan="2">n.a.</td><td rowspan="2">SML</td><td rowspan="2" colspan="3">SML</td></tr>
<tr><td>TSA</td><td>9 $</td><td>0.1</td><td colspan="2">QM(+SML)&</td></tr>
<tr><td rowspan="2">729

75105</td><td rowspan="2">DIDP</td><td>Plasticiser</td><td>9 $</td><td>n.r.</td><td colspan="2">n.a.</td><td rowspan="2">SML</td><td rowspan="2" colspan="3">SML</td></tr>
<tr><td>TSA</td><td>9 $</td><td>0.1</td><td colspan="2">QM(+SML)&</td></tr>
</table>

n.r.: not relevant
n.a.: not authorised
* Packaging made from glasses with lid containing a plasticized gasket is usually considered as a single use material
# only permitted in polyolefins
$ SML(T) is sum of DINP and DIDP
& if QM complies, the SML needs to be tested
@ infant formulae and follow-on formulae as defined by Directive 2006/141/EC) and processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC

<u>Restriction in articles</u>

Based on the opinions of RAC and SEAC (ECHA, 2017a), the Commission concluded that the phthalates DEHP, DBP, BBP and DIBP pose an unacceptable risk to human health and introduced a restriction (Commission Regulation (EU) 2018/2005). According to this restriction[8], DEHP, DBP, BBP and DIBP shall not be placed on the market after 7 July 2020 in articles, individually or in any combination of these phthalates, in a concentration equal to or greater than 0,1 % by weight of the plasticised material in the article (safe some exemptions). The restriction also introduces a ban on the placing on the market of toys and childcare articles containing DIBP (placing on the market of toys and childcare articles containing DEHP, DBP and BBP under certain conditions was already banned).

DINP and DIDP are restricted for those toys and child care articles which can be placed in the mouth by children. These phthalates should not be present in concentrations greater than 0.1 % by weight of the plasticised material.

It has to be noted however that certain product categories, among other FCM, do not fall within the scope of these restrictions. As described above, specific restrictions for the use of the 5 phthalates DBP, BBP, DEHP, DINP and DIDP in plastic food contact materials, are set out in Regulation 10/2011.

2. Data and Methodologies

2.1. Data

In accordance with the ToR provided by the European Commission, the CEP Panel used all the information available to the ECHA RAC on DBP, BBP and DEHP in the context of the submitted restriction dossier (ECHA, 2017a).

As the opinion was being developed, some areas of interest that were not included in the data package from ECHA emerged. Literature searches were thus performed to complement the information available in the ECHA RAC opinion (ECHA, 2017a). These were specifically targeted to the following areas:

- Other effects than reproductive toxicity for DBP, BBP and DEHP, namely immunological, metabolic and neurological effects. These searches of the literature from 2016 to 2018 were conducted to obtain an overview of the recent research trends focusing on these effects. The outcome of these searches is described in the recommendations (8) and uncertainties (6) sections of this opinion.
- Exposure data (dietary exposure and food occurrence data) and data on reproductive effects of DINP and DIDP, since these two phthalates were not part of the ECHA RAC opinion (2017a), but were added to the ToR of this opinion with the request to focus the assessment on their reproductive effects.

In addition to the literature search on the reproductive toxicity of DINP and DIDP, two other ECHA reports were used to support the evaluation of these substances: ECHA's review report on DINP and DIDP (ECHA, 2013), and the ECHA RAC opinion on the proposal for harmonised classification and labelling of DINP (ECHA, 2018).

A summary of all the different literature searches performed for this opinion can be found in Table 3.

[8] Commission Regulation (EU) 2018/2005, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32018R2005

Table 3: Summary of the targeted literature searches performed

Search	Database(s) used	Search timespan	Date performed	Additional information
Immunological effects of DEHP, DBP and BBP	Web of Science	2016-2018	23/02/2018	Advanced search Indexes: SCI-EXPANDED, ESCI, CCR-EXPANDED Language: English
Metabolic effects of DEHP, DBP and BBP			22/02/2018	
Neurological effects of DEHP, DBP and BBP			23/02/2018	
Dietary exposure and occurrence data of DINP and DIDP	Web of Science	2005-2018	03/10/2018	Advanced search Indexes: SCI-EXPANDED, ESCI, CCR-EXPANDED Language: English
Reproductive effects of DINP and DIDP	Web of Science, Scopus, PubMed and TOXLINE	No time restraints	26/03/2018-04/04/2018	Advanced search Indexes: SCI-EXPANDED, ESCI, CCR-EXPANDED Language: English (for Web of Science) n/a for Scopus, PubMed and TOXLINE

2.2. Methodologies

The assessment was conducted in line with the principles described in the EFSA 'Guidance on transparency in the scientific aspects of risk assessment' (EFSA, 2009) and following the relevant existing guidance's of EFSA Scientific Committees, i.e. the Guidance on Uncertainty Analysis in Scientific Assessments (EFSA Scientific Committee, 2018a) and the Draft guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (EFSA Scientific Committee, 2018b).

3. Exposure assessment

3.1. Food consumption data

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database) provides a compilation of existing national information on food consumption at individual level. Details on how the Comprehensive Database is used are published in the Guidance of EFSA (2011a). The food consumption data gathered by EFSA in the Comprehensive Database are the most complete and detailed data currently available in the EU. The latest version of the Comprehensive Database updated in 2018[9], contains results from a total of 60 different dietary surveys carried out in 25 different Member States covering 119,458 individuals. The age classes considered are the following:

- •Infants: <12 months old
- •Toddlers: ≥12 months to <36 months old
- •Other children: ≥36 months to <10 years old
- •Adolescents: ≥10 years to <18 years old
- •Adults: ≥18 years to <65 years old
- •Elderly: ≥65 years to <75 years old
- •Very elderly: ≥75 years old.

Four additional surveys provided information on specific population groups: 'Pregnant women' (≥15 to ≤45 years old for Latvia; 17 to 46 years for Portugal) and 'Lactating women' (≥28 to ≤39 years for Greece; 18 years to 45 years for Estonia). For chronic exposure assessment, food consumption data were available from 53 different dietary surveys carried out in 22 different European countries. When for one particular country and age class two different dietary surveys were available, only the most recent one was used. This resulted in a total of 38 dietary surveys selected to estimate chronic dietary exposure.

Dietary surveys and the number of subjects available for chronic exposure assessment to phthalates are described in Table A2 (Annex A). Consumption data were collected using single or repeated 24-h or 48-h dietary recalls or dietary records covering from 3 to 7 days per subject. Because of the differences in the methods used for data collection, direct country-to-country comparisons can be misleading. Detailed information on the different dietary surveys available in the Comprehensive Database can be found on the dedicated page of the EFSA website (http://www.efsa.europa.eu/en/food-consumption/comprehensive-database).

3.2. FoodEx Classification

Consumption and occurrence data were classified according to the FoodEx classification system (EFSA, 2011b). FoodEx is a food classification system developed by EFSA in 2009 with the objective of simplifying the linkage between occurrence and food consumption data when assessing the exposure to hazardous substances. The system consists of a large number of individual food items aggregated into food groups and broader food categories in a hierarchical 'parent–child' relationship. It contains 20 main food categories (first level), which are further divided into subgroups having 140 items at the second level, 1,261 items at the third level and reaching about 1,800 endpoints (food names or generic food names) at the fourth level.

3.3. Occurrence data

3.3.1. Chemical occurrence data submitted to EFSA

Data on the levels in food of the phthalates listed in Table 4 were extracted from the EFSA Chemical Occurrence database (EFSA database) which contains analytical data submitted by Member States via a continuous annual call for data. At the time of data extraction[10], a total of 4,432 analytical chemical occurrence results on phthalates were available. All data were submitted to EFSA according to the data model 'Standard sample description' (SSD1 or SSD2) (EFSA, 2010a, 2013) by different data provider organisations and stored in the EFSA scientific data warehouse (SDWH). The SSD data model contains different data elements (database fields) and several coded standard terminologies for non-free-text data elements. The field names and terms mentioned in the present report refer to the SSD1 model.

[9] https://www.efsa.europa.eu/en/press/news/180426

[10] Data extraction from the EFSA database was performed on 08/06/2018.

Chemical occurrence data were thoroughly evaluated, including cleaning and validation steps. Special attention was paid to correct application of the used food classification codes, identification of duplicates and accuracy in reporting of different parameters such as 'Analytical methods', 'Reporting unit', 'Sampling strategy'. Upon identification of potential inconsistencies, data providers were contacted to provide clarification. For instance, 147 analytical results were removed because the reported limits of quantification were higher than the SMLs set out in Regulation (EU) No 10/2011 and samples were reported as left censored (full details of data cleaning are reported in Annex A - Table A.1). A total of 4,285 analytical results were finally available after data cleaning (Table 4).

Table 4: Analytical results on phthalates present in the EFSA database after data cleaning. Phthalates under evaluation in this assessment are marked with *

Substance entry	Abbreviated name	N
Dimethyl phthalate	DMP	273
Phthalic acid, diethyl ester	DEP	268
Diallyl phthalate		254
Diisopropyl phthalate		245
Dibutyl phthalate *	DBP	372
Diisobutyl phthalate	DIBP	235
Di-*n*-pentyl phthalate		211
Benzyl butyl phthalate *	BBP	276
Dicyclohexyl phthalate		255
Di-*n*-hexyl phthalate		254
Di-*n*-octyl phthalate		261
Bis(2-ethylhexyl)phthalate *	DEHP	467
Diisononyl phthalate *	DINP	323
Di-*n*-decyl phthalate		253
Diisodecyl phthalate *	DIDP	338

The left-censored data (analytical data reported below the limit of detection (LOD)/limit of quantification (LOQ)) were treated by the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO/IPCS, 2009). This method is also indicated in the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010b), as an option for the treatment of left-censored data. According to this guidance, the lower bound (LB) and upper bound (UB) approach should be used for chemicals likely to be present in the food (e.g. naturally occurring contaminants, nutrients and mycotoxins). For the LB approach, results below the LOQ or LOD were replaced by zero; for the UB approach, the results below the LOD/LOQ were replaced by the LOD/LOQ, respectively.

After data cleaning, a total of 4,285 analytical results on 15 phthalates in different foods were present in the dataset. Results were submitted by institutions from five different EU countries and results for the five phthalates of interest covered in this opinion (DBP, BBP, DEHP, DINP and DIDP) are shown in Table 5. Sampling year spanned from 2009 until 2016, most of the samples available in the EFSA database were collected in 2009 (Table 6). All data were reported on a whole weight basis ('as sampled'). The number of analytical results reported according to food category (FoodEx Level 2) is shown in Table A_3 of Annex A.

Table 5: Number of samples present in the EFSA database for phthalates according to reporting country

Substance	Reporting country (number of samples)				
	Belgium	**Czech Republic**	**Spain**	**United Kingdom**	**Lithuania**
DBP	.	117	20	235	.
BBP	.	.	20	253	3
DEHP	102	118	20	224	3
DINP	101	.	.	221	1
DIDP	101	.	.	236	1

. : not reported

Table 6: Number of samples in the EFSA database according to sampling year

Substance	Sampling year (number of samples)						
	2009	2010	2011	2012	2014	2015	2016
DBP	186	49	29	26	21	42	19
BBP	199	54	.	.	.	23	.
DEHP	185	39	71	86	21	45	20
DINP	180	41	42	59	.	1	.
DIDP	190	46	41	60	.	1	.

. : not reported

In relation to the analytical methods, for the vast majority of data, gas chromatography coupled to mass spectrometry or an electron capture detector was reported as the analytical method used. For 125 data values, the analytical method was not reported. When reported, recovery was 100%.

Reported LOQs (Table 7) for the phthalates of interest were relatively high, especially if compared to the ones reported in the literature (3.3.2). This is likely due to the fact that: i) phthalates are ubiquitous, therefore achieving low limits of quantification is analytically difficult; ii) analytical methods were probably developed to enforce legislative limits rather than to achieve high sensitivity. Moreover, very limited information on packaging was reported and in most of the cases the information on packaging was not available.

Table 7: Statistics on the LOQs (µg/kg) reported in the EFSA database

Substance	N	Left-censored	Min	P25	Median	P75	P95	Max
DBP	372	95.2%	0.35	19.7	40.3	50	100	267.7
BBP	276	99.6%	6.3	26	51.7	100	271	1000
DEHP	467	79.9%	0.7	72.1	100	1000	1000	1000
DINP	323	97.2%	186	1153	2629	5000	5322	7442
DIDP	338	100.0%	94	718	1999	5000	5624	8853

The reported samples were 100% left-censored for DIDP, whereas for the others (DBP, BBP and DINP) the percentage of left-censored results was above 95%. For DEHP only, quantified results were about 20% of the total, with 25 out of 49 food categories not fully left-censored. The distribution of analytical results across different food types (at level 2 of FoodEx classification) is reported in Table A.4 of Annex A. The predominant number of left-censored results produced a large difference between UB and LB mean concentrations for the different phthalates and FoodEx categories; as an example, the mean content of DBP in vegetable oil ranged from 5.2 µg/kg under the LB scenario up to 39.1 under the UB one. Data for DBP were reported in 46 food categories (FCs), of which only for 6 quantified sample(s) were reported. For BBP out of the 45 FCs, only in 1 FC not left-censored data were reported (Vegetable oil, n = 12, mean BBP content 174-219 for LB-UB). For DEHP, out of 49, only in 25 FCs not fully left-censored data were reported. For DIDP, data were reported for 49 FC, all of the data were left-censored and mean UB content was as high as 5000 µg/kg. For DINP, only 5 out of 44 FCs for which data were reported presented not left-censored data. The mean content of phthalates under the UB scenario was in general higher for the categories with the highest percentage of left-censored results due probably to higher limits of quantification.

Considering the i) limited number of samples per FC; ii) the predominance of left-censored data for the large majority of FC and phthalates; iii) the relatively high LOQs, and iv) the limited availability of information on packaging material, the CEP Panel decided to gather occurrence data on phthalates from the literature to perform an alternative assessment of exposure.

3.3.2. Chemical occurrence data reported in scientific literature

Papers referenced in the ECHA RAC opinion (ECHA, 2017a) on DBP, BBP and DEHP were considered and complemented with specific searches for literature on DINP and DIDP (they were not covered by the ECHA RAC opinion) and on occurrence in specific foods not covered in the literature from the

ECHA RAC. A list of the papers from which data were gathered can be found in Table 8. Only papers reporting on samples collected after 2008 were included in the dataset in order to consider the impact of Commission Directive 2007/19/EC[11], which entered into force that year.

Table 8: Studies considered for deriving chemical occurrence values used for exposure assessment to phthalates

Reference	Country	Considered matrix	Reported statistics
Van Holderbeke et al., 2014	Belgium	Different types of food	Median
Sakhi et al., 2014	Norway	Different types of food	One pooled sample*
Nanni et al., 2011	Italy	Oils of different types	Mean
Montuori et al., 2008	Italy	Bottled water	Median
Amiridou and Voutsa, 2011	Greece	Bottled water	Median
Domínguez-Morueco et al., 2014	Spain	Tap water	Median
Gärtner et al., 2009	Germany	Baby food	Mean
Chatonnet et al., 2014	France	Wines and spirits	Median
Blanchard et al., 2013	France	Bottled and tap water	Mean

* Consisting of 2 or 3 brands

Information on the levels of phthalates in food from Total Diet Studies (TDS) was not included in this dataset because of methodological differences in concentration determination (typically samples belonging to different food groups are pooled and prepared as for consumption before analytical determination). TDS provided exposure estimates which were discussed together and compared with the results obtained in the EFSA exposure estimates based on occurrence data from literature (3.4.3).

A brief description of the information gathered from the literature on occurrence of phthalates in food is reported below.

Van Holderbeke et al., 2014 (Belgium) (Food and packaging materials)

According to the authors, this paper aimed to obtain data on phthalates in a large variety of food products and packaging materials sold on the Belgian market; to understand possible contamination pathways of phthalates; and estimate dietary exposure to phthalates in the Belgian population. It follows the work by Fierens et al. (2012a) and Sioen et al. (2012), where a first screening measurement campaign was conducted between 2009 and 2010, in which the phthalates were analysed in 388 food products and 12 packaging materials. The paper includes data from a more targeted measurement campaign with 203 extra food products and 18 extra packaging materials analysed, occurring between 2010 and 2011. Food products, in which high phthalate contents were determined before (e.g. bread) were investigated in more detail and some additional food groups not considered before, were also analysed. Samples from the following food groups were analysed: fruits and vegetables, milk and dairy products, cereals and their products, meat and meat products, fish and fish products, fats and oils, snacks, condiments and sauces, miscellaneous, baby foods, beverages, vegetarian food, eggs, boiling water (pasta/rice). Also different packaging materials were collected for analyses. The surveys included DBP, BBP and DEHP, but not DINP or DIDP. The paper presents the number of positive samples for each phthalate in the different food and packaging groups for the two measurement campaigns together. DEHP occurrence ('positives') ranged from 57% in beverages to 100% in vegetarian food, with occurrence higher than 80% for milk and dairy products, cereals and cereal products, meat and fish and its products, snacks, condiments and sauces and baby food. BBP occurrence ranged for 14% in meat and meat products to 88% in baby food samples. BBP was also detected in 83% of condiments and sauces samples and in ca. 75% of the cereals and fats and oils. DBP occurrence ranged from 21% in fats and oils to 100% in baby food and in boiling water to pasta/rice. Results for phthalate concentrations are given for the two campaigns together as minimum, maximum and median descriptors. DEHP was the phthalate detected in higher

[11] Commission Directive 2007/19/EC of 30 March 2007 amending Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with food and Council Directive 85/572/EEC laying down the list of simulants to be used for testing migration of constituents of plastic materials and articles intended to come into contact with foodstuffs. Available online: https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32007L0019.

concentrations in all food groups, with a median of 100 µg/kg in milk and milk products, 93 µg/kg in fats and oils and ca. 50 µg/kg in cereals and its products and snacks. BBP was detected in much lower median concentrations, up to 2.2 µg/kg in condiments and sauces. DBP showed median concentrations ranging up to 4.4 µg/kg in cereals and snacks and 3.2 µg/kg in miscellaneous foods.

Sakhi et al., 2014 (Norway) (Food)

The aim of the study by Sakhi et al. (2014) was to determine the concentration of ten different phthalates (as well as bisphenol A) in foods and beverages purchased on the Norwegian market and estimate the daily dietary exposure in the Norwegian adult population. Thirty-seven different food items and beverages, grouped into appropriate FCs, were selected based on two criteria: (i) basic food items that were commonly consumed in a typical Norwegian diet, (ii) foods and beverages that were likely to contain these chemicals. For most of the food items and beverages, the three most sold brands were purchased and a composite sample (pool) was made of 1 - 3 brands. All the food items and beverages were purchased in a regular grocery store in Oslo in April 2012. The following food groups were included: grain and grain products, milk and dairy products, meat and meat products, fish and fish products, fats, fruits and vegetables, ready to eat, snacks, beverages, condiments and egg. The phthalates studied included DBP, BBP, DEHP, DINP and DIDP.

Values of phthalate concentrations were reported as median lower bound, minimum and maximum. The detection frequency of phthalates in the food items varied depending on the phthalate. DBP was detected in 23 out of 37 samples (62%), BBP in 11 out of 37 samples (30%), DEHP in 24 out of 37 (65%) food items, followed by DINP which was detected in 31 out of 37 (84%) of the food items. DIDP was detected in 14 out of 37 samples (38%). Among the different phthalates, the highest concentrations were found for DEHP and DINP. The food items with the highest concentrations of total phthalates were buns, chocolate spreads, margarine, canned dinners, sliced salami, cheese spreads, sausages and hard cheese. Among the food categories, grain and grain products and ready to eat dinners had the highest number of phthalates with median concentration above the LOQ. The food item with highest concentrations of each phthalate were: Norwegian brown cheese with 31 µg/kg DBP, minced meat with 78 µg/kg BBP, margarine with 323 µg/kg DEHP, buns with 734 µg/kg DINP and hamburgers with 13 µg/kg DIDP.

Montuori et al., 2008; Amiridou and Voutsa, 2011; Blanchard et al., 2013; Domínguez-Morueco et al. (2014) (Italy, Greece, France, Spain) (Bottled and tap water)

Concentration of phthalates in drinking water is expected to be relatively low because of the lipophilic character of these substances. On the other hand, water is consumed in high amounts and it is used by many in the preparation of infant formula. Occurrence data on phthalates in drinking water is scarce, particularly for tap water.

Data on bottled water were available from the work of Montuori et al. (2008). A total of 71 commercial brands of water from 16 different Italian regions were analysed. The water was bottled in glass or in polyethylene terephthalate (PET) (71 in PET and 71 in glass). The concentration of the phthalates was higher in PET as compared to in glass. DEHP was below the LOD (0.01 µg/L) in water packaged in either materials. The median value for DBP in water packaged in PET was 0.23 µg/L and in glass was 0.04 µg/L. The occurrence of BBP, DINP and DIDP was not investigated. Amiridou and Voutsa (2011) analysed phthalates (along with other substances) in bottled waters. Moreover, the influence of storage of water bottles outdoors, under natural conditions, was also investigated. They analysed 6 water brands in PET and polycarbonate, collected in Greece. The prevailing phthalate was DEHP with a median concentration of 0.35 µg/L. DBP was found at lower concentrations, with a median of 0.04 µg/L. BBP was not found at detectable concentrations (LOD 0.03 µg/L). DINP and DIDP were not included in this study.

In the study from Blanchard et al. (2013), the occurrence of 6 phthalates (including DBP, BBP, DEHP) in drinking water (both tap and bottled), in common foodstuffs and in ambient air (both indoor and outdoor) was investigated in the urban centre of Paris. Fifteen brands of PET bottled water were tested (plain spring water n = 3, plain mineral water n = 8 and sparkling mineral water n = 4). Tap water distributed in Paris (n = 3) was also tested. For bottled water, DEHP prevailed with 0.13 and

0.15 µg/L in plain and sparkling water, followed by DBP with 0.12 and 0.09 µg/L. BBP displayed lower concentrations (<0.01 µg/L). No significant differences were observed between plain water and sparkling bottled water concentrations. For tap water, the same distribution profile was observed but with concentrations ca. 2–3 times lower (p<0.01 with mean values of 0.06 µg/L for DEHP and 0.04 µg/L for DBP).

Data on concentrations in tap water was also available from Domínguez-Morueco et al. (2014) for phthalates in the main drinking water supply areas for the Region of Madrid. Water was collected in 7 different locations from taps in private residences. Five phthalates were targeted, including DBP, BBP and DEHP. In the tap water, the mean concentration for DBP was 0.63 µg/L. DEHP and BBP were not detected with LODs respectively of 0.46 µg/L and 0.19 µg/L.

<u>Chatonnet et al. 2014 (France) (Wines and spirits)</u>

Phthalates have good solubility in ethanol and therefore they migrate into wines and spirits according to the ethanol concentration. Data on phthalates concentration in French wines (100) and grape spirits (30) marketed in Europe or intended for export (Chatonnet et al., 2014) were reported. DBP, DEHP and BBP were the most frequently detected phthalates. While only 15% of the samples contained quantifiable concentrations (>10 µg/kg) of DEHP and BBP, 59% of the wines contained DBP with a median value as high as 59 µg/kg. Only 17% of the samples did not contain any detectable phthalates. In the spirits analysed, DBP (median 105 µg/kg) and DEHP (median 350 µg/kg) were the substances at the highest concentrations, as well as the most frequently detected (90% of samples). BBP was present in 40% of the samples at a mean of 26 µg/kg. DINP and DIDP were not found in detectable concentrations (LOD: 20 µg/L, LOQ: 50 µg/L).

<u>Gärtner et al. 2009 (Germany) (Baby food and packaging)</u>

These authors analysed phthalates in recycled paper and paperboard as well as in dry infant food packed in paper/board. Twenty samples of infant foods (4 milk powders, 7 cereal flakes, 9 semolina powders) were purchased from retail stores in Berlin, Germany. They represented typical domestic brands. DBP ranged from 53 µg/kg in milk powder to 100 µg/kg in baby rice cereals. BBP was not detected at a LOD of 7 µg/kg and DEHP was detected at values lower than LOQ (= 50 µg/kg). The occurrence of DINP and DIDP was not investigated in this study.

<u>Nanni et al. 2011 (Italy) (Vegetable oils)</u>

Phthalates migrate readily into oils and fatty food in general, therefore, these products frequently show occurrence of one or more phthalates, and occasionally extremely high concentrations are reported. Regarding vegetables oils, although these are not typically consumed as such, they are used as ingredients in many other foods. DBP, DEHP and DINP (but not BBP and DIDP) were analysed for in samples (172 in total) of eight types of vegetable oils collected in Italy (Nanni et al., 2011); these being extravirgin olive oil (34 samples), sunflower oil (27), peanut oil (27), corn oil (23), various seed oils (22), soybean oil (16), olive oil (16) and olive pomace oil (7). DINP was the phthalate found at the highest levels, contributing from 57% (extra virgin olive oil) to 95% (corn oil) of the total phthalate content, followed by DEHP which constituted from 3% (corn oil) to 37% (extra virgin olive oil) of the total phthalate content. DINP concentrations ranged from 971 µg/kg in sunflower oil to 2884 µg/kg in olive oil and 2982 µg/kg in corn oil. DEHP concentrations ranged from 77 µg/kg in soybean oil to 1262 µg/kg in olive oil. DBP was detected at lower concentrations, from 22 µg/kg in soybean oil to 360 µg/kg in olive oil.

3.3.2.1. Procedures and assumptions used to match literature occurrence data to the Comprehensive Database

In most of the studies, only summary statistics were presented for aggregated food groups. The level of food sample aggregation and the number of samples per food category varied from one study to the other. The considered studies reported different statistical parameters (i.e. mean or median) for the analysed food samples organised in groups (see Table 8), and the one available was used when inputting the occurrence data. Not all papers reported the specific LOQs associated with each of the FCs at a sufficient level of detail. Therefore, all the categories reported as left censored were substituted by 0 (LB approach).

In order to match the occurrence data gathered from literature with the consumption data from the Comprehensive Database, a FoodEx code was assigned to each food descriptor reported in the studies. In the majority of the cases, the link was straight forward (e.g. "Tree nuts" FoodEx code assigned to "Nuts"). However, broad FoodEx categories were used for generic food descriptors (e.g. "Cheese" FoodEx code assigned to "Cheese"). This assumption enlarged the number of foods for which the presence of phthalates was considered in the assessment of exposure. In addition, when the same FoodEx code was assigned to more than one food descriptor the highest chemical occurrence mean/median was included in the dataset. The full detail of inputted data along with the list of food descriptors and FoodEx codes is reported in Annex B (Tables B1 to B7). Also, when more than one chemical occurrence mean/median value was available from different studies for the same FoodEx code, the highest mean/median value was used in the assessment of exposure. The dataset used for the exposure assessment is available in Annex C Table C1_Levels.

3.4. Estimation of dietary exposure

As suggested by the EFSA Working Group on Food Consumption and Exposure (EFSA, 2011a), dietary surveys with only 1 day per subject were not considered for chronic exposure as they are not adequate to assess repeated exposure. Similarly, subjects who participated only 1 day in the dietary studies, when the protocol prescribed more reporting days per individual, were also excluded for the chronic exposure assessment. Not all countries provided consumption information for all age groups, and in some cases the same country provided more than one consumption survey. For calculating chronic dietary exposure to phthalates, food consumption and body weight data at the individual level were accessed in the Comprehensive Database. Occurrence data and consumption data were linked at the relevant FoodEx level.

To carry out the exposure assessment from the EFSA chemical occurrence dataset, for the five phthalates under consideration (DBP, BBP, DEHP, DINP and DIDP) the mean occurrence value was calculated for each food sample type collected in different countries (effectively, pooled European occurrence data). Chronic dietary exposure was calculated per individual by combining the mean occurrence value with the average daily consumption for each food type, at individual level per dietary survey and age class.

Consequently, individual average exposures per day and body weight were obtained for all individuals. On the basis of distributions of individual exposures, the mean and 95th percentile exposure were calculated per survey and per age class. Dietary exposure was assessed using overall European LB and UB mean occurrence of each phthalate. The contribution (%) of each FC to the overall mean dietary chronic exposure of DBP, BBP, DEHP, DINP and DIDP was calculated for each age group and dietary survey.

The EFSA occurrence database highlighted certain limitations for phthalates (detailed in sections 3.3.1) therefore, as an alternative option, chemical occurrence values were also extracted from relevant literature on phthalates in a variety of food items available on the European market. A description of the papers and the strategy used to derive concentration is explained in section 3.3.2; the strategy and assumptions used to match literature occurrence data to cosmption data is also described in 3.3.2.1. For the five phthalates under consideration the mean (or median if only that was available from the papers) occurrence value for each phthalate per food group was considered. Occurrence data and consumption data were linked at the relevant FoodEx level. Then the average daily consumption for each food for every individual person, per dietary survey and age class was calculated. Chronic dietary exposure was calculated per individual by combining the mean/median occurrence value with the average daily consumption for each food type, at individual level per dietary survey and age class. Mean and high (95th percentile) chronic dietary exposure per dietary survey and age class were calculated from the exposure at the individual level. All analyses were run using the SAS Statistical Software (SAS enterprise guide 5.1).

Furthermore, the CEP Panel decided to group DBP, BBP, DEHP and DINP into a common assessment group and to allocate potency factors relative to DEHP as the reference substance (see 4.9.1). In order to correctly assess the high (P95) exposure to the GroupPhthalates, the potency factors were used to calculate the level/concentration of the GroupPhthalates expressed as DEHP Equivalents in each of the FCs for which occurrence levels were available for at least one of the phthalates. These levels were then combined with the food consumption in order to estimate the exposure to the GroupPhthalates. Consequently, an aggregated exposure assessment to these phthalates was carried out using the following equation at the level of chemical occurrence data for each food category:

GroupPhthalates concentration expressed as DEHP Equivalents ([GPDEq], µg/kg food) = DEHP*1 + DBP*5 + BBP*0.1 + DINP*0.3.

For DIDP, which was not included in the common assessment group (see section 4.9.1), an individual exposure assessment was carried out.

3.4.1. Results: dietary exposure assessment based on occurrence data reported to EFSA

The CEP Panel estimated the chronic dietary exposure to DBP, BBP, DEHP, DINP and DIDP across different European countries and age groups using the EFSA chemical occurrence database described in section 3.2.2; the results of the exposure assessment are reported in Annex B (B.8 to B.11) including the mean and 95th percentile of chronic exposure for each of the phthalates, providing both the LB and UB results per population group (Table B.9 and table B.10).

As described in section 3.3.1, exposure estimates based on EFSA occurrence data present a large uncertainty due to the limited amount of quantified FCs, the high LOQs and the high amount of left-censored data. As a consequence, exposure results present a large difference between LB and UB chronic estimates. For example, the maximum mean and 95th percentile exposure in infants for DBP ranged from 0.02 (LB) up to 2.2 (UB) µg/kg bw per day and from 0.08 (LB) up to 4.1 (UB) µg/kg bw per day, respectively.

3.4.2. Results of dietary exposure assessment based on occurrence data reported in scientific literature

Mean and P95 percentile exposure results per age group and country are summarised in Tables 9-14, all results are presented in Annex C.

3.4.2.1. Results of dietary exposure assessment

The mean chronic exposure to DBP (Table 9) ranged from 0.042 µg/kg bw per day for elderly (from Latvia), up to 0.769 µg/kg bw per day (infants from France). The P95 exposure to DBP ranged from 0.099 µg/kg bw per day elderly (from Latvia) up to 1.503 µg/kg bw per day for infants (from France). Both mean and P95 exposure to DBP for pregnant and lactating women were in the range of the values estimated for adults.

Table 9: Summary of the estimated chronic dietary exposure to DBP in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to DBP			P95 exposure to DBP		
Population class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	0.190	0.769	10	0.710	1.503
Toddlers	14	0.122	0.492	12	0.212	0.943
Other children	19	0.100	0.481	19	0.169	0.866
Adolescents	18	0.051	0.284	17	0.099	0.489
Adults	19	0.053	0.274	19	0.160	0.507
Elderly	18	0.042	0.300	18	0.099	0.595
Very elderly	15	0.046	0.261	10	0.225	0.511
Pregnant women	2	0.076	0.114	2	0.198	0.311
Lactating women	2	0.066	0.104	2	0.141	0.174

n = number of food consumption surveys

The mean chronic exposure to BBP (Table 10) ranged from 0.009 µg/kg bw per day for the very elderly (from Estonia), up to 0.207 µg/kg bw per day for infants (from France). The P95 exposure to BBP ranged from 0.021 µg/kg bw per day for adolescents (from Cyprus) up to 0.442 µg/kg bw per day for infants (from France). Both mean and P95 exposure to BBP for pregnant and lactating women were in the range of the values estimated for adults.

Table 10: Summary of the estimated chronic dietary exposure to BBP in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to BBP			P95 exposure to BBP		
Population class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	0.071	0.207	10	0.197	0.442
Toddlers	14	0.033	0.109	12	0.072	0.347
Other children	19	0.023	0.102	19	0.038	0.268
Adolescents	18	0.012	0.045	17	0.021	0.139
Adults	19	0.018	0.035	19	0.038	0.100
Elderly	18	0.016	0.040	18	0.041	0.105
Very elderly	15	0.009	0.042	10	0.038	0.092
Pregnant women	2	0.015	0.015	2	0.024	0.029
Lactating women	2	0.015	0.030	2	0.027	0.088

n = number of food consumption surveys

The mean chronic exposure to DEHP (Table 11) ranged from 0.446 µg/kg bw per day for the very elderly (from Estonia), up to 3.459 µg/kg bw per day for toddlers (from Italy). The P95 exposure to DEHP ranged from 0.902 µg/kg bw per day for the very elderly (from UK) up to 6.148 µg/kg bw per day for infants (from France). Both mean and P95 exposure to DEHP for pregnant and lactating women were in the range of the values estimated for adults.

Table 11: Summary of the estimated chronic dietary exposure to DEHP in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to DEHP			P95 exposure to DEHP		
Population class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	0.573	3.010	10	1.033	6.094
Toddlers	14	1.528	3.459	12	2.659	6.148
Other children	19	1.316	2.992	19	2.087	5.389
Adolescents	18	0.586	1.790	17	1.093	2.945
Adults	19	0.482	1.326	19	0.911	2.217
Elderly	18	0.507	1.239	18	0.990	2.069
Very elderly	15	0.446	1.202	10	0.902	1.941
Pregnant women	2	0.735	0.795	2	1.216	1.565
Lactating women	2	0.810	0.825	2	1.437	1.448

n = number of food consumption surveys

The mean chronic exposure to DINP (Table 12) ranged from 0.232 µg/kg bw per day for very elderly (from UK) up to 4.270 µg/kg bw per day for toddlers (from Italy). The P95 chronic exposure to DINP ranged from 0.446 µg/kg bw per day for very elderly (from UK) up to 7.071 µg/kg bw per day for other children (from Italy).

Table 12: Summary of the estimated chronic dietary exposure to DINP in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to DINP			P95 exposure to DINP		
Population class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	0.263	3.082	10	0.858	6.553
Toddlers	14	0.812	4.270	12	1.798	6.578
Other children	19	0.788	4.049	19	1.525	7.071
Adolescents	18	0.334	2.365	17	0.659	3.927
Adults	19	0.252	1.810	19	0.517	2.957
Elderly	18	0.244	1.777	18	0.494	3.112
Very elderly	15	0.232	1.659	10	0.446	2.641
Pregnant women	2	0.386	0.889	2	0.798	2.382
Lactating women	2	0.492	0.807	2	1.017	1.820

n = number of food consumption surveys

The mean chronic exposure to DIDP (Table 13) ranged from 0.001 µg/kg bw per day for infants (from Italy) up to 0.057 µg/kg bw per day for toddlers (from Denmark). The P95 chronic exposure to DIDP ranged from 0.008 µg/kg bw per day for adolescents (from Finland) up to 0.095 µg/kg bw per day for other children (from Bulgaria).

Table 13: Summary of the estimated chronic dietary exposure to DIDP in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to DIDP			P95 exposure to DIDP		
Population class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	0.001	0.032	10	0.024	0.090
Toddlers	14	0.020	0.057	12	0.044	0.091
Other children	19	0.011	0.044	19	0.026	0.095
Adolescents	18	0.003	0.034	17	0.008	0.074
Adults	19	0.010	0.022	19	0.022	0.046
Elderly	18	0.009	0.025	18	0.018	0.056
Very elderly	15	0.013	0.021	10	0.026	0.038
Pregnant women	2	0.013	0.016	2	0.026	0.033
Lactating women	2	0.012	0.014	2	0.023	0.030

n = number of food consumption surveys

The mean chronic aggregated exposure to GroupPhthalates (expressed as DEHP equivalents) (Table 14) ranged from 0.865 µg/kg bw per day for infants (from Estonia) up to 7.205 µg/kg bw per day in toddlers (from Italy). The P95 ranged from 1.640 µg/kg bw per day for elderly (from Estonia) up to 11.738 µg/kg bw per day for infants (from Spain).

Table 14: Summary of the estimated chronic aggregated dietary exposure to GroupPhthalates in 8 population groups (minimum–maximum across the dietary surveys in µg/kg bw per day); exposure estimated using data from literature (lower bound only)

	Mean exposure to GroupPhthalates			P95 exposure to GroupPhthalates		
Population Class	**n**	**Min**	**Max**	**n**	**Min**	**Max**
Infants	11	1.851	7.179	10	4.676	11.738
Toddlers	14	3.115	7.205	12	4.778	11.455
Other children	19	2.095	6.619	19	3.389	11.165
Adolescents	18	0.983	3.922	17	1.818	6.440
Adults	19	0.997	3.240	19	2.027	5.295
Elderly	18	0.865	3.276	18	1.640	5.404
Very elderly	15	0.887	3.009	10	1.914	4.924
Pregnant women	2	1.231	1.634	2	2.134	3.579
Lactating women	2	1.288	1.590	2	2.296	2.693

n = number of food consumption surveys

In general, for all phthalates considered in this assessment, the minimum and maximum chronic exposure for infants, toddlers and other children were higher than for all the other population groups, both for mean and P95 values. Exposure to phthalates for pregnant and lactating women was in the range of the values estimated for adults.

3.4.2.2 Sources of dietary exposure to phthalates

Examining the data from the above described exposure estimates (based on occurrence data from literature) in more detail, an attempt was made to identify the main dietary sources of exposure. An extensive description of the sources of exposure to individual phthalates by population group and survey/country is reported in Annex C Table C4; some considerations on certain sensitive population groups are outlined in the following paragraphs.

Infants

FoodEx Level 2 Categories 'Infant formulae, powder', 'Infant formulae, liquid', 'Vegetable oil, 'Follow-on formulae, liquid', 'Follow-on formulae, powder', 'Breakfast cereals', 'Cereal-based food for infants and young children' each contributed to the DBP exposure by more than 10% of the total in at least one survey. 'Infant formula' (up to 65% in Bulgarian infants) and 'Vegetable oil' (up to 45% in Italian infants) were the largest contributors to infant exposure to DBP.

'Infant formulae, liquid', 'Infant formulae, powder', 'Follow-on formulae, liquid', 'Follow-on formulae, powder', 'Ready-to-eat meal for infants and young children', 'Vegetable oil' and 'Mixed meat' each contributed to the BBP exposure by more than 10% of the total in at least one survey. "Infant formulae, liquid" (up to 70% in Finnish infants) and "Infant formulae, powder" (up to 56% in Bulgarian infants) were the largest contributors to infant exposure to BBP.

'Liquid milk', 'Cheese', 'Vegetable oil', 'Infant formulae, liquid', 'Ready-to-eat meals for infants and young children', 'Fermented milk products', 'Infant formulae, powder', 'Bread and rolls' each contributed to the DEHP exposure by more than 10% of the total in at least one survey. 'Liquid milk' (up to 47% in Italian infants) and "Cheese" (up to 36% in children from the UK) were the largest contributors to infant exposure to DEHP.

'Vegetable oil', 'Liquid milk', 'Cheese', 'Bread and rolls' each contributed to the DINP exposure by more than 10% of the total in at least one survey. "Vegetable oil" (up to 79% in Spain) and 'Liquid milk' (up to 66% in Latvia) were the largest contributors to infant exposure to DINP.

'Breakfast cereals', 'Fine bakery wares', 'Vegetable products', 'Bread and rolls', 'Fish meat', 'Jam, marmalade and other fruit spreads' each contributed to the DIDP exposure by more than 10% of the total in at least one survey. 'Breakfast cereals' (up to 80% in Finish infants) and 'Fine bakery wares' (up to 71% in Portuguese infants) were the largest contributors to infant exposure to DIDP.

In relation to GroupPhthalates exposure, the top 2 categories contributing to the exposure were 'Infant formulae, liquid' and 'Vegetable oil' for infants.

Toddlers

FoodEx Level 2 Categories 'Vegetable oil', 'Breakfast cereals', 'Infant formulae, liquid', 'Follow-on formulae, liquid', 'Cereal-based food for infants and young children' , 'Fermented milk products', 'Bread and rolls', 'Fine bakery wares', 'Ready to eat soups' and 'Tap water' each contributed to the DBP exposure by more than 10% of the total in at least one survey in toddlers; 'Vegetable oil' (up to 79% in Italian toddlers) and breakfast cereals (up to 40% in Danish toddlers) were the top 2 contributors to toddlers exposure to DBP.

'Mixed meat', 'Vegetable oil', 'Follow-on formulae, liquid', 'Infant formulae, liquid', 'Bread and rolls', 'Follow-on formulae, powder', 'Pastes, pâtés and terrines', 'Ready-to-eat meals for infants and young children', 'Fine bakery wares', 'Breakfast cereals' each contributed to the BBP exposure by more than 10% of the total in at least one survey in toddlers; 'Mixed meat' (up to 57% in Estonian toddlers) and 'Vegetable oil' (up to 51% in Italian toddlers) were the top 2 contributors to toddlers exposure to BBP.

'Cheese', 'Vegetable oil', 'Liquid milk', 'Bread and rolls', 'Fermented milk products', 'Animal fat' each contributed to the DEHP exposure by more than 10% of the total in at least one survey . 'Cheese' (up to 42% in French toddlers) and 'Vegetable oil' (up to 40% in Italian toddlers) were the top 2 contributors to toddler exposure to DEHP.

'Vegetable oil', 'Liquid milk', 'Cheese', 'Bread and rolls', 'Sausages', 'Fine bakery wares' each contributed to the DINP exposure by more than 10% of the total in at least one survey . 'Vegetable oil; (up to 73% in Italian toddlers) and ‘Liquid Milk’ (up to 53% in Finnish toddlers) were the largest top 2 contributors to DINP in toddlers.

‘Breakfast cereals’, ’Bread and rolls’, ‘Fine bakery wares’ and ‘Sausages’ each contributed to the DIDP exposure by more than 10% of the total in at least one survey. ‘Breakfast cereals’ (up to 77% in Finnish toddlers) and ‘Bread and rolls’ (up to 74% in Bulgarian toddlers) were the largest top 2 contributors to DIDP in toddlers.

In relation to GroupPhthalates exposure, the top 2 categories contributing to the exposure were Vegetable Oil’ and ‘Cheese’ for toddlers.

<u>Pregnant and Lactating women</u>

It should be noticed that for pregnant and lactating women, only 4 surveys (Portugal, Greece, Latvia, Estonia) were available. Key findings in relation to sources follow.

For DBP, ‘Vegetable oil’, ‘Breakfast cereals’, ‘Tap water’ and ‘Vegetable oil’ each contributed to the DBP exposure by more than 10% of the total in at least one survey.

For BBP, ‘Mixed meat’, ‘Vegetable oil’, ‘Fine bakery wares’ and ‘Bread and rolls’ each contributed to the BBP exposure by more than 10% of the total in at least one survey.

For DEHP, ‘Vegetable oil’, ‘Cheese’ and ‘Bread and rolls’ each contributed to the DEHP exposure by more than 10% of the total in at least one survey.

For DINP, ‘Vegetable oil’, ‘Cheese’, ‘Bread and rolls’ and ‘Sausages’ each contributed to the DINP exposure by more than 10% of the total in at least one survey.

For DIDP, ‘Bread and rolls’, ‘Breakfast cereals’, ‘Fine bakery wares’ , ‘Sausages’ and ‘Cereal-based dishes’ each contributed to the DIDP exposure by more than 10% of the total in at least one survey.

In relation to GroupPhthalates exposure, the top 2 categories contributing to the exposure were ‘Vegetable Oil’ and ‘Cheese’ for Pregnant and Lactating women.

3.4.3. Dietary exposure data reported in Total Diet Studies

TDS results are reported here for comparison with the above-derived exposure estimates made using occurrence data on phthalates from the literature and information on food consumption from the EFSA Comprehensive Database.

<u>UK TDS (Bradley et al., 2013)</u>

According to the authors, twenty composite food samples collected for the 2007 TDS were analysed. The UK TDS samples comprise 20 broad food groups obtained from retail outlets in 24 towns throughout the UK. In total, 119 subcategories of food are combined into the 20 groups (bread, fresh fruit, fruit products, dairy products, oils and fats, milk, nuts, beverages, meat products, offal, green vegetables, eggs, miscellaneous cereals, fish, sugar and preserves, canned vegetables, poultry, carcass meat, other vegetables, and potatoes). The relative proportion of each food category within a group reflects its importance in the average UK household diet. Foods are grouped so that commodities known to be susceptible to contamination (e.g. offal, fish) are kept separate, as are foods which are consumed in large quantities (e.g. bread, potatoes, milk).

A short summary of concentration data is provided in the following paragraphs:

DBP was present in seven food groups (bread, oils and fats, nuts, meat products, cereal, fish and carcass meat) in the range of 6 to 28 µg/kg.

BBP was present in one food group (bread) at 8 µg/kg.

DEHP was present in eleven food groups (bread, dairy, oils and fats, nuts, meat products, cereal, fish, sugar and preserves, poultry, carcass meat and other vegetables) in the range of 35 to 789 µg/kg.

DINP and DIDP were not detected in any food group, which is why all the LB estimates for these 2 phthalates are zero. The analytical method used had high LOD values for these two isomeric phthalates which is why the UB estimates are so high.

These concentration data were then combined with food consumption data from the National Diet and Nutrition Survey to provide estimates of dietary exposure for average and high-level (P97.5) UK consumers within different age categories. Exposure values are estimated from a range (lower – upper bound) of mean concentrations, i.e. where individual sample analyses were less than the LOD, the concentration is expressed as zero (LB), or as equal to the LOD (upper bound) and the exposure calculated based on the body weights of the individuals in the survey. The estimates made by the authors are shown in Table 15.

Table 15: Estimated mean and 97.5th percentile of dietary exposure (μg kg/bw per day, LB-UB values) as reported in FSA (2010)

Population class		DBP	BBP	DEHP	DINP	DIDP
Toddlers: >1.5 to 2.5 years	mean	0.2-0.6	0.03-0.8	3.4-5.2	0-17.4	0-39.6
	P97.5	0.4-1.0	0.07-1.3	6.9-9.9	0-30.7	0-72.7
Toddlers: >2.5 to 3.5 years	mean	0.2-0.6	0.03-0.7	3.2-4.7	0-14.3	0-33.5
	P97.5	0.4-0.8	0.07-1.1	6.3-7.9	0-26.9	0-64.6
Toddlers: >3.5 to 4.5 years	mean	0.2-0.5	0.03-0.6	3.1-4.3	0-12.1	0-28.5
	P97.5	0.4-0.8	0.07-1.0	5.7-6.8	0-20.8	0-49.8
Young people: 4-6 years	mean	0.2-0.5	0.03-0.6	3.2-4.2	0-10.3	0-24.0
	P97.5	0.4-0.7	0.06-0.9	5.5-6.7	0-16.2	0-39.4
Young people: 7-10 years	mean	0.2-0.4	0.02-0.4	2.6-3.2	0-7.5	0-17.7
	P97.5	0.3-0.6	0.05-0.7	4.6-5.2	0-12.5	0-28.6
Young people: 11-14 years	mean	0.1-0.2	0.02-0.3	1.9-2.3	0-4.9	0-11.9
	P97.5	0.2-0.4	0.04-0.5	3.4-4.0	0-9.3	0-21.1
Young people: 15-18 years	mean	0.1-0.2	0.02-0.2	1.5-1.9	0-3.9	0-9.3
	P97.5	0.2-0.3	0.03-0.4	2.7-3.2	0-6.9	0-16.1
Adults	mean	0.1-0.2	0.02-0.3	1.8-2.3	0-4.7	0-10.8
	P97.5	0.2-0.3	0.04-0.5	3.4-4.0	0-8.2	0-18.5
Free living elderly	mean	0.1-0.2	0.02-0.2	1.3-1.5	0-3.3	0-7.7
	P97.5	0.2-0.3	0.03-0.4	2.4-2.9	0-6.4	0-14.4
Institutional elderly	mean	0.1-0.1	0.02-0.1	1.5-1.3	0-3.2	0-7.5
	P97.5	0.2-0.3	0.03-0.4	2.6-3.1	0-7.7	0-18.9

Ireland TDS (FSAI, 2016)

According to the authors, the most commonly consumed foods in Ireland, based on food consumption data, were analysed and dietary exposure to each chemical was then estimated using the food consumption data and the level of the particular chemical present in each food.

The food consumption data used were derived from the National Adult Nutrition Survey (NANS) (IUNA, 2011), which investigated habitual food and beverage consumption in a representative sample (n = 1,500) of adults aged 18 years and over in the Republic of Ireland during 2008 - 2010 and the National Children's Food Survey (NCFS), which investigated habitual food and drink consumption in 594 children, aged 5 - 12 years, from the Republic of Ireland during 2003 – 2004 (IUNA, 2005).

The choice of foods for this TDS was based on the list as determined in the previous TDS (FSAI, 2011) and additional information available from more recent food consumption surveys, in particular brand information available in the most recent adult food consumption survey. The following food groups were analysed: cereals, dairy, eggs, meat, fish, potatoes, vegetables, fruit, dried fruit, nuts and seeds, herbs and spices, soups, sauces, sugar and preserves, confectionary, beverages, fats and oils, snacks, composites (pizza).

For each foodstuff, a number of sub-samples (typically five), were purchased. The selection of brands was based on interrogation of the brand information in the food consumption databases. Sampling of the foods was conducted by the FSAI in autumn of 2012 and a total of 141 samples (comprising 1,043 sub-samples) were sent for preparation and analysis. Food was mainly purchased in the major retailers located in Dublin. Tap water was sourced from a variety of private households attached to the public water supply. Where required, foods were prepared ready for consumption by the laboratory before analysis.

The recoded food consumption data and chemical occurrence data were combined using the probabilistic web-based Creme software. For the purpose of the survey, a semiprobabilistic approach was used, i.e. the single aggregate-sample-based occurrence levels were combined with population food intake distribution data. Results are expressed as LB and UB values. Analytical results below the LOD were set at zero (<LOD = 0), whereas for UB calculations, analytical results recorded as below the LOD were assumed to be present at the LOD (<LOD = LOD). Both UB and LB values were expressed as mean intake and high intake (97.5th percentile, P97.5) on a bw basis. The estimates of dietary exposure made by the authors are shown in Table 16.

Table 16: Estimated exposure of phthalates of the Irish children and adult population from all food groups (µg kg/bw per day) as reported in FSAI, 2016

	Children				**Adult population**			
	Mean		P97.5		Mean		P97.5	
	LB	**UB**	**LB**	**UB**	**LB**	**UB**	**LB**	**UB**
DBP	0.02	0.3	0.07	0.52	0.08	0.4	0.45	0.95
BBP	0.04	0.22	0.12	0.38	0.03	0.25	0.12	0.51
DEHP	0.37	0.79	0.82	1.45	0.25	0.64	0.64	1.2
DINP	2.36	5.59	11.22	14.93	1.02	2.78	7.06	8.81
DIDP	0.02	4.01	0.11	7.39	0.03	2.2	0.25	4.17

<u>France TDS infants (ANSES, 2016a, b)</u>

According to the authors, the study looked at 4 age groups on the basis of dietary diversification during the age span of 1 to 36 months. A very detailed and comprehensive sampling plan was devised and executed to ensure that the samples purchased and analysed, were as fully representative as possible in describing the diets of the age ranges covered. In brief, each month, a sub-sample of each composite sample was purchased and the 12 sub-samples were pooled after one year. A total of 5,484 food items were purchased and prepared. The sampling took place between July 2011 and July 2012. The purchases were made in a single region of France (Center region). The authors observed that the food sampling mainly targeted infant products, for which a single factory generally serves the entire territory (by brand or manufacturer). As a result, geographic variability is limited for these products. The sampling plan was said to cover more than 95% of the diet of children under 36 months.

The estimates of dietary exposure made by the authors are shown in Table 17.

Table 17: Estimated dietary exposure (μg kg/bw per day) for French infants below 3 years from the total population, as reported in ANSES (2016a, b)

		Mean		P90	
	Population class	**LB**	**UB**	**LB**	**UB**
DEHP	1-4 month	0.01	0.68	0.02	0.85
	5-6 month	0.09	0.60	0.27	0.82
	7-12 month	0.24	0.68	0.54	1.01
	13-36 month	0.54	0.83	0.96	1.27
DINP+DIDP	1-4 month	0.01	6.68	0.00	8.49
	5-6 month	0.09	5.22	0.34	6.50
	7-12 month	0.37	4.77	0.97	6.20
	13-36 month	0.69	3.91	1.27	5.19
BBP	1-4 month	0.00	0.33	0.00	0.43
	5-6 month	0.01	0.27	0.05	0.34
	7-12 month	0.01	0.24	0.03	0.30
	13-36 month	0.01	0.17	0.02	0.24
DBP	1-4 month	0.00	0.34	0.00	0.43
	5-6 month	0.00	0.27	0.01	0.34
	7-12 month	0.00	0.23	0.01	0.29
	13-36 month	0.01	0.17	0.02	0.24

Higher detection rates of BBP were observed in prepared dishes for infants packaged in plastic compared to those packaged in glass. Moreover, statistically higher DEHP concentrations were measured in prepared meat (or fish) and vegetable dish packaged in plastics as compared to those packaged in glass.

3.5. Exposure via FCM

Phthalates are used in many consumer products and their presence in the environment is ubiquitous. As a consequence, food can be contaminated from environmental pollution and from contact with different materials through the production process and by contacting with packaging materials. A food product will contact different materials, not only plastics, that are potential sources of contamination throughout its 'farm-to-fork' chain. Additionally, each phthalate has different use patterns, corresponding to typical incorporation in different FCM and in other polymeric goods. Therefore, the relative importance of the different steps of the contamination chain may also be highly variable. As a consequence, assessing the contribution of FCM, and particularly plastics, to the exposure of consumers to phthalates is complex.

It is required to i) differentiate environmental sources of phthalates in food from contamination of food as a result of migration from plastic FCM, and ii) correlate the phthalate occurrence in specific foods with the plastic FCM used, which may in principle be easy to ascertain (such as the visible packaging of retail foods) or may be more or less out of view (such as materials and articles used in primary production, processing and transport).

Fierens et al. (2012b) investigated the occurrence of several phthalates including DBP, BBP and DEHP in raw cow's milk and feed from Belgian farms in order to determine their most relevant contamination pathways. DINP and DIDP were not included in the study. Considering the findings for the specific phthalates of interest here, DBP was not detected in raw milk samples while BBP and DEHP were found. DEHP was by far the most frequent and highest detected phthalate, although a trend of decreasing occurrence in cow's milk, due to replacement by other plasticisers, was observed. The levels of DEHP averaged 400 $\mu g/kg_{fat}$ in summer and 300 $\mu g/kg_{fat}$ in winter. Differences were observed to a smaller degree for BBP (<15 µg/kg$_{fat}$ in summer and 15 – 21 µg/kg$_{fat}$ in winter). Variations between winter/summer and farms were attributed possibly to different feed composition. FCM of the mechanical milking process was considered an important contamination pathway of raw milk with BBP and DEHP: these phthalates were not detected in milk manually milked and were detected at up to 18 and 123 µg/kg$_{fat,}$ respectively, in mechanically milked milk. The storage tank to accumulate the milk before further processing was also a source of DEHP through migration, and concentrations up to 338 µg/kg$_{fat}$ were found.

In a subsequent study, the impact of the processing and packaging line on phthalate occurrence in milk was assessed (Fierens et al., 2013). DEHP increased from 364 µg/kg$_{fat}$ in the raw milk to 426 µg/kg$_{fat}$ after pasteurisation, and to 478 µg/kg$_{fat}$ before packaging. After packaging, the level further increased to 630 µg/kg$_{fat}$ in cans and to 523 µg/kg$_{fat}$ in plastic pouches. DBP was detected only at the point just before packaging (32 µg/kg$_{fat}$) and after packaging the concentrations increased to 52 and 60 µg/kg$_{fat}$, respectively, when packaged in cans and in pouches. BBP was detected only in milk after packaging at 12 µg/kg$_{fat}$ in cans and 53 µg/kg$_{fat}$ in pouches (Fierens et al., 2013).

Bradley et al. (2013) attempted to differentiate environmental and migration sources by considering that the latter would imply similar profiles of phthalates (type and ratio of concentrations) in food and the respective packaging. Phthalates were detected in 9 out of 29 packaging materials taken from the following foods: tomato relish, strawberry yoghurt, fruit drink, fried chicken breast, ham and cheese wrap, crispbreads, lasagne sheets, tofu and sage, and onion stuffing. The concentration values for DBP, DEHP, DINP and DIDP were used to calculate the worst case migration values assuming 100% transfer to the food. However, no correlation could be found between the packaging analysis and the phthalate levels determined in the food.

Bread is consumed typically at high frequency. Findings in the Belgian market showed relatively high concentrations of DEHP (1,038 µg/kg), DBP (19 µg/kg) and BBP (7 µg/kg) in bread. The source seemed to be contaminated flour and FCM used during production, such as coated baking trays. The location of the production site was found to affect the phthalate levels. The contribution of the packaging material on phthalate contamination in bread was further explored by comparing absolute contents of phthalates in bread samples with absolute phthalate levels measured in the respective paper bags. Results indicated that DBP most likely migrated from the packaging into bread, while the bag could not be the most important contamination source of BBP and DEHP in these bread samples (van Holderbeke et al. 2014). By examining the concentration-depth profile of phthalates in apple, bread, cheese and salami, the authors concluded that food preparation (i.e. baking, mixing of ingredients, pasteurisation etc.) is introducing phthalates in Belgian food products rather than migration from the packaging (Van Holderbeke et al. 2014).

The contamination source for vegetable oils is very difficult to trace. There is evidence that environmental contamination occurs as concluded by the concentration of e.g. DBP and DEHP found in olive oil samples collected in industrial and non-industrial areas, and all processed in oil presses free of phthalate-containing materials. Levels of DBP and DEHP ranged respectively: <25 - 150 µg/kg and <50 - 5000 µg/kg for samples collected close to an industrial area and an airport, while these phthalates were below the LOD (8 µg/kg for DBP and 20 µg/kg for DEHP) in samples collected in non-industrial sites (Ierapetritis et al., 2014). DINP and DIDP were below the LOD (200 µg/kg) in all samples. Raffination (mainly deodoration) decreases phthalate concentrations, when contact with phthalate-containing materials is prevented (Nanni et al., 2011). Furthermore, the authors concluded that the final packaging does not affect the phthalate concentration level, as comparing the results for different oils packaged in different packaging materials. For corn oil, soybean oil and olive oil there was no statistically significant difference in DBP, DEHP or DINP levels between the different packaging materials; similarly for DEHP and DBP concentrations in sunflower oil. The only significant differences found were for DINP in sunflower oil and for DINP and DEHP in extra virgin olive oil, when the package was tinplate cans, although the authors cautioned that it was based on a small number of samples and without confirmation of the nature of the internal coating of the tinplate cans (Nanni et al., 2011).

Mineral waters collected in Italy (142 samples, 71 in PET and 71 in glass bottles) showed higher concentrations for DBP (0.23 µg/L) packaged in PET as compared to water packaged in glass (DBP 0.04 µg/L). DEHP was below the LOD (0.01 µg/L) in all samples. The occurrence of phthalates in the glass bottled-water was attributed to other FCM from the storage/bottling line (Montuori et al., 2008).

No information was provided on the type of closure ('cap') on the bottles. If the closure or its sealing gasket/liner (if any) was a plastic then it could be a more important source of phthalates than the bottle material (glass or PET) *per se*.

Chatonnet et al. (2014) investigated phthalate concentrations in French wines (100) and grape spirits (30) marketed in Europe or intended for export. In wines, phthalates content above LOQ (10 µg/L) was detected in 59% (DBP) and 15% (BBP and DEHP) of the samples. For spirits, 90% of samples had DBP and DEHP and 40% had BBP above the LOQ (10 µg/L). DINP and DIDP were neither detected in wines nor in spirits (LOD = 20 µg/L). However, they were detected in a few samples of packaging materials. Only traces of e.g. DBP and DEHP were detected in plastic stoppers, liners of screw caps and microgranulated cork stoppers (Chatonnet et al., 2014). This indicates that the packaging is not the source of contamination. The analyses of other FCM used in the production and bottling processes showed that epoxy coating used in vats contained high level of DBP and was a major source of contamination. DEHP was found in high levels in tank seals (30,000 µg/g, or 3% w/w) and plastic hoses (ca. 15,800 and 200,000 µg/g, 1.5 and 20% w/w), which also contained DINP and DIDP albeit in lower concentrations (Chatonnet et al., 2014).

Beer packaged in different packaging materials was found to present no statistically different concentrations of phthalates between metal cans or glass or aluminium bottles (Carnol et al., 2017). BBP was found in only 1 out of 15 samples (1.5 µg/L) of beer packed in glass bottle. DBP in beer ranged from 7 to 37 µg/L in metal cans and from 0.6 to 35 µg/L in glass bottles. DEHP ranged from 0.2 to 0.7 µg/L in metal cans and from 0.05 to 1.7 µg/L in glass bottles. The bottles had a crown cap with a gasket and the cans and the aluminium bottles were coated internally. Results seem to indicate that the production process is the predominant source of contamination, but there was no information available on the concentration of phthalates in the raw materials used for brewing the beer.

Di Bella et al. (2014) studied the impact of preparing coffee drinks using an espresso machine operating with coffee pods or capsules. The results indicated that for DBP and DEHP, brewing the coffee in the machine increased the phthalate amount in the coffee drink (as compared to the amount in the powder alone) 1.3 to 3.2 times, as result of contact both with machine parts and with the capsules/pods at the brewing temperature. For example, one dose of brewed coffee contained 131 and 143 ng of DBP and DEHP respectively, whereas the corresponding quantity of powder used contained only 41 and 57 ng, respectively. In addition, the migration of DEHP from the sealing ring of a moka coffeepot was studied during consecutive uses. The amount of DEHP in the brewed coffee increased significantly to ca. 1,200 ng in one coffee drink as compared to the amount in powder (ca. 200 ng). This migration declined successively with the number of pot uses; after 240 coffees were prepared the migration was not detectable and only the coffee powder itself gave the phthalates detected in the coffee drink. No information on the initial concentration of DEHP in the sealing ring or on its size (weight and contact area) was available. BBP and DINP were not detected in coffee drinks or powders (LOD respectively 0.036 and 0.889 mg/L).

A study on phthalates in Norwegian foods and beverages compared the total concentration of phthalates in food items packed in plastic with those packed in other materials. The results indicated that the difference between food items packed in plastic compared to other packaging materials (paper, cardboard, metal and glass) was not significant for short-chain phthalates (up to C4; sum of dimethyl phthalate (DMP), diethyl phthalate (DEP), DBP, DIBP). For longer-chain phthalates, however, (sum of BBP, dicyclohexyl phthalate (DCHP), DEHP, di-*n*-octyl phthalate (DnOP), DINP and DIDP) significantly higher concentrations were found in food items packed in plastic (Sakhi et al., 2014). Unfortunately, this analysis was not presented separately for each phthalate.

In conclusion, notwithstanding a number of published studies designed to investigate the source of phthalates in foodstuffs and the possible contribution from FCM, there is not a sufficient body of evidence to come to firm conclusions. On balance, the studies indicate that primary packaging (i.e. for retail foods) is not the main source or even a major source of contamination of the 5 phthalates under consideration here, albeit with a few exceptions for specific foods. More usually the phthalates found in food are attributed to 'background contamination' although this could also include the use of FCM during primary production, processing and transport. In a few cases the major source is clear, such as when plasticised tubing or gaskets have been used. Compared to the situation for FCM in general, the picture for specifically plastic FCM is even less clear. It does seem likely that FCM in general and plastics in particular, make a contribution to the levels of DBP, BBP, DEHP, DINP and DIDP found in foodstuffs overall, but this cannot be quantified using the information available. This lack of information could be addressed via a call for data, as pointed out in section 8.

3.6. Human biomonitoring data

Because phthalates are rapidly metabolised and almost completely excreted via urine within 24 h, most of the biomarkers of exposure used are specific metabolites generated in the human body and eliminated in urine. Monoester metabolites are the major urinary biomarkers of the short-chain phthalates, whereas for the long-chain phthalates the monoester is further metabolised and the secondary, oxidised metabolites (see 4.1) are the main metabolites excreted in human urine (Anderson et al., 2001, 2011; Wittassek et al., 2008).

Although several sets of biomonitoring data exist for DBP, BBP, DEHP and DIBP, as reported in the ECHA RAC opinion (2017a), the assessment relies mainly on the data generated in the EU DEMOCOPHES project, due to its representativeness of the EU countries, the large sample size and the recent period of sample collection (2011-2012). In this study, several phthalate metabolites were measured in urine (spot morning samples) of 6–11 year old children and their mothers (median age = 39 years). Urinary metabolite concentrations were normalised against creatinine. Data reported by ECHA RAC (2017a) did not include urinary metabolites measurements for DINP and DIDP.

ECHA estimated the daily intake from morning spot urine samples on the basis of the fraction of the phthalate diester excreted in urine (FUE values) as defined by Frederiksen et al. (2013). For DEHP, FUE values were those reported by Anderson et al. (2011), namely 6.2%, 10.9% and 14.9% for MEHP, 5-oxo-MEHP and 5OH-MEHP, respectively. FUE values of 74% for MBP from DPB, 73% for MBzP from BBP and 70% for Mono-isobutyl phthalate (MIBP) from DIBP were used, based on data published by Anderson et al. (2001, 2011), Seckin et al. (2009) and Koch et al. (2012), respectively.

ECHA used the 95th percentile urinary exposure levels from DEMOCOPHES as an estimate of the reasonable worst case of exposure. Calculated for Europe (i.e. the 17 participating countries, incl. Switzerland), overall intake estimates (geometric mean) for children were 3.3, 1.0, 0.2 and 1.4 µg/kg bw per day for DEHP, DBP, BBP and DIBP, respectively. Corresponding values for mothers were 2.1, 0.7, 0.1, 0.9 µg/kg bw per day, respectively (ECHA, 2017a). The values, as reported in Table 18, are close to those reported by Myridakis et al. in Greece (2015), based on a biomonitoring study not included in the DEMOCOPHES project. ECHA also calculated exposure per country and noted that there were quite large differences across countries (as also concluded in Den Hond et al., 2015).

Table 18: Overall intake estimates (µg/kg bw/day) from DEMOCOPHES (calculated for "Europe"), based on Den Hond et al. (2015) (Table adapted from ECHA, 2017a)

	N	Median	P95	Maximum
Children				
DEHP	1816	3.3	12	256
DBP	1355	1.0	4	25
BBP	1816	0.2	1.2	17
DIBP	1355	1.4	5.0	49
Mother				
DEHP	1800	2.1	8.3	123
DBP	1347	0.7	2.1	65
BBP	1800	0.1	0.7	14
DIBP	1347	0.9	3.2	12

In the ECHA RAC assessment, studies that combined the duplicate diet method or changes in the diet (fasting or low-phthalate diet) with biomonitoring were used to estimate the fraction of exposure that can be attributed to exposure via food (ECHA, 2017a). On the basis of these studies, ECHA RAC assumed that 75% of the intake of DEHP is attributable to food (incl. drinks), while for DBP, BBP and DIBP the assumed contribution from food is lower (25%).

3.7. Modelling of exposure from different sources

As described in 3.6, the human biomonitoring data were used as the main source of information for exposure assessment in the ECHA opinion (2017a). In addition, exposure to phthalates from different sources, i.e. indoor environment (air and dust), food (environmental contamination and FCM), articles (e.g. sandals, erasers, sex toys), was modelled mainly to identify sources that contribute to phthalates exposure (see Table 19). The contribution of food to the overall exposure was about 30% for DEHP, DBP and BBP (for infants, mean exposure scenario), whereas for the highly exposed infants food contributed much less to the overall exposure (around 10%). No conclusion was drawn on the fraction of contribution from FCM to the exposure from food/ overall exposure.The estimates for food were comparable with those derived in the EFSA assessment.

Table 19: Aggregated exposure from indoor environment, food and contact with articles for each phthalate (μg/kg bw/day) (from ECHA, 2017a)

	Infants			**Children**			**Women**		
	Typical	RWC	MC PWC	Typical	RWC	MC PWC	Typical	RWC	MC PWC
DEHP									
Indoor	4.22	21.85	21.85	0.93	5.51	5.51	0.48	2.52	2.52
Food	4.66	7.09	7.09	3.50	5.38	5.38	1.49	2.86	2.86
Articles	3.49	27.32	27.67	2.39	17.91	17.26	2.12	7.63	12.06
Total	12.37	56.26	56.61	6.82	28.80	28.15	4.09	13.01	17.45
Monte Carlo			42.98			22.38			14.17
DBP									
Indoor	0.28	1.47	1.47	0.04	0.27	0.27	0.02	0.12	0.12
Food	0.70	1.24	1.24	0.20	0.30	0.30	0.08	0.16	0.16
Articles	1.20	9.22	6.48	0.83	6.22	4.39	0.74	2.65	3.17
Total	2.18	11.93	9.19	1.07	6.79	4.96	0.84	2.92	3.45
Monte Carlo			6.63			4.63			3.27
DIBP									
Indoor	0.27	1.41	1.41	0.04	0.25	0.25	0.02	0.11	0.11
Food	1.03	9.02	9.02	0.42	0.64	0.64	0.14	0.28	0.28
Articles	1.06	8.16	6.74	0.73	5.50	4.49	0.65	2.34	3.09
Total	2.37	18.59	17.18	1.19	6.40	5.39	0.82	2.74	3.48
Monte Carlo			12.19			4.94			3.28
BBP									
Indoor	0.08	0.42	0.42	0.01	0.08	0.08	0.01	0.03	0.03
Food	0.15	0.24	0.24	0.12	0.21	0.21	0.05	0.12	0.12
Articles	0.31	2.43	1.75	0.21	1.59	1.13	0.19	0.68	0.77
Total	0.54	3.09	2.41	0.34	1.87	1.41	0.25	0.83	0.92
Monte Carlo			1.90			1.25			0.83

Typical = Typical case scenario
RWC = Reasonable worst case scenario
RWC MC = Monte Carlo simulation of the reasonable worst case scenario

4. Hazard identification and characterisation

4.1. Toxicokinetics

Due to the fact that this opinion is related to phthalates used in plastic FCM, only the oral route was considered for toxicokinetics data.

4.1.1. Absorption

The uptake of phthalates depends on several factors, including the dose and route of exposure, as well as the molecular weight of the compound. Measurements in rodents exposed orally to low doses of phthalates indicate that gastrointestinal absorption is rapid and that observed levels are close to 100% for DBP and BBP, and about 50% for DEHP, DINP and DIDP (INSERM, 2011). Studies carried out by Koch et al. (2004, 2005) on a healthy volunteer who was administered a single oral dose of deuterium-labelled DEHP indicate that in humans the absorption of this phthalate is approximately 75%. It must be noted that part of the absorption occurs after hydrolysis in the gastrointestinal tract of the parent compound into the primary metabolite monoester phthalate (see section 3.2.1.3).

4.1.2. Distribution

Once absorbed, phthalates are rapidly and widely distributed to tissues. Experimental animal data resulting from oral exposure indicate that parent compounds and metabolites are mainly localised in blood, liver, intestine, adipose tissue and kidney, but the knowledge about the distribution of phthalates and metabolites in the human body is limited. DBP, BBP, DEHP, DINP and DIDP and/or related metabolites can be transferred to the fetus during gestation as shown in rodents (Singh et al, 1975; Kurata et al., 2012; Clewell et al., 2013a), and in humans (Frederiksen et al., 2007; Wittassek et al., 2009; Enke et al. 2013; Arbuckle et al., 2016). There is no evidence of tissue accumulation for these phthalates or their metabolites.

4.1.3. Metabolism

In rodents as in humans, the biotransformation of phthalates involves several metabolic pathways that are broadly common to all phthalic acid diesters with saturated alkyl chains. The first step is the hydrolysis of the dialkyl phthalate to the corresponding monoester under the action of esterases present in the digestive tract, releasing the alkyl chain in the form of an alcohol. The shorter-chain-length dialkyl phthalates (e.g. DBP) are predominantly metabolised by ester hydrolysis to the simple monoester phthalates, which are excreted in the urine, usually after glucuronidation.

For phthalates having a longer alkyl chain, including branched alkyl chain, such as DEHP and DINP, the monoesters then undergo oxidation on the alkyl chain that can take place on the terminal carbon (oxidation in ω) or subterminal (ω-1), but also in ω-2 position. These oxidations are catalysed by cytochrome P450 enzymes. Other oxidation steps can take place, catalysed mainly by the aldehyde dehydrogenases, leading to the formation of an oxo derivative or an aldehyde, with the aldehyde giving rise to an acid under the action of an aldehyde dehydrogenase. The carboxylated metabolite can then undergo a series of β-oxidations or decarboxylations resulting in a reduction in the length of the carboxyl chain. A large number of different oxidised metabolites can result and be eliminated as such or after glucuronic acid conjugation.

For example, DEHP is converted to its primary monoester metabolite, mono(2-ethylhexyl)phthalate (MEHP), which in a multistep oxidative pathway by ω- and ω-1-oxidation of the aliphatic side chain is further metabolised to hydroxy-, oxo- and carboxy- biotransformation products, which are eliminated in urine, mainly following conjugation with glucuronic acid (Figure 1:). As indicated in Table 20, in population studies, 5cx-MEPP was found to be the principal urinary metabolite, followed by 5OH-MEHP, 5oxo-MEHP, 2cx-MEHP and MEHP (Preuss et al., 2005; Silva et al., 2006).

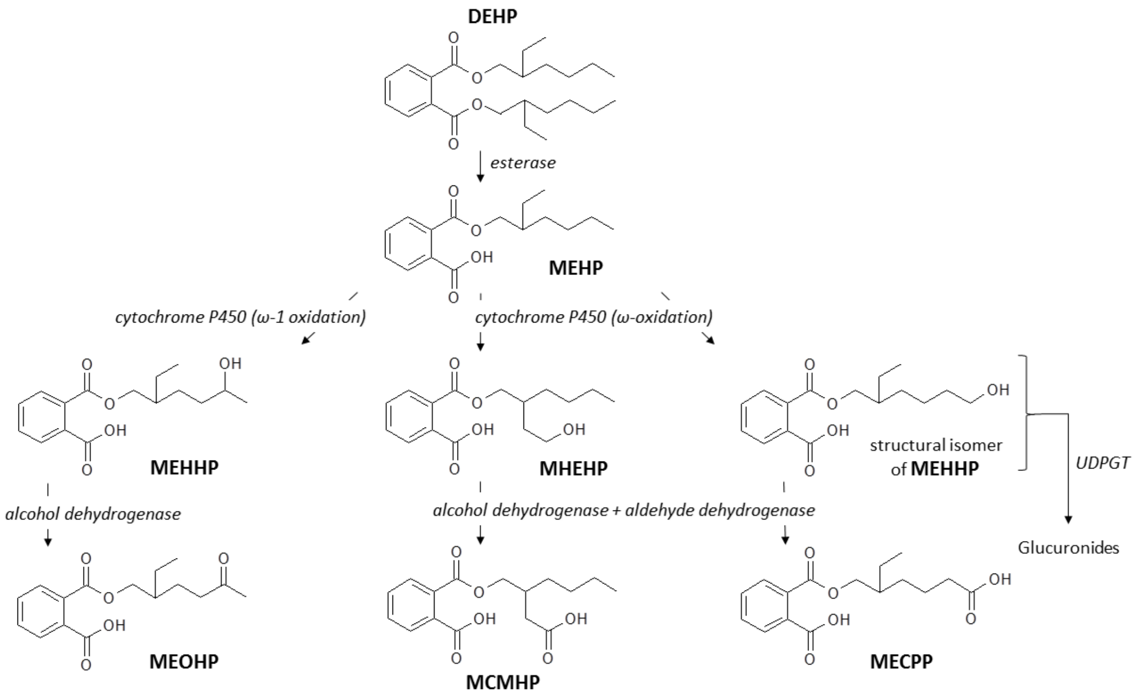


Figure 1: Major metabolic pathways of DEHP in Humans (adapted from Ito et al., 2014). See Table 20 for abbreviations.

DBP is metabolised to mono-*n*-butyl phthalate (MBP) which may be further oxidised to other metabolites (oxo-, hydroxy- and carboxy- metabolites) and conjugated to glucuronic acid (Silva et al., 2007). Both rats and humans excrete MBP as the major urinary DBP metabolite (Silva et al., 2007).

BBP is metabolised to mono-benzylphthalate (MBzP) and mono-butylphthalate (MBP), and glucuronides of these primary metabolites. In humans, MBzP is the major urinary metabolite of BBP (Anderson et al., 2001).

DINP and DIDP are metabolised in the same way as DEHP by hydrolysis and subsequent ω- and ω-1 oxidation. However, as DINP and DIDP are a mixture of various alkyl isomers, a variety of monoester, hydroxy-, oxo-, and carboxy- metabolites are formed and eliminated in urine (Wittassek and Angerer, 2008).

4.1.4. Elimination

In rats as in humans, low molecular weight phthalates such as DBP and BBP, as well as DEHP, are predominantly eliminated in urine. For phthalates of higher molecular weight such as DINP and DIDP, elimination is both faecal and urinary (McKee et al., 2002). In the rat, a substantial part of fecal elimination is due to the excretion of biliary metabolites. The estimated half-life values for the phthalates discussed in this opinion are below 24 hours (Koch et al., 2006; Wittassek and Angerer, 2008).

Table 20: Major urinary metabolites of the dialkyl ortho-phthalates discussed in this opinion

Parent compound	Metabolites	Acronym
Di-*n*-butyl-phthalate (DBP)	Mono n-butyl-phthalate	MBP
Butylbenzyl-phthalate (BBP)	Monobenzyl-phthalate	MBzP
	Monobutyl-phthalate	MBP

Di(2-ethylhexyl)-phthalate (DEHP)	Mono(2-ethylhexyl)-phthalate	MEHP
	Mono(2-ethyl-5-oxohexyl)-phthalate	MEOHP, 5oxo-MEHP
	Mono(2-ethyl-5-hydroxyhexyl)-phthalate	MEHHP, 5OH-MEHP
	Mono-(2-ethyl-6-hydroxyhexyl)-phthalate	MEHHP, 6OH-MEHP
	Mono2-(2-hydroxyethylhexyl)-phthalate	MHEHP
	Mono(2-carboxymethylhexyl)-phthalate	MCMHP, 2cx-MMHP
	Mono(2-ethyl-5-carboxypentyl)-phthalate	MECPP, 5cx-MEPP
Diisononyl-phthalate (DINP)	Monoisononyl-phthalate	MINP
	Mono(carboxyisooctyl)-phthalate	MCIOP, cx-MINP
	Mono(hydroxyisononyl)-phthalate	MHINP, OH-MINP
	Mono(oxoisononyl)-phthalate	MOINP, oxo-MINP
Diisodecyl-phthalate (DIDP)	Monoisodecyl-phthalate	MIDP
	Mono(carboxyisononyl)-phthalate	MCINP, cx-MIDP
	Mono(hydroxyisodecyl)-phthalate	MHIDP, OH-MIDP
	Mono(oxoisodecyl)-phthalate	MOIDP, oxo-MIDP

The levels of phthalate metabolites in human urine are representative of the exposure to the respective parent phthalates that occurred within the last 24 h (Koch et al., 2009). Human metabolism studies have shown that for short-chain phthalates such as DBP or BBP, the monoesters (MBP or MBzP) are the major urinary metabolites. Their urinary excretion represents approximately 70% of the oral dose (Anderson et al., 2001). Regarding the long-chain phthalates such as DEHP, DINP and DIDP, the monoester is further metabolised, resulting in a number of oxidative metabolites. Only 2-7% of the dose is excreted as the simple monoester, whereas the secondary, oxidised metabolites are the main metabolites excreted in human urine, as free or conjugated compounds (Wittassek and Angerer, 2008; Wittassek et al., 2011). Secondary metabolites and corresponding glucuronide conjugates can degrade over time in urine when samples are stored at 25°C and 4°C, but are stable for at least one year at -70°C (Samandar et al., 2009).

Reported phthalate half-lives in rodents were from 3.6 h for DBP (Chang, 2013) to approximately 14 h for DIDP (Kato et al., 2007). Although published toxicokinetics data are insufficient for most phthalates to properly calculate half-lives in humans, for DBP, BBP, DEHP, DINP and DIDP, the estimated values vary from approximately 6 h for low molecular weight phthalates (DBP, BBP) to 18-36 h for long-chain phthalates (DINP, DIDP) (Schmid and Schlatter, 1985; Anderson et al., 2001, 2011; Koch et al., 2004, 2006, 2012; Koch and Angerer, 2007; Wittassek et al., 2011; Saravanabhavan and Murray, 2012). In addition, for a given phthalate, elimination kinetics vary between metabolites. For example, the oxidized DEHP metabolites exhibited considerably longer half-lives of elimination and hence considerably later maxima of urinary excretion than the simple monoester MEHP. Therefore, the timing of urine collection relative to exposure events and its frequency are the crucial factors contributing to the temporal variation of urinary levels of phthalate metabolites. Several studies investigated the patterns of within- and between-person and of within-and between-day variability (Fromme et al., 2007; Preau et al., 2010; Kumar and Sivaperumal, 2016). For MEHHP, a metabolite of DEHP used as biomarker of exposure, the largest variation of urinary concentrations in spot urine samples was found to be related to the variation of each person throughout the day (51% of variance). The within-person variability between days was also high (32% of variance) and about twice the variation attributed to differences between persons (17% of variance) (Preau et al., 2010). Comparison of phthalate metabolite data in spot, first morning and 24-h urine samples of the same subjects showed moderate intra-class correlation coefficients (ICC, i.e. ratio of subject variation to total variance) for MBP and MBzP (approximately 0.5), indicating that the contribution of between-subject variation to total variance is more than the within-subject variation (Kumar and Sivaperumal, 2016). In such cases, single urinary sample collected over a specific duration of the day may be sufficient (Peck et al., 2010). In contrast, the metabolites of DEHP, DINP and DIDP showed low ICC (<0.4) indicating the higher contribution of within-subject variation to the total variance. This variation could be minimised by collecting multiple urine samples, preferably at different times of the day (Preau et al., 2010).

4.2. Repeated dose toxicity

The most sensitive toxicological effects of DBP, BBP and DEHP identified thus far are related to adverse effects on sexual function and fertility, and on development and these have led ECHA to classify these chemicals as reproductive toxicants (Repr. 1B). The reproductive effects on young male offspring are observed at lower doses than in adults and these effects were considered for the establishment of the PoDs. ECHA's evaluation is in full agreement with the critical N/LOAELs identified by EFSA in 2005, which were used as PoDs for the derivation of the TDIs for these three phthalates (EFSA, 2005a, b, c). The main target organs for repeated dose toxicity other than reproductive organs (in particular testis) were liver and kidney for which the lowest NOAELs identified by ECHA RAC (2017a) for DBP, BBP and DEHP were 152, 151 and 28.9 mg/kg bw per day, respectively. As these NOAELs are clearly higher than the PoDs for reproductive/developmental toxicity, they were not further taken into account by the CEP Panel in this assessment.

For DINP and DIDP, the most sensitive toxicological effects are related to the liver. The PoDs were based on hepatotoxicity observed in adult animals, and the respective NOAELs were used by EFSA to set the TDIs (EFSA, 2005d, e).

The following sections on genotoxicity and carcinogenicity, immunotoxicity, neurotoxicity, and metabolic effects, focus on DBP, BBP and DEHP since, according to the terms of reference, the evaluation of DINP and DIDP should focus on reproductive toxicity only.

4.3. Genotoxicity and carcinogenicity

In agreement with ECHA assessment (ECHA, 2017b), the Panel noted that overall the *in vitro* and *in vivo* data on mutagenicity or chromosomal damage for DBP, BBP and DEHP do not give rise to a concern for genotoxicity.

The Panel also noted the classification of DEHP by IARC (2012) as possibly carcinogenic to humans (Group 2B) based on the discussion of possible modes of action in addition to the peroxisome proliferator activated receptors (PPAR)α-mediated effects (Rusyn and Corton, 2012). Considering the absence of genotoxicity, the discussed mode of action for DEHP-induced rodent hepatocarcinogenesis and the DEHP-induced lesions in Leydig cell possibly associated with Leydig cell tumours in rats, the Panel considered that these effects are linked to doses above the NOAEL identified for the reproductive toxicity of DEHP. No carcinogenicity studies are available for DBP, except for an oral rat study with prenatal exposure (GD 12-21 with high doses of 100 and 500 mg/kg bw per day) in which no DBP-induced increases in Leydig cell hyperplasia and adenomas in male offspring were found (Barlow et al., 2004). BBP tested negative for carcinogenicity in mice while some tumours of doubtful significance were reported in pancreas and urinary bladder of rats (ECHA, 2017b). Consequently, the tumour data were not further considered by the CEP Panel in the current risk assessment of DBP, BBP and DEHP.

4.4. Immune effects

ECHA RAC noted in its assessment (2017a) that several studies suggested adverse effects of phthalate exposure on the immune system, in particular leading to allergy, asthma and eczema. For instance, Braun et al. (2013) reviewed epidemiological data showing associations between exposure to DBP, BBP and DEHP and asthma and eczema. "Children from homes with high concentrations of phthalates in dust had high incidences of allergy, asthma, rhinitis and eczema (Bornehag et al., 2004; Hsu et al., 2012; Kolarik et al., 2008)". "Higher maternal BBP exposure in pregnancy was associated with early-onset eczema in children (Just et al., 2012)". Studies in mice and rats showed that DEHP could enhance the sensitisation to allergens (adjuvant effect), and this was suggested as an underlying risk factor in the increase in severity of asthma (Guo et al., 2012; You et al., 2014). Increased serum immunoglobulin E (IgE) responses were seen after 52 days exposure of adult mice to very low doses of DEHP (30 µg/kg bw per day) (Guo et al., 2012). Tonk et al. (2012) examined developmental and immunological effects of 1 to 1,000 mg DEHP/ kg bw per day in juvenile and adult male rats, and found effects on immune parameters in juvenile males beginning from around 1 mg/kg bw per day, i.e. at lower doses than those affecting reproductive organ weights. Overall, ECHA concluded that these studies indicated that reproductive toxicity may not be the most sensitive endpoint for the effects of DEHP, that the DNELs selected for the current combined risk assessment may not be sufficiently protective for immunological effects, and that there is a need for further robust data to perform a risk assessment regarding adverse effects on the immune system.

The CEP Panel agrees with the conclusions by ECHA (2017a), based on the literature reviewed in their report, that the effects on the immune system may be a more sensitive endpoint compared to reproductive toxicity. This aspect was considered in the uncertainty analysis (Table 27) and in the recommendations (section 8).

4.5. Neurological and neurodevelopmental effects

ECHA noted in its assessment (2017a) that "altered neurodevelopment has been associated with high phthalate exposures in children, as reviewed by Miodovnik et al. (2014). Numerous behavioural disorders including autism spectrum disorders, ADHD[12], learning disabilities, and altered play behaviour have been associated with higher phthalate exposure in humans (reviewed by Braun et al., 2013). Animal studies examining behavioural effects of phthalate exposure have shown some effects that may be related to altered sex differentiation, whereas other behavioural effects are not clearly linked with disruption of sex hormones. Different modes of action for phthalate effects on neurodevelopment have been proposed, including interference with the thyroid hormone system, altered calcium signalling, relation to activation of peroxisome proliferator activated receptors (PPARs) in brain and altered lipid metabolism (Miodovnik et al., 2014)."

ECHA concluded that neurodevelopment effects have not been elucidated yet (ECHA, 2017b). However, it was noted in the ECHA assessment (2017a) that "The Dossier Submitter considered the available data to provide as yet only weak evidence for an effect of phthalates on neurodevelopment and behaviour. However, RAC notes that the available epidemiological and experimental data do indicate that such effects cannot be excluded. It is acknowledged though that the available studies do not provide robust dose response data that are important for PoD and DNEL setting."

The CEP Panel agrees with the conclusions by ECHA (2017a) that potential neurological or neurodevelopmental effects may contribute to the uncertainties in the risk assessment of phthalates. This aspect was considered in the uncertainty analysis (see section 6) and in the recommendations (section 8).

[12] Attention Deficit Hyperactivity Disorder

4.6. Metabolic effects

A metabolic disorder is caused by errors in the body's metabolism — the ability to turn food into energy and dispose waste. Disturbances in glucose or lipid metabolism may lead to metabolic syndrome, diabetes or obesity. ECHA (2017a) stated regarding effects on metabolism that "Associations between prenatal phthalate exposure and obesity or diabetes in adulthood have been investigated in epidemiological studies, and *in vitro* and animal studies have provided mechanistic knowledge indicating obesogenic effects of phthalates, e.g. by promoting differentiation of and accumulation of lipid in lipid cells (reviewed by Kim and Park, 2014). The fetal period is considered critical to phthalate exposure, but few studies had been able to clarify the role of prenatal exposure to phthalates in the obesity epidemic."

The Dossier Submitter of the ECHA opinion considered "the available data to provide as yet only weak evidence for an effect of phthalates on metabolism. Although RAC considers that such an effect cannot be excluded, it is acknowledged that the data are insufficient as to PoD and DNEL derivation. RAC therefore supports the Dossier Submitter's approach to include the possibility for these effects in the uncertainty analysis and in the socio economic analysis (SEA)" (ECHA, 2017a). In the uncertainty analysis, it was stated that "a number of experimental and epidemiological studies suggested possible effects on the metabolic system and neurological development. It is not clear from the data whether the selected DNELs based on reproductive toxicity are sufficiently protective against these other effects." Therefore, the effects of phthalates on metabolism on the RCR were unknown.

The CEP Panel agreed with the above-mentioned conclusions on metabolic effects by ECHA (2017a), based on the three reviews (by Kim and Park, 2014; Gore et al., 2015; Legler et al., 2015) that were included in the ECHA opinion. However, in order to draw conclusions with less uncertainty regarding metabolic effects of these phthalates, it will be necessary to look into each experimental study included in these reviews more thoroughly. EFSA has not performed such a scrutiny of these individual papers in this opinion. This aspect was considered in the uncertainty analysis (see section 6) and in the recommendations (section 8).

4.7. Reproductive toxicity in animals

The CEP Panel based its evaluations of the reproductive effects of DBP, BBP and DEHP on the ECHA assessment (2017a, b) in combination with the EFSA opinion on these phthalates (EFSA, 2005 a,b,c). The evaluations of the reproductive effects of DINP and of DIDP are based on the EFSA opinions (EFSA, 2005 d,e), an ECHA report on DINP and DIDP (ECHA, 2013), and also taking into account the ECHA RAC opinion on harmonised classification and labelling of DINP (ECHA, 2018). The CEP Panel also searched for studies on reproductive effects for DINP and DIDP published after 2005 (see 2.2 for more information on the searches).

4.7.1. DBP

EFSA (2005a) based its TDI for DBP of 0.01 mg/kg bw per day on a LOAEL of 2 mg DBP/kg bw per day identified in a developmental toxicity study in rats (Crj:CD(SD)IGS) (dietary exposure gestation day (GD) 15 - postnatal day (PND) 21) and making use of an uncertainty factor of 200 (Lee et al., 2004). Effects observed were reduced spermatocyte development on PND 21 and mammary gland changes in adult males in all treated groups. Reduced AGD and increased nipple retention were observed at 1000 mg DBP/kg bw per day. No effects were seen for these parameters at 200 mg DBP/kg bw per day. Another study also reviewed in the EFSA opinion is that by Mylchreest et al. (2000), in which a NOAEL of 50 mg DBP/kg bw per day was identified for nipple retention in male F1-rats exposed *in utero* from GD 12 to 21. The doses tested in this latter study were 0, 0.5, 5, 50, 100 and 500 mg DBP/kg bw per day by gavage.

ECHA (2017a) made reference to the above mentioned EFSA opinion and like EFSA, it proposed to use the LOAEL of 2 mg DBP/kg bw per day from the study by Lee et al. (2004) as PoD. A study that was not described in the EFSA opinion (2005a) is that of Zhang et al. (2004), which identified decreased AGD in F1-males and effects on male reproductive organs and sperm production in rats exposed *in utero* and during lactation (GD 1-PND 21). The doses in this study were 50, 250 or 500 mg DBP/kg bw per day; the NOAEL of the study was 50 mg DBP/kg bw per day. All the other studies assessed in the ECHA opinion that were published after 2005 reported effects only at higher dose levels of DBP.

Overall, the CEP Panel did not identify any study reviewed by ECHA (2017a, b) which could give rise to a LOAEL or NOAEL lower than those previously identified by EFSA (2005a). The CEP Panel concurred with the choice of both EFSA (2005a) and ECHA (2017a) on the critical effect, reported by Lee et al. (2004), of reduced spermatocyte development and effects on the mammary gland, which occurred at a LOAEL of 2 mg DBP/kg bw per day.

4.7.2. BBP

EFSA (2005b) based its TDI for BBP of 0.5 mg/kg bw per day on a NOAEL of 50 mg/kg bw per day identified in a dietary two-generation reproductive toxicity study in CD rats and making use of an uncertainty factor of 100 (Tyl et al., 2001, 2004). The effect observed was reduced AGD in F1- and F2- males at birth in the 250 mg BBP/kg bw per day group. In this study, also a high dose level of 750 mg BBP/kg bw per day was included.

ECHA (2017a) also identified the NOAEL of 50 mg BBP/kg bw per day in the study of Tyl et al. (2004) as PoD. In its report, ECHA further described the study of Aso et al. (2005) as a key study. In this two-generation reproductive toxicity study in rats (Crj:CD(SD)IGS), decreased AGD was observed in the F2-males at all dose groups (100, 200 and 400 mg/kg bw per day by gavage) and therefore a LOAEL of 100 mg BBP/kg bw per day was identified. In a two-generation reproductive toxicity study of Nagao et al. (2000) (doses 0, 20, 100 and 500 mg BBP/kg bw per day by gavage) in Sprague Dawley rats, a NOAEL of 100 mg BBP/kg bw per day was identified based on effects on reproductive organs and preputial separation. In addition, a study by Ahmad et al. (2014) was described in which albino rats were dosed by gavage with 0, 4, 20 or 100 mg BBP/kg bw per day from GD 14 to parturition. At 100 mg/kg bw per day (LOAEL) reductions in the weight of the reproductive organs and altered sperm counts and motility were seen.

ECHA combined the LOAELs of 100 mg BBP/kg bw per day from the studies of Aso et al. (2005) and Ahmad et al. (2014), and the NOAEL of 100 mg BBP/kg bw per day from the study of Nagao et al. (2000) with the results of the study of Tyl et al. (2004) in which a NOAEL of 50 mg BBP/kg bw per day was determined. An overall NOAEL of 50 mg BBP/kg bw per day was identified.

Overall, the CEP Panel did not identify any study reviewed by ECHA (2017a, b) which could give rise to a LOAEL or NOAEL lower than those previously identified by EFSA (2005b). The CEP Panel concurred with the choice of both EFSA (2005b) and ECHA (2017a) on the critical effect, reported by Tyl et al. (2004), of reduced AGD in F1- and F2- males at birth in the 250 mg BBP/kg bw per day group, from which a NOAEL of 50 mg BBP/kg bw per day was identified.

4.7.3. DEHP

EFSA (2005c) based its TDI for DEHP of 0.05 mg/kg bw per day on the NOAEL of 5 mg/kg bw per day from the multi-generation reproductive toxicity study of Wolfe and Layton (2003) using an uncertainty factor of 100. The effect observed was testicular toxicity in F1 and F2 animals.

ECHA (2017a) stated that the studies of Wolfe and Layton (2003), Andrade et al. (2006) and Christiansen et al. (2010) were the critical studies for the NOAEL selection for DEHP of 4.8 mg/kg bw per day.

The CEP Panel agreed with the pivotal studies mentioned in the ECHA RAC opinion (2017a) for DEHP, which are further described below.

> The NOAEL of the three-generation reproductive toxicity study in Sprague Dawley rats of Wolfe and Layton (2003) was also selected as critical by ECHA (2017). In this study, rats were exposed to dietary concentrations of DEHP of 1.5, 10, 30, 100, 300, 1,000, 7,500 and 10,000 mg DEHP/kg diet (n = 17 per sex group), corresponding to 0.1, 0.47, 1.4, 4.8, 14, 46, 359 and 543 mg/kg bw per day in F2 animals. As DEHP was found in control feed, the control group received 1.5 mg DEHP/kg diet. Testicular effects were most prominent in F1 and F2 animals, and a NOAEL of 100 mg/kg diet corresponding to 4.8 mg/kg bw per day in F2 animals was determined.

One of the other studies considered as critical by ECHA (2017) was the study by Andrade et al. (2006) in which groups of pregnant Wistar rats (n = 11-16 per group) were treated by gavage with wide ranges of doses; low doses (0, 0.015, 0.045, 0.135, 0.405 and 1.215 mg DEHP/kg bw per day) and high doses (0, 5, 15, 45, 135 or 450 mg DEHP/kg bw per day) were administered from GD 7 to PND 21. According to the authors, the LOAEL was 5 mg DEHP/kg bw per day, based on one F1-animal with cryptorchidism in this group. This effect was also observed in one F1-animal of the 135 and 405 mg DEHP/kg bw groups out of 19-20 animals. In the 15 mg DEHP/kg bw group, higher delayed preputial separation and decreased daily sperm production was observed. ECHA decided not to take the result of this study into consideration as this LOAEL was based only on cryptorchidism found in one F1 animal. The CEP Panel agreed with this view.

In the study of Christiansen et al. (2010) in rats, a LOAEL of 10 mg DEHP/kg bw per day was proposed by the authors based on reduced AGD and increased nipple retention in F1-animals exposed perinatally (GD 7-PND 16). The authors combined the results of two separate studies in this publication. The studies were performed in groups of pregnant Wistar rats administered with 0 (n = 30), 3 (n = 14), 10 (n = 14), 30 (n = 13), 100 (n = 15), 300 (n = 7), 600 (n = 6) or 900 (n = 7) mg DEHP/kg bw per day. According to the authors, the NOAEL of the studies was 3 mg DEHP/kg bw per day. ECHA considered that the LOAEL of 10 mg/kg bw of these studies would not change the overall NOAEL for the determination of the DNEL, as the effects seen were considered to be mild.

From the ECHA RAC opinion (2017a), the Panel also identified the studies which could have possible lower or equal NOAELs or LOAELs compared to those from the three critical studies used to identify the NOAEL (Grande et al., 2006; Gray et al., 2009; Meltzer et al., 2015; Hannon et al., 2016; Zhang et al., 2013a,b). The Panel agreed with the ECHA's approach, based on the design and/or reliability of these studies, to exclude or only use them as supporting evidence for the derivation of the HBGV. Furthermore, ECHA described 4 studies in rats (Wilson et al., 2007; Noriega et al., 2009; Howdeshell et al., 2007, 2008 and Hannas et al., 2011), one study in mice (Liu et al., 2008) and one study in marmosets (Tomonari et al., 2006), for which higher NOAELs were identified and which were therefore not taken into consideration for the derivation of HBGVs.

Overall, the CEP Panel did not identify any study reviewed by ECHA (2017a, b) which could give rise to a LOAEL or NOAEL lower than those previously identified by EFSA (2005). The CEP Panel concurred with the choice of both EFSA (2005b) and ECHA (2017a) on the critical effect on the testis in F1-animals, reported by Wolfe and Layton (2003), from which a NOAEL of 4.8 mg DEHP/kg bw per day was identified.

4.7.4. DINP

In the EFSA opinion on DINP (EFSA, 2005d), the AFC Panel based its risk assessment on the effects on the liver, reproduction and development. The Panel considered that the pivotal effect was the effect on the liver (increased incidence of spongiosis hepatis), increased levels of liver enzymes and increased absolute and relative liver and kidney weights from the study in Fisher 344 rats by Exxon (1986; also cited as Lington, 1997). The AFC Panel (EFSA, 2005d) identified a NOAEL of 15 mg DINP/kg bw per day for non-peroxisomal proliferation-related chronic hepatic and renal effects in rats, and applied an uncertainty factor of 100 to derive a TDI of 0.15 mg DINP/kg bw per day.

As regards developmental toxicity, in the EFSA opinion (EFSA, 2005d), a dietary two-generation reproductive toxicity study in rats (CRL:CD(SD)BR) including a one-generation range-finding study was reviewed (Exxon, 1996a,b; published by Waterman et al., 2000). The LOAEL of this two-generation reproductive toxicity study, in which 0, 0.2, 0.4 or 0.8% DINP was administered in the diet, was 114 mg DINP/kg bw per day based on lower body weight and hepatic changes. A decrease in mean offspring weight after administration of 0.2% in the diet (159 mg DINP/kg bw per day) was considered as the LOAEL for reproductive effects. The Panel noted that in this study AGD and nipple retention were not among the studied parameters.

The AFC Panel (EFSA, 2005d) further identified in a prenatal developmental study (Exxon, 1994, published by Waterman et al., 1999) a NOAEL of 500 mg DINP/kg bw per day for maternal and developmental toxicity (dilated renal pelvis and hydroureter). In this study, doses of 0, 100, 500 or

1000 mg DINP/kg bw per day were administered by gavage to Sprague Dawley rats from GD 6 to GD 15. In addition, from a prenatal developmental study in rats (BASF, 1995a, b), a NOAEL of 200 mg DINP/kg bw per day was identified for developmental toxicity (rudimentary cervical and accessory 14th ribs). In this study in Wistar rats, doses of 0, 40, 200 or 1000 mg DINP/kg bw per day were administered by gavage from GD 6 to GD 15.

ECHA has evaluated the developmental toxicity of DINP in 2013 (together with DIDP in relation to entry 52 of Annex XVII to the REACH Regulation) and in 2018 (under the process of harmonised classification and labelling (CLP)). Studies included in these two ECHA assessments and considered relevant by the CEP Panel are described below.

ECHA (2013) re-evaluated DINP and identified a NOAEL of 100 mg DINP/kg bw per day and a LOAEL of 500 mg DINP/kg bw per day in the developmental study from Exxon (Exxon, 1994, published by Waterman et al., 1999). In this re-evaluation, the NOAEL was based on the increased incidence of skeletal and visceral variations which were observed at dose levels lower than those causing dilation of renal pelvis and hydroureter.

The effects of DINP on fetal male sexual development were studied in Sprague Dawley rats by Clewell et al. (2013a). Pregnant rats were exposed by gavage to 0, 50, 250 or 500 mg DINP/kg bw per day from GD 12 to GD 19. Decreased fetal testosterone production and histopathological changes (multinucleated gonocytes, MNGs) were observed at a dose of 250 mg DINP/kg bw per day (LOAEL). The NOAEL of this study was 50 mg DINP/kg bw per day. The administration period of this study covered the sensitive period of masculinisation, in contrast to the earlier studies evaluated by EFSA in 2005 (Exxon 1994 published by Waterman et al 2000, Exxon 1994 published by Waterman et al. 1999, and BASF 1995 a,b). The study by Clewell et al. (2013a) was therefore considered as the critical study for reproductive effects.

Increase in MNG's was also seen in the studies of Boberg et al. (2011) (corrigendum Boberg et al., 2016) and Clewell et al. (2013b). Boberg administered pregnant Wistar rats by gavage from GD 7 to PND 17 with vehicle, 300, 600, 750 or 900 mg DINP/kg bw per day and studied the effects on fetal testosterone, nipple retention, AGD, sperm and behaviour in the Morris Water Maze test. Female offspring dosed with DINP performed better than controls for spatial learning, indicating masculinisation of behaviour in DINP-exposed females. The NOAEL of this study was 300 mg DINP/kg bw per day based on histopathological effects in the testis (MNGs) at the dose of 600 mg DINP/kg bw per day. Clewell et al. (2013b) studied male sexual development in Sprague Dawley rats after dietary administration from GD 12 to PND 14 of 0, 760, 3,800 and 11,400 mg DINP/kg diet. On PND 2, DINP induced MNGs (3,800 mg/kg diet equivalent to 190 mg DINP/kg bw per day) and Leydig cell aggregates (LCAs) (11,400 mg/kg diet) on PND 2, and reduced AGD (11,400 mg/kg diet) on PND 14. However, DINP did not alter AGD, nipple retention or reproductive tract malformations on PND 49 in any of the tested groups.

Hannas et al. (2011) studied the effects of DINP and other phthalates on fetal testosterone production and gene expression levels and detected that DINP was less potent in disrupting fetal testis endocrine function than DEHP, but did significantly reduce the fetal testosterone production on GD 18 at 500 mg/kg bw per day. Sprague Dawley rats were administered by gavage with 0, 100, 300, 500, 625, 750 or 875 mg/kg bw per day from GD 14-18.

Adamsson et al. (2009) did not detect a decrease in fetal testosterone on GD 19.5 at a dose of 750 mg DINP/kg bw per day. Pregnant Sprague Dawley rats were dosed with 0, 250 or 750 mg DINP/kg bw per day from GD 13.5-17.5. The measurement of fetal testosterone was performed 2 days after the last dosing. This is in contrast to the studies of Clewell et al. (2013a) and Hannas et al. (2011) in which a reduction in fetal testosterone was found within one day after the last administration. In the case of the study by Clewell et al. (2013a) the changes in testicular testosterone levels seemed transient, since the effect was observed at 2 h after dosing, but not anymore at 24 h.

ECHA (2013) further noted that DINP has anti-androgenic potency but may also exhibit its effects through other modes of action.

Furthermore, studies for other reproductive effects, which were seen mainly at higher doses than those described above and in addition studies found in the literature search[13] performed by EFSA in 2018 are described below.

Only Lee et al. (2006 a, b) observed effects on AGD at very low levels (2 mg/kg bw per day). ECHA considered that this study had critical limitations and the CEP Panel agreed with this view. No effects on AGD were found by Masutomi et al. (2003), Gray et al. (2000) and Clewell et al. (2013 a, b) at doses of approximately 750 mg DINP/kg bw per day. Chen et al. (2017)* noted after reanalysis of the publicly available data that no statistical difference for AGD was observed at the highest dose level (900 mg DINP/kg bw per day) in the study of Boberg et al. (2011). Furthermore, some other discrepancies were noted in this study as described in the publication of Chen et al. (2017)*.

Nipple retention was noted in male pups by Gray et al. (2000) and Boberg et al. (2011) at doses of 750 mg/kg bw per day.

Reduced sperm count, reduced sperm motility/quality parameters were described in studies by Kwack et al. (2009 , 2010): 500 mg DINP/kg bw per day for 4 weeks to male Sprague Dawley rats; Gray et al. (2000): 750 mg DINP/kg bw per day from GD 14 – PND 3 to pregnant Sprague Dawley rats; and Boberg et al. (2011): 600 mg DINP/kg bw per day and higher from GD 7 – PND 17 to pregnant Wistar rats. Degeneration of meiotic spermatocytes and Sertoli cells, scattered cell debris in ducts in epididymis and decrease in number of corpora lutea were described in Masutomi et al. 2003 and 2004, at 20,000 mg DINP/kg diet (equivalent to 1,000 mg DINP/kg bw per day).

According to ECHA (2013), only the highest dose (500 mg DINP/kg bw per day) can be considered positive in the Hershberger assay (Lee and Koo, 2007) in which anti-androgenic properties were tested.

Li et al. (2015)* described that *in utero* exposure to DINP induced fetal Leydig cells (FLC) aggregation, and reduced expression levels of FLC genes (Insl3) at as low as 10 mg/kg bw per day. However, DINP was less potent to affect the steroidogenic capacity of the fetal testis although it potently inhibited the expression levels of some steroidogenic enzymes.

No estrogenic potential of DINP was detected in two different test systems (Sedha et al., 2015*). Doses of 276 and 1380 mg DINP/kg bw per day were administered orally to immature female rats (20 days old) once daily for 3 and 20 days in uterotrophic and pubertal assay, respectively. The animals were sacrificed on day 4 and day 41 in case of 3-day uterotrophic and 20-day pubertal assay, respectively.

It was noted by ECHA (2013) that "DINP has anti-androgenic properties and it could be appropriate to include this substance in a combined risk assessment of phthalates with anti-androgenic properties". Further, in 2018, ECHA RAC concluded that no classification for DINP for either effects on sexual function and fertility or for developmental toxicity was warranted (see sections 1.3.4 and 4.9.1).

Overall, the CEP Panel concurred with the NOAEL identified in the ECHA opinion (ECHA, 2013) of 50 mg DINP/kg bw per day based on the decreased fetal testosterone production and histopathological changes (MNGs) reported in the study of Clewell et al. (2013a). The additional studies mentioned by ECHA support this NOAEL for reprotoxic effects.

The CEP Panel noted that two CAS numbers exist for DINP, i.e. CAS No. 68515-48-0 for 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, and CAS No. 28553-12-0 for 1,2-Benzenedicarboxylic acid, 1,2-diisononyl ester. Considering that the first formulation is a "cruder" version of DINP, including also decyl fractions, the question arises whether both formulations have equivalent toxicological profiles. Consequently, the Panel reviewed a paper from Hannas et al. (2011), who demonstrated that both formulations induced a virtually identical dose-dependent reduction of fetal testicular testosterone production. The authors reported that "curve fit results comparing these two DINP formulations are statistically indistinguishable". Based on the equivalent potency of both

[13] In this section, when a study was found in the additional literature search performed by EFSA in 2018 as stated in section 2.2, the respective study is marked with an asterisk (*).

formulations for the induction of the described effect, the Panel concludes that no differentiation of the two DINP formulations is needed in the assessment of the reproductive toxicity.

4.7.5. DIDP

In the EFSA opinion on DIDP (EFSA, 2005e), the AFC Panel based its risk assessment on the effects on liver in dogs with a NOAEL of 15 mg/kg bw per day (Hazleton, 1968) and on a NOAEL of 33 mg DIDP/kg bw per day for decreased survival in the F2-offspring in a two-generation reprotoxicity study in rats (Exxon, 1997, 2000 published by Hushka et al., 2001). The Panel applied an uncertainty factor of 100 to derive a TDI of 0.15 mg DIDP/kg bw per day.

In the EFSA opinion (EFSA, 2005e), two dietary two-generation reproductive toxicity studies in Sprague Dawley rats and a one-generation range finding study were described (Exxon, 1997, 2000 published by Hushka et al., 2001). The test diets were fed during the whole duration of the studies. In the first two-generation reproduction study, 0, 0.2, 0.4 or 0.8% DIDP was fed in the diet. In the second study, 0, 0.02, 0.06, 0.2 or 0.4% DIDP was fed in the diet. In addition to the standard reproductive toxicity effects, in this latter study, AGD, nipple retention, vaginal patency and preputial retention were measured to assess the potential for endocrine-mediated effects. These parameters were not included in the first two-generation reproduction study. The NOAEL for reproductive effects based on survival indices mainly in the F2-offspring was 0.06% in the diet (33 mg DIDP/kg bw per day). The LOAEL for these effects was 114 mg DIDP/kg bw per day. The fertility was not affected in these studies. Furthermore, in a prenatal developmental toxicity study in rats a NOAEL for developmental effects of 40 mg DIDP/kg bw per day was identified based on increased variations in skeletal and visceral variations (Hellwig et al., 1997). DIDP was dosed at levels of 0, 40, 200, or 1,000 mg DIDP/kg bw per day by gavage from GD 6 to 15. Increased incidence of skeletal variations was observed in the prenatal developmental toxicity study in rats by Waterman et al. (1999) at a dose of 500 mg DIDP/kg bw per day. In this study, dose levels of 0, 100, 500 and 1,000 mg DIDP/kg bw per day were administered by gavage from GD 6 to 15; the NOAEL identified in this study was 100 mg DIDP/kg bw per day.

ECHA evaluated new scientific evidence concerning DIDP in 2013 (ECHA, 2013) and noted also that the critical effect on reproduction for DIDP was decreased survival of F2-pups in both two-generation reproductive toxicity studies reported by Exxon Biomedical Sciences (1997; 2000) and published by Hushka et al. (2001). A dose of 33 mg DIDP/kg bw per day was considered as the NOAEL for this effect and 114 mg DIDP/kg bw per day as the LOAEL. These were the same studies as used by EFSA (EFSA, 2005e) to identify the NOAEL for reproductive effects.

ECHA (2013) described for developmental toxicity also the same two studies (Hellwig et al., 1997; Waterman et al., 1999) with a NOAEL of 40 and 100 mg/kg bw per day, respectively, as in the EFSA opinion of 2005 (EFSA, 2005e).

In a study by Hannas et al. (2012), no reduction of fetal testicular testosterone levels or affected gene expression was observed after exposure during the critical window (GD 14-18 dose up to 1500 mg/kg bw per day). ECHA (2013) therefore considered that DIDP did not induce substantial anti-androgenic activity in the available studies and the CEP Panel agreed with this view.

The CEP Panel performed an literature search on reproductive effects (see 2.2) and found no new studies that would change the NOAEL for reproductive effects, as identified by EFSA in 2005.

Overall, the CEP Panel concurred with the NOAEL of 33 mg DIDP/kg bw per day for reproductive effects in rats (based on pup mortality), which was also identified by EFSA in 2005 and ECHA in 2013, and agreed that DIDP did not exhibit anti-androgenic activity.

4.7.6. Summary of the critical reproductive effects

Considering the above described literature on reproductive effects, a summary of the critical reproductive effects of the five phthalates can be found in Table 21, together with the effect levels and pivotal study references.

Table 21: Summary of the critical reproductive effects for the five phthalates

Phthalate	Critical reproductive effect	N(L)OAEL (mg/kg bw per day)	Reference	Additional information
DEHP	Testicular effects in F1 and F2 males	LOAEL:14 NOAEL: 4.8	Wolfe and Layton, 2003	Multigeneration study in Sprague Dawley rats: 1.5, 10, 30, 100, 300, 1,000, 7,500, and 10,000 DEHP mg/kg diet, corresponding to 0.1, 0.47, 1.4, 4.8, 14, 46, 359 and 543 mg/kg bw per day in F2 animals
	AGD decreased and number of nipples increased in males	LOAEL:10 NOAEL: 3	Christiansen et al., 2010	Time-mated Wistar rats exposed from GD 7- PND 16 by gavage
BBP	AGD decreased at birth in F1 and F2 pups	LOAEL: 250 NOAEL: 50	Tyl et al., 2004	Two-generation reproductive toxicity study in CD rats
	AGD decreased on PND 4	LOAEL: 100	Aso et al., 2005	Two-generation reproductive toxicity study in Crj: CD (SD) IGS rats by gavage
	AGD decreased at birth, relative testis weight, histopathology findings testis in male F1 pups	LOAEL: 500 NOAEL:100	Nagao et al., 2000	Two-generation reproductive toxicity study in Sprague Dawley rats by gavage
DBP	Reduction of spermatocyte development on PND 21 and mammary gland (vacuolar degeneration alveolar cells) in males in postnatal week 11	LOAEL: 2	Lee et al., 2004	Pregnant CD(SD)IGS rats exposed from GD 15-PND 21
DINP	Reduced foetal testosterone level, and histopathological changes (MNG)	NOAEL: 50	Clewell et al., 2013a	Sexual development of fetal male Sprague Dawley rats
DIDP	Mortality of neonatal F2 pups was increased	NOAEL: 33	Exxon Biomedical Sciences (1997; 2000), Hushka et al. 2001	Two-generation reproductive toxicity studies in Sprague Dawley rats

4.8. Human studies on reproductive effects

In the ECHA assessment (2017a, b), it was suggested that phthalate exposure *in utero* is associated with congenital malformations of the male reproductive organs (e.g. cryptorchidism), reduced semen quality, reduced male reproductive hormone levels, and changes in pubertal timing (Welsh et al., 2008; den Hond and Schoeters, 2006; Jacobson-Dickman and Lee, 2009). In the ECHA opinion, it was stated that "The effects of the phthalate syndrome observed in rats have also been observed in humans and it has been suggested to have a human counterpart known as the "testicular dysgenesis syndrome". Cryptorchidism, hypospadias and poor sperm quality are risk factors for each other in humans. These conditions are also predictive of testicular germ cell cancers. Increasing evidence also link reduced AGD in humans to this group of risk factors. The single symptoms and combinations thereof are also risk factors for reduced fecundity. Epidemiological studies provide further evidence that the effects seen in rats from exposure to the four phthalates are relevant in humans at observed exposure levels in the population". However, ECHA also stated that "Unfortunately, the available epidemiology studies are associated with such uncertainties that the studies do not allow to conclude on a direct causal relationship between the effects investigated (congenital malformation of the male genitalia, semen quality, pubertal timing and testicular cancer) and phthalate exposure. Besides, anti-androgenic effects are not unique to certain phthalates; numerous other chemicals show these effects as well. It is therefore difficult, if not impossible, to give a robust or quantitative indication of the contribution of the phthalates to the infertility problems and increases in hormone dependent cancers observed in humans, solely on the basis of epidemiological data".

The CEP Panel's evaluation focused on epidemiological studies that investigated the role of phthalate exposure on reproductive outcomes. The evaluation was mainly concentrated on prospective epidemiological studies investigating the role of *in utero* exposure to phthalates and AGD, a well-known early sexually dysmorphic marker for endocrine disrupting chemicals. The reasons for focusing on these studies are the following: the study design that permits to establish a cause and effect relationship; timing of exposure during a critical period of sexual development (prenatally); a mechanistic link between fetal testosterone levels, AGD and hypospadias in animal studies; and a relevant outcome in animal studies.

Epidemiological studies on reproductive outcomes conducted so far and reviewed in this opinion have many methodological shortcomings. The main problem is the small sample size of the studies, which reduces the likelihood of detecting a true effect. Thus, underpowered studies because of low sample size and/or small effects may easily lead to false negative results.

Many of the epidemiological studies, except the cohort studies on phthalates and AGD, were cross-sectional, which is of limited value for assessing whether there is a true exposure-outcome relationship. The main weakness of this type of study design is that the measurement of the exposure and of the outcome occurs at the same time, which precludes from making causal inferences. Misclassification of the exposure can also be a limitation of the studies reviewed, leading to increased uncertainty of the risk estimates. In addition, most of the studies used single spot urine samples, which may not allow for the large within-person-variability in urine concentration of phthalate metabolites. A study by Frederiksen et al. (2013) suggested that single spot urine can be used to characterise exposure to phthalate metabolites in epidemiological studies. However, a recent study by Sun et al. (2017) suggested that even a single 24-h urine sample is not sufficient. Sun et al. (2017) measured two 24-h urine samples in 47 subjects and showed that the ICC for all phthalate metabolites (MBzP, MEHHP, MECPP, MEOHP, MEP, MBP, MEHP) were lower than 0.30, except for MBzP (ICC = 0.55). The authors suggested that at least three 24-h urine samples would be needed to reach a reliable measurement of long-term phthalate exposure. The ICC values vary between 0 and 1, and conventionally, an ICC value of ≥0.75 indicates excellent reproducibility, 0.4 to 0.75 indicates fair to good reproducibility, and <0.4 indicates poor reproducibility. As the ICC increases, the reliability of a single spot urine sample for characterising longer-term exposure increases. A study conducted within the Women in the Nurses' Health Study and Nurses' Health Study II (n = 40) which measured two spot urines (1 to 3 years apart) showed that for most phthalate metabolites (MEP, MnBP, MBzP, MEHHP, MEOHP, and MECPP) a fair or nearly fair within-person stability over time was observed (ICC = 0.39-0.53) (Townsend et al., 2013). When the ICC is low, the within-person variation is high, suggesting that individual spot urine samples may not provide a reliable characterisation of an individual's longer-term exposure level.

Another limitation of the epidemiological studies was the lack of control for potential confounding factors such as the exposure to other endocrine-disrupting chemicals.

Overall, there is some evidence that links phthalate exposure *in utero* and reduced AGD in male newborns based on the available epidemiological studies and consideration of biological plausibility. There is insufficient evidence to link phthalate exposure and changes in reproductive hormone levels and semen quality in adults. Larger epidemiological studies with better exposure characterisation and controlling of confounders would be necessary. There is insufficient evidence to link phthalate exposure and changes in pubertal timing in children, and phthalate exposure and hypospadias. The conclusions of the CEP Panel are in agreement with the ECHA evaluation (2017a, b) regarding the anti-androgenic effect of phthalate exposure observed in the epidemiological studies. The Panel also agrees with the high level of uncertainties found in the epidemiological studies reviewed, as described above.

4.9. Derivation of health-based guidance values

In EFSA's previous evaluations of the phthalates DBP, BBP, DEHP, DINP and DIDP (EFSA, 2005a, b, c, d, e) TDIs for the respective substances were established based on the NOAEL approach for deriving a PoD. In the meantime, however, in the light of further scientific developments and considerations, the benchmark dose (BMD) method has gained importance. As stated by EFSA's Scientific Committee (SC) in its latest guidance on the use of the BMD approach for risk assessment (EFSA Scientific Committee, 2017), the benchmark dose approach is a scientifically more advanced method compared to the NOAEL approach for deriving a Reference Point (RP)[14] (i.e. Benchmark Dose Levels, BMDLs). The application of this guidance was therefore strongly recommended by the EFSA Scientific Committee. Therefore, for this re-evaluation, after having reviewed and selected the critical studies and effects for reprotoxicity, data were extracted to attempt BMD fitting of the dose-response curves. The studies and critical effects selected for BMD analysis are shown in Table 22.

Table 22: Summary of the type of data presented in the critical studies for reproductive effects for the five phthalates

Phthalate	Reference	Animal model Critical effect(s)	Type of dose-response data
DEHP	Wolfe and Layton, 2006	Sprague Dawley rats	
		Testicular changes (gross-observations) in F1 and F2 males	Quantal
	Christiansen et al., 2010	Male Wistar rats	
		AGD decreased	Continuous
		number of nipples increased	Continuous
DBP	Lee et al., 2004	male CD(SD)IGS rats	
		Reduction of spermatocyte development PND 21	Quantal or ordinal (quantitative severity scale needed)[(a)]
		mammary gland effects (vacuolar degeneration alveolar cells) PNW 11	Quantal or ordinal (quantitative severity scale needed) [(a)]

[14] RP is an equivalent term for Point of Departure (PoD) (EFSA Scientific Committee, 2017).

BBP	Tyl et al., 2004	Male CD (SD) IGS rats	
		AGD decreased at birth in F1 and F2 pups	Continuous
	Nagao et al., 2000	Sprague Dawley rats F1 male pups	
		AGD decreased at birth	Continuous
		relative testis weight	Continuous
		histopathology findings testis	Quantal
	Aso et al., 2005	Crj: CD (SD) IGS rats	
		AGD decreased on PND 4 in	Continuous
DINP	Clewell et al., 2013a	Sprague Dawley rats, males	
		Reproductive effects: decreased fetal testosterone	Continuous
DIDP	Hushka et al., 2001	Sprague Dawley rats	Quantal(b)
		Decreased survival of F2 pups	

(a): In Lee et al., 2004, a qualitative scale is provided with each histopathological observation (i.e. minimal ±, slight +, moderate ++, severe +++)
(b): Processed data to calculate percentage of survival in different time points

The distinction between the data types to be extracted is important for statistical reasons. In Table 22, the type of data for each critical effect is specified. For continuous data, the individual observations would ideally serve as the input for a BMD analysis. When no individual but only summary data are available, the BMD analysis may be based on the combination of the mean, the standard deviation (or standard error) of the mean, and the sample size for each treatment group. Using summary data as the input for the software is technically possible, but it may lead to slightly different results compared with using individual data (EFSA Scientific Committee, 2017). In the case of quantal data, the number of affected individuals and the sample size are needed for each dose group. Ordinal data could be regarded as an intermediate data type; it arises when a severity category (minimal, mild, moderate etc.) is assigned to each individual/observation, for example in histopathological observations. Ordinal data could be reduced to quantal data, but this implies loss of information and is not recommended (EFSA Scientific Committee, 2017).

When extracting the data for the selected critical effects, it was observed that for most of them the data were not reported in a way that would allow data reanalysis for the purpose of BMD modelling. In the case of multigenerational animal studies, where the effects of interest are measured in the pups, there is a need to take into account litter effects when performing any kind of statistical analysis or modelling. When the treatment is given to the dams, the experimental unit is the pregnant dam and not the individual offspring, therefore the statistical unit of measure should be the litter and not the pup. The BMD approach modelling tools allow for litter effects to be taken into account when reanalysing the data (EFSA Scientific Committee, 2017). However, for these models to take into account litter effects in an appropriate manner, individual pup data should be "tagged" with the information of which litter they belong to; this is the preferred type of data for the modelling. Alternatively, reported individual litter average data (one mean response per litter) could be used. In the case of the critical studies and effects selected, the data was reported as summary data (mean) of all litters per dose, not individual litter data (Nagao et al., 2000; Tyl et al., 2004; Aso et al., 2005 and Christiansen et al., 2010; Clewell et al., 2013a), or unprocessed data was not available (Hushka et al., 2001) which prevented the reanalysis of the data for BMD modelling. In the case of the critical effects with histopathological data, the problems of integrating them into the BMD model were related to no clear dose-response relationship (Wolfe and Layton, 2006; Nagao et al., 2000) or to the difficulty to interpret the data and the dose-response without an integrated quantitative severity scale of the histopathological findings in the case of Lee et al. (2004). Hence, it was concluded that it was not possible to make use of the BMD approach for the above-mentioned critical studies and effects for reprotoxicity, and to therefore use again the NOAEL approach for deriving the PoDs in this assessment.

Regarding the selection of uncertainty factors, although the available database on toxicokinetics indicated that variability in the toxicokinetics parameters was lower than this component of the default uncertainty factors, the CEP Panel considered that the available data were not sufficiently robust to derive chemical specific adjustment factors. Therefore, the Panel decided to use the default uncertainty factor of 100 to derive the TDI from the NOAEL[15] (200 for LOAEL).

For DBP, a LOAEL of 2 mg DBP/kg bw per day for reduced spermatocyte development and effects on the mammary gland was identified from the study of Lee et al. (2004). The CEP Panel proposes to apply to this PoD an uncertainty factor of 200[16] (an extra factor of 2 because of the use of the LOAEL instead of the NOAEL) for deriving a HBGV.

For BBP, a NOAEL of 50 mg BBP/kg bw per day was identified from the pivotal study of Tyl et al. (2004) based on reduced AGD in F1- and F2- males at birth in the 250 mg BBP/kg bw per day group. The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.

For DEHP, a NOAEL of 4.8 mg DEHP/kg bw per day based on effects on the testis in F1-animals was identified from the study of Wolfe and Layton (2003). The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.

For DINP and DIDP, EFSA set stand-alone TDIs in its evaluations of 2005 (EFSA, 2005d,e) based on liver effects (0.15 mg/kg bw per day):

- the TDI of 0.15 mg/kg bw per day for DINP is based on a NOAEL of 15 mg DINP/kg bw per day for non-peroxisomal proliferation-related chronic hepatic and renal effects in rats and an uncertainty factor of 100 (Exxon, 1986; Lington, 1997).
- the TDI of 0.15 mg/kg bw per day for DIDP is based on a NOAEL of 15 mg DIDP/kg bw per day for liver effects in 13-weeks study in dogs (as observed in a study by Hazleton, 1968) and an uncertainty factor of 100.

The CEP Panel concluded that the effect on the liver is still the most sensitive endpoint for these two phthalates. However, the possibility to establish HBGVs for reproductive effects for DINP and DIDP was explored, in order to evaluate whether a grouping (based on reproductive effects) with the other three phthalates was appropriate.

For DINP, a NOAEL of 50 mg DINP/kg bw per day based on the decreased fetal testosterone production and histopathological changes (MNGs) was identified in the study of Clewell et al. (2013a). The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.

For DIDP, a NOAEL of 33 mg DIDP/kg bw per day for reproductive effects in rats (based on pup mortality) was identified in the study by Exxon Biomedical Sciences (1997, 2000, published by Hushka, 2001). The CEP Panel proposes to apply to this PoD an uncertainty factor of 100 for deriving a HBGV.

4.9.1. Rationale for grouping of phthalates

Based on urine data from various biomonitoring studies, simultaneous exposure to multiple phthalates was demonstrated (ECHA, 2017a) for the general population and for sensitive groups such as pregnant women (fetuses) and infants below 16 weeks. Therefore, the risk assessment of phthalates should take into account the possibility of grouping these substances into a common assessment group as proposed in the recent EFSA Scientific Committee Draft guidance document on Mixtures (EFSA Scientific Committee, 2018b).

In 2005, the EFSA AFC Panel issued a statement on the possibility of allocating a group-TDI for DBP, BBP, DEHP, DINP and DIDP (EFSA, 2005f). Based on the toxicological data existing at that time it was noted that the first three substances act on the same target organ (the testis) but thatthe profile of effects at the hormonal and cellular level is not identical. In addition, the latter two substances, i.e. DINP and DIDP, primarily affect the liver as the most sensitive target organ. Also in this case, the AFC Panel noted that the endpoints indicated that different mechanisms are involved. Consequently, no group-TDI could be established by the AFC Panel for these phthalates (EFSA, 2005f). However, the

[15] See also EFSA Scientific Committee, 2012

[16] ECHA (2017) used a factor of 3 (total UF 300) for the extrapolation from LOAEL to NAEL.

AFC Panel proposed to establish a group restriction for DINP and DIDP, considering that they are mixtures that overlap chemically and cannot analytically be distinguished clearly in the case of co-occurrence. Consequently, a SML(T) of 9 mg kg was established in the Regulation 10/2011.

Meanwhile toxicological studies reporting on combined effects of phthalates on the male reproductive tract in rats are available as mentioned by ECHA (2017a, b). Therefore, the CEP Panel re-evaluated the suitability of a combined risk assessment of phthalates based on the ECHA considerations. ECHA provided a rationale for the grouping of DEHP, DBP, DIBP[17] and BBP based mainly on the following considerations:

- structural similarity
- similar use and exposure pattern
- similar toxicokinetics
- similar reproductive toxicity related to anti-androgenic effects
- inhibition of the testosterone production in fetal rats
- changes in germ cell differentiation.

The above-mentioned rationale for grouping is in line with the application of a component-based approach suggested in EFSA Scientific Committee draft guidance on Mixtures (EFSA Scientific Committee, 2018b) and with criteria used for the grouping of substances by other scientific advisory bodies and international experts in this field.

Results from studies by Howdeshell et al. (2008), Hannas et al. (2011; 2012) and Clewell et al. (2013b) suggest that there is substantial evidence of dose-additive effects of several structurally similar phthalates based on a similar MoA, i.e. the reduction of testosterone production in fetal rats. The CEP Panel agrees that this MoA can be considered as a key event in the anti-androgenic action of these phthalates and consequently a cumulative risk assessment of these phthalates would be appropriate. According to the ToR, the CEP Panel restricted the current evaluation to those phthalates which are authorised for use in plastic food contact materials according to Regulation (EU) No 10/2011, i.e. DBP, BBP, DEHP, DINP and DIDP.

As described in section 4.7, the CEP Panel considers the reduction of the fetal testosterone production in rats induced by DBP, BBP and DEHP as a critical step in the reproductive toxicity of the phthalates. This anti-androgenic effect provides the mechanistic insight into the plausibility and validity of grouping together these phthalates.

For DINP, the CEP Panel acknowledges that ECHA RAC (2018) did not agree on the proposal to classify DINP as toxic for reproduction, based on the absence of effects fulfilling the classification criteria in the CLP Regulation. Similarly, the CEP Panel considered that some anti-androgenic effects of DINP, e.g. the reduction of fetal testosterone production and AGD may be considered transient and/or less pronounced compared to other phthalates with harmonised classification as Repr. 1 B (among others DBP, BBP, DEHP). However, the Panel considered that the study results on DINP described in 4.7.4. suggested an anti-androgenic MoA. The Panel noted that a two-generation study with DINP that was considered by ECHA (Waterman et al., 2000) did not investigate some important reproductive toxicity endpoints such as AGD or nipple retention. Consequently, the reproductive toxic and developmental effects - considered by the RAC as not sufficient for classification in the context of the CLP process - would nevertheless raise concern as it seems plausible that even small or transient DINP effects could contribute to the reproductive toxicity of phthalates after combined exposure. Furthermore, the Panel also noted that the use of DINP has increased over recent years, in part as a replacement for DEHP (ECPI, 2010). Due to the similar reproductive toxicity pattern of DINP compared to DBP, BBP and DEHP, and its prominent use in consumer products, the inclusion of DINP in the combined risk assessment was considered justified and necessary.

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[17] Not included in the CEP Panel's assessment as DIBP is not authorised for use in plastic food contact materials according to Regulation (EU) No 10/2011.

For DIDP, no reduction of fetal testicular testosterone levels or affected gene expression was observed after exposure during the critical window (GD 14-18, dose up to 1,500 mg/kg bw per day) (Hannas et al., 2012). ECHA (2013) considered that DIDP did not induce substantial anti-androgenic activity in the available studies. Furthermore, ECHA (2013) noted: "DIDP seems to have a different toxicological spectrum and/or potency regarding reproductive toxicity than several other phthalates, such as DINP, DEHP and DBP which potentially cause androgen deficiency during male development. The most sensitive reproductive effect for DIDP, reduced neonatal survival in the second generation, is observed only at high dose for e.g., DINP. The most sensitive effect for DINP, reduced foetal testicular T [i.e testosterone] levels, is not observed with DIDP". The CEP Panel agreed with this view (see also section 4.7.5) and therefore proposed not to include DIDP in the grouping of phthalates for reproductive toxicity due to its lack of anti-androgenic effects. Since the liver toxicity occurs at a lower level than the reproductive effects (based on decreased survival of F2 pups; Hushka et al., 2001), the TDI for liver effects (as established by EFSA, 2005e) takes priority and a HBGV for reproductive toxicity is not elaborated further.

In conclusion, the CEP Panel noted that the arguments brought forward by ECHA (2017a, b) for the grouping of the phthalates (3.3.10.) can also be applied to DINP. It should be noted that like other phthalates, DINP has effects both on the reproductive system and the liver, but in the case of DINP the liver is the more sensitive target organ, i.e. hepatotoxicity is the pivotal effect for the risk assessment of DINP. Based on these considerations the Panel concludes that a cumulative risk assessment of DBP, BBP, DEHP and DINP in a component-based approach is appropriate. Further, for DIDP, due to the absence of effects on the foetal testicular testosterone levels and its liver toxicity, it is not included in the group.

5. Risk characterisation

5.1. Approach to derive a group-TDI

According to the EFSA Scientific Committee Draft guidance (2018b) a refinement of the grouping of substances in mixtures can be performed by the identification of an "index compound", for which robust toxicological data are available, along with the calculation of a Relative Potency Factor (RPF) for each component in the mixture to estimate potency-related exposure. In case of reproductive toxic phthalates, the most robust toxicological data are published for DEHP, and it was therefore identified as the index compound.

While the different potencies in lowering the fetal testosterone levels could be used to derive RPFs for the phthalates, it should be considered that the effect *per se* may not be adverse and seems to be transient (3.2.3.4.). The Panel notes that RPFs based on the hormonal effect would neglect the differences in the NOAELs agreed on by ECHA (2017a) and EFSA (2005a, b, c, d, e). Consequently, the Panel concluded that it would be more appropriate to establish the RPFs for the phthalates under consideration using HBGVs derived from their respective reproductive N(L)OAELs, even though they have related but differing toxicological endpoints in the animal studies (Table 21). Having established DEHP as the index compound, this would lead to a group-TDI of 0.05 mg/kg bw per day, expressed as DEHP equivalents.

It should be noted that the TDIs for DBP, BBP and DEHP are based on reproductive toxic effects (with the testis as target organ) and therefore the compounds can be grouped simply and directly. This is not appropriate for DINP, for which the TDI is based on liver effects. Consequently, for the grouping, instead of using the TDI for liver effects, a HBGV for DINP based on testicular effects could be used.

This approach would give rise to two limit values for DINP. The first, an individual TDI for its liver toxicity. The second, a HBGV that would need to be incorporated into the group-TDI for phthalates stemming from their reproductive toxicity, in case there was co-exposure to DINP (from foods or other sources) along with the other grouped phthalates, at an exposure level that might not itself give rise to a risk of liver toxicity from DINP, but would contribute (albeit by a lower potency) to the overall reprotoxicity effects of the group as a whole.

The Panel decided on a hybrid approach, considering that it would be prudent to include DINP within the group-TDI based on reprotoxic (anti-androgenic) effects, but recognising that the reproductive effects of DINP occurred at doses around three-fold higher than the most sensitive liver effect. This being the case, the RPF should be adjusted upwards to also protect against liver effects of DINP. The outcome of these considerations are summarised in Table 23. The conclusion is the establishment of a group-TDI for the phthalates of 0.05 mg/kg bw per day (expressed as DEHP equivalents), for the sum of DEHP (RPF=1), BBP (RPF=0.1), DBP (RPF=5) and DINP (RPF=0.3).

Table 23: Calculation of RPFs

	DEHP	BBP	DBP	DINP (reproductive effects)
N(L)OAEL (mg/kg bw per day)	4.8	50	2.0	50
Uncertainty factor (UF)	100	100	200	100
Additional assessment factor	n/a	n/a	n/a	3.3[(b)]
HBGV (mg/kg bw per day)	0.05	0.5	0.01	0.15
HBGV (µg/kg bw per day)	50	500	10	150
RPF[(a)]	= 1.0 (index compound)	0.1	5.0	0.3

(a): Calculated from the ratio of the HBGV of DEHP (as the index compound) to the HBGVs of the three other phthalates
(b): Additional assessment factor to account for the more sensitive liver effects. Calculated by dividing the NOAEL for reproductive effects (50 mg/kg bw per day) by the NOAEL for liver effects (15 mg/kg bw per day), and rounded to 3.3
n/a: not applicable

5.2. Risk characterisation

The estimation of exposure to phthalates from the consumption of food is described in section 3.4.2.1. Table 24 provides a summary of the range of exposures (min-max) for all age groups and for all countries. The GroupPhthalates estimates were derived using the appropriate RPF applied to the original food concentration data sourced from the literature.

Table 24: Exposure estimates (µg/kg bw per day) from food as calculated in section 3.4.2.1. Ranges are the min-max for all ages, all surveys and all countries

	Mean	P95
DBP	0.042 - 0.769	0.099 - 1.503
BBP	0.009 - 0.207	0.021 - 0.442
DEHP	0.446 - 3.459	0.902 - 6.148
DINP	0.232 - 4.270	0.446 - 7.071
GroupPhthalates (DBP, BBP, DEHP, DINP, potency adjusted) expressed as DEHP equivalents	0.865 - 7.205	1.640 - 11.738
DIDP	0.001 – 0.057	0.008 – 0.095

The highest estimated exposure for GroupPhthalates, calculated as DEHP equivalents, is in the range of 0.9 to 7.2 for the mean consumer and 1.6 to 11.7 µg/kg bw per day for the high P95 consumers.

Given that there are some limitations in using occurrence data from the literature and that the exposure estimates are LB, it is of interest to compare the exposure estimates with those derived in other assessments, i.e. the three TDS reported in section 3.4.3. Those TDS data were recalculated by applying the RPFs and summed up to derive GroupPhthalates estimates. They are summarised in Table 25 for comparison with the estimates derived by EFSA. Lacking access to the original TDS data, only the sum of means for the grouped phthalates were derived, since summing up P95 or P97.5 values, from a statistical point of view would be incorrect:

- UK TDS: For the 10 different age groups in the UK TDS, GroupPhthalates mean LB exposure ranges from 1.8 to 4.4 and at the UB from 3.0 to 13.5 µg/kg bw per day, as DEHP equivalents, respectively.
- Ireland TDS: The LB-UB estimates for mean exposure to GroupPhthalates, as DEHP equivalents, ranged from 1.2 to 4.0 for children and 1.0 to 3.5 µg/kg bw per day for adults, respectively.
- France TDS: For children aged 1 to 36 months, LB-UB estimates for mean exposure to GroupPhthalates, as DEHP equivalents, ranged from 0.013 to 4.4 for ages 1-4 months, 0.12 to 3.5 for ages 5-6 months, 0.4 to 3.3 for ages 7-12 months, and 0.8 to 2.9 µg/kg bw per day for ages 13-36 months, respectively.

Table 25: Exposure estimates from food, by various authors

Short study description (see above for details)		**Estimate of exposure in µg/kg bw per day, as DEHP equivalents**
EFSA CEP Panel (2019), min-max for all age groups and all countries	mean LB P95 LB	0.9 - 7.2 1.6 - 11.7
UK TDS, range for all age group	mean LB mean UB	1.8 - 4.4 3.0 - 13.5
Ireland TDS, LB-UB range, mean exposures	Children Adults	1.2 - 4.0 1.0 - 3.5
France TDS, LB-UB range, average exposure, Children	1-4 months 5-6 months 7-12 months 13-36 months	0.013 - 4.4 0.12 - 3.5 0.4 - 3.3 0.8 - 2.9

Table 25 shows that the mean exposure estimates derived for this opinion are in line with, and are often higher than those reported in other studies.

Comparing the GroupPhthalates exposure estimates for the mean consumer, i.e. 0.9 - 7.2 µg/kg bw per day, with the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents), resulting in contribution of 1.8 to 14% of the TDI.

For high (P95) consumers exposure to GroupPhthalates ranging from 1.6 to 11.7 µg/kg bw per day, resulting in 3 to 23% contribution to the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents).

These conclusions cover all European population groups (all countries, all surveys, all age groups), including children and women of child-bearing age.

For DIDP, which is not included in the GroupPhthalates due to its lack of anti-androgenic effects, a separate risk analysis was conducted. Exposure estimates (Table 24), derived for all population groups (all countries, all surveys, all age groups), ranged from 0.001 - 0.057 µg/kg bw per day at the mean, and from 0.008 - 0.095 µg/kg bw per day at the P95. These estimates were found to be far below the TDI for DIDP of 150 µg/kg bw per day, which is based on liver effects.

5.2.1. Contribution from FCM

The above reported estimates concern exposure from food containing phthalates from all sources (e.g. FCM, environment). The ToR requires the assessment of the contribution from plastic FCM to the TDI for these authorised phthalates.

Clearly the contribution of plastics, or even FCM more generally, cannot exceed 100% of the exposure estimates from food and so these estimates, being 3 to 23% of the group-TDI for the high consumers, places a hard ceiling on any contribution from FCM. As described in section 3.5, the CEP Panel examined several papers with the aim to establish the potential contribution from plastic FCM to exposure, with a view to compare such exposure to the group-TDI for these authorised phthalates. However, the CEP Panel noted that in general there is not enough information available to make firm conclusions on the contribution from plastic FCM.

6. Uncertainty analysis

6.1. Exposure assessment

A qualitative evaluation of the inherent uncertainties in the dietary exposure assessment of phthalates was performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2007), as shown in Table 26.

Table 26: Uncertainty analysis for the exposure assessment

Source of uncertainty	Direction (+[(a)]/- [(b)])	Comment
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/-	
Use of data from food consumption surveys covering only a few days to estimate high percentiles (95th) long-term (chronic) exposure	+	
Matching of reported occurrence levels to food items in the EFSA Comprehensive Food Consumption Database: uncertainties to exactly which types of food the levels refer to	+/-	
Possible national differences in occurrence levels in the different food categories	+/-	
Extrapolation of occurrence data to the whole of Europe while data are mainly from two countries plus few data from many other countries/providers (EFSA Chemical Occurrence Database)	+/-	
Extrapolation of occurrence data from few Member States to the whole of Europe (occurrence data from the literature)	+/-	

Occurrence data from literature (publication bias)	+	
Methodology for handling left-censored data (LB approach)	-	Left-censored data set to 0.
Limited number of studies (literature) and samples; unbalanced number of studies per compound	+/-	The general agreement between exposure estimates using the food monitoring studies, the urinary biomarker studies and the TDS studies, indicate that coverage is adequate.
Co-occurrence of phthalates, it has been assumed that all phthalates of interest always occur at the same time in all foods at the highest of the mean/median values reported for that food group	+/-	Few studies have monitored all of the phthalates in the group
Analytical uncertainty for phthalates that are mixtures (distinction of DINP and DIDP)	+	DIDP may have been misidentified and reported as DINP. Few studies (if any) report DIDP so misidentification in the other direction is unlikely.
Analytical uncertainty for non-mixture phthalates (DBP, BBP, DEHP)	+	The analytical challenge for phthalates analysis are now well recognised but problems with analytical blanks can still compromise LOD/LOQs giving higher UB exposure estimates and possibly erroneous 'positive' occurrences.
Linking literature values and their food description with food categories from EFSA database	+	Taking a result for a food sample as an example of the broader food group.
Contribution of plastic FCM to exposure compared to other dietary and non-dietary sources and background levels	+	This is a large uncertainty. The indications are that plastic FCM might make a rather small contribution overall (10-20% of total exposure).
Materials and articles (plastic FCM) used in the home?	-	This aspect is not considered in depth. Wrapping films plasticised with phthalates are not used. Use of other FCM containing phthalates is not expected to make a major impact, especially since many would be for repeated use where migration (if any) would decline on reuse.
Pattern of use of phthalates and time trend	+/-	Collection of occurrence data after entry into force of regulation. DEHP substitution by alternatives such as DINP and DIDP, and now by DINCH, DEHTP, etc.

(a): + for overestimation of the risk
(b): - for underestimation of the risk

Several uncertainties were identified in assessing the exposure to phthalates of interest from all sources, and in particular from plastic FCM. On the one hand, the approach applied was conservative by assuming that all foods always contained all phthalates of interest at the maximum mean/median level reported in the literature, which would lead to considerable overestimation of exposure. On the other hand, the use of the LB approach will have resulted in an underestimation of exposure from those foods where in the absence of a detected/quantified value a zero value was assigned. Given the many different sources of uncertainties, and opposing directions of the latter, it is impossible to reliably determine the overall direction of uncertainty in this assessment. However, given that the derived estimates are in reasonably good agreement with exposure assessments reported in the literature and with the human biomarker studies, the influence of the identified uncertainties appear to be minor. Concerning plastic FCM contribution, in absence of reliable information on exposure contribution from plastic FCM, assuming a 100% contribution of plastic FCM to total estimated exposure from all sources would result in a potential gross overestimation of source contribution.

6.2 Hazard identification and characterisation

A qualitative evaluation of the uncertainties in the hazard identification and characterisation of phthalates was performed, as shown in Table 27.

Table 27: Uncertainty analysis for the hazard identification and characterisation

Source of uncertainty	Direction (+[(a)]/-[(b)])	Comment
Use of NOAEL/LOAEL values for the derivation of RPFs instead of BMDLs	+/-	The BMD approach - may be more accurate - may provide higher or lower values than the NOAELs, and therefore different potency factors.
Derivation of RPFs from NOAELs/LOAELs/BMDLs of studies with different experimental design	+/-	
Use of standard uncertainty factors of 100 or 200	+/-	Difference between humans and rodents, differences between individuals, prenatal exposure. Use of substance specific adjustment factors was not explored (due to the ToR).
Endpoints other than reproductive toxicity not assessed (immunotoxicity, neurotoxicity, metabolic effects)	-	There are some reports in the literature which claim that these effects may occur at lower doses than than those for reproductive toxicity.
Any literature regarding reproductive toxicity for DBP, BBP, DEHP after ECHA publication not considered.	+/-	Only for DINP and DIDP (as not covered by the ECHA RAC 2017 opinion) were updated searches conducted (see Table 3).
No comprehensive review and no weight of evidence approach conducted	+/-	Due to the time limitations and the ToR
Common assessment group and assumption of simple dose addition	+/-	Experimental data show no synergy or antagonism (only tested for the endpoint testosterone production).
Common assessment group may not be complete (e.g. DIBP only covered in a narrative)	-	Other substances may act in the same way, but this was not evaluated in this opinion.

DBP. Uncertainty around the identified NOAEL	+	The TDI for DBP was based on the LOAEL (1-3 mg/kg bw per day) of one study (Lee et al., 2004; exposure from GD 15 to PND 21) with some shortcomings and using an uncertainty factor of 200. Two other two-generation reproduction toxicity studies with DBP (Mylchreest et al., 2000 and Zhang et al., 2004) showed a NOAEL of 50 mg/kg bw per day.
Reproductive toxicity of DINP	+	Some anti-androgenic/ reproductive toxic effects of DINP might be transient and/or not relevant for inclusion into the group.
Hybrid TDI (covering both reprotoxicity and liver toxicity) for DINP	+	Liver toxicity covered by the RPF raised from 0.1 to 0.3.

(a): + for overestimation of the risk
(b): - for underestimation of the risk

The Panel concluded that while some sources of uncertainty could lead to an overestimation of the risk and several others could lead to an over- or underestimation of the risk, none of these sources is expected to have a major impact on the risk characterisation of the phthalates under evaluation – except for the risk characterization of DBP-induced reproductive toxicity for which a new weight of evidence approach may be appropriate. However, substantial uncertainties in the CEP Panel's assessment of the phthalates used in plastic FCM are related to the ToR requesting EFSA (i) to use information available to ECHA (2017) on DBP, BBP and DEHP and (ii) data on DINP and DIDP, focusing on reproductive effects (see 1.1 and 1.2). Whilst the Panel agrees with ECHA (2017) that potential phthalate-induced adverse effects, such as effects on neurodevelopment, the immune system or the metabolic system, could be more sensitive endpoints compared to the reproductive toxicity, EFSA was requested "to notify the Commission without delay if during the assessment the Panel identifies significant health risks". Due to the limited time for completion of the opinion and the large amount of new evidence available since the 2005 publication of the EFSA AFC Panel's assessments of DBP, BBP, DEHP, DINP and DIDP (EFSA, 2005a, b, c, d, e), the Panel considered it unfeasible to perform a comprehensive review of all the new data on these phthalates.

In addition to these limitations, the Panel also noted that other reprotoxic phthalates, such as DIBP, may increase the risk of phthalate-induced anti-androgenic and potential other effects in consumers exposed to these substances simultaneously with the phthalates under evaluation. This was considered a further important source of underestimation of the risk.

In the absence of a comprehensive review for the phthalates under evaluation, the CEP Panel considered a qualitative approach for the uncertainty analysis of hazard identification and characterisation appropriate. No extra uncertainty factor for the potential effects other than reproductive toxicity could be proposed since due to the time limitation of this assessment (ToR) no weight of evidence approach could be performed.

7. Conclusions

As requested by the ToR of the mandate received from the European Commission, EFSA updated its 2005 risk assessments of certain phthalates (DBP, BBP, DEHP, DINP and DIDP) authorised for use as plasticisers and technical support agents in plastic FCM, and evaluated whether the authorisation under Regulation (EU) No 10/2011 is still in accordance with the FCM Regulation.

Exposure

Occurrence data on phthalates in food were obtained from the literature referenced in the ECHA RAC opinion (2017a) on DBP, BBP and DEHP and complemented with additional literature search on DINP and DIDP and on specific foods not covered in the literature from ECHA RAC.

Occurrence data available in the EFSA Chemical Occurrence database was not suitable for exposure assessment because of severe limitations, e.g. high LOQs and LODs and high percentage of left-censored data.

Estimates of dietary exposure (ranges of the min-max estimates for all ages, all surveys and all countries) were obtained by combining occurrence data with the consumption data from the EFSA Comprehensive Database and were as follows:

- DBP mean of (0.042 - 0.769) and P95 of (0.099 - 1.503), µg/kg bw per day
- BBP mean of (0.009 - 0.207) and P95 of (0.021 - 0.442), µg/kg bw per day
- DEHP mean of (0.446 - 3.459) and P95 of (0.902 - 6.148), µg/kg bw per day
- DINP mean of (0.232 - 4.270) and P95 of (0.446 - 7.071), µg/kg bw per day
- DIDP mean of (0.001 – 0.057) and P95 of (0.008 – 0.095), µg/kg bw per day)

These estimates are in reasonably good agreement with those reported in TDS for the UK, Ireland and France.

Hazard characterisation

The review of the literature focused mainly on the reproductive effects of DBP, BBP, DEHP, DINP and DIDP. The critical effects of each of the phthalates and the derived individual TDIs are reported below:

- For DBP, a LOAEL of 2 mg DBP/kg bw per day for reduced spermatocyte development and effects on the mammary gland was identified from a developmental toxicity study in rats. By applying an uncertainty factor of 200[18], the TDI was set to 0.01 mg/kg bw per day.
- For BBP, a NOAEL of 50 mg BBP/kg bw per day was identified from a multi-generation study in rats, based on reduced AGD in F1- and F2- males at birth in the 250 mg BBP/kg bw per day group. By applying an uncertainty factor of 100, the TDI was set to 0.5 mg/kg bw per day.
- For DEHP, a NOAEL of 4.8 mg DEHP/kg bw per day based on effects on the testis in F1-animals was identified from a three-generation reproductive toxicity study in rats. By applying an uncertainty factor of 100, the TDI was set to 0.05 mg/kg bw per day.
- For DINP, a NOAEL of 15 mg DINP/kg bw per day for non-peroxisomal proliferation-related chronic hepatic and renal effects in rats was identified. An uncertainty factor of 100 was applied for deriving the TDI of 0.15 mg/kg bw per day for DINP.
- For DIDP, a NOAEL of 15 mg DIDP/kg bw per day for liver effects in dogs was identified. An uncertainty factor of 100 was applied for deriving the TDI of 0.15 mg/kg bw per day for DIDP.

For all the five phthalates, the critical effects and the individual TDIs are fully in line with what EFSA established in 2005.

[18] ECHA (2017a) used a factor of 3 (total UF 300) for the extrapolation from LOAEL to NAEL.

With regards to the grouping of phthalates the CEP Panel considered the anti-androgenic effect, i.e. reduction of the fetal testosterone production in rats, as a common mode of action and critical step for reproductive toxicity. On this basis the CEP Panel included DBP, BBP, DEHP and DINP into the same group-TDI.

- Although the Panel considered liver effects to be the most sensitive endpoint for DINP, it also noted its anti-androgenic capability. To account for the different potencies towards these endpoints an additional assessment factor of 3.3 was used in the group TDI.
- DIDP was not included in the group-TDI as its reproductive effects (i.e decreased survival rate in F2) are not considered to be associated with anti-androgenicity. Therefore, DIDP maintained its individual TDI for liver effects of 0.15 mg/kg bw per day.

The group-TDI was calculated by means of relative potency factors with DEHP taken as the index compound as it has the most robust toxicological dataset. The relative potency factors were calculated from the ratio of the TDI for DEHP to the HBGVs of the three other phthalates. The group-TDI was established to be 0.05 mg/kg bw per day, expressed as DEHP equivalents.

Risk characterisation

An aggregated dietary exposure assessment to DBP, BBP, DEHP and DINP was carried out. The following equation was applied at the level of chemical occurrence (concentration) data for each food category:

GroupPhthalates concentration expressed as DEHP Equivalents ([GPDEq], µg/kg food) = DEHP*1 + DBP*5 + BBP*0.1 + DINP*0.3

The highest estimated exposure for GroupPhthalates was in the range of 0.9 to 7.2 for the mean consumer and 1.6 to 11.7 µg/kg bw per day for the high (P95) consumers.

Comparing the GroupPhthalates exposure estimates for the mean consumer with the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents), it can be concluded that this exposure contributes 1.8 to 14% of the group-TDI.

As regards the high (P95) consumers, it can be concluded that the exposure amounts to 3 to 23% of the group-TDI of 50 µg/kg bw per day (expressed as DEHP equivalents).

These conclusions cover all European population groups (all countries, all surveys, all age groups), including children and women of child-bearing age.

As regards DIDP, not being included in the group-TDI, the mean (0.001 - 0.057 µg/kg bw per day) and the P95 exposure levels (0.008 - 0.095 µg/kg bw per day) are far below the TDI of 150 µg/kg bw per day for all population groups (all countries, all surveys, all age groups).

Contribution from plastic FCM

The CEP Panel noted that there is not enough information available to make firm conclusions on what contribution migration from plastic FCM makes to dietary exposure to phthalates.

The above estimates concern dietary exposure from food containing phthalates from different sources of contamination, e.g. FCM, environment, etc. Clearly, the contribution of plastics, or even FCM more generally, cannot exceed the total estimates from food, being 3 to 23% of the group-TDI for the high consumers.

Uncertainties

Amongst several sources of uncertainty identified in a qualitative uncertainty analysis, the main impacts on risk assessment could be attributed to:

- Lack of an in depth evaluation of toxicity endpoints other than reproduction, i.e. neurodevelopment, immune and/or metabolic system, that could be more sensitive. This could lead to an underestimation of the risk based on the currently proposed group approach focusing on the reprotoxic/anti-androgenic effects.

- Co-exposure to other phthalates not authorised for use in plastic food contact materials, e.g. DIBP, with potential reprotoxic/anti-androgenic and/or other relevant effects.

8. Recommendations

The Panel noted that individual SMLs are currently set out in Regulation 10/2011 for DBP, BBP and DEHP, while for DINP and DIDP a SML(T) is applicable (see 1.3.5). With regards to the toxicological database, the Panel noted that there was no evidence of anti-androgenicity for DIDP. However, it is currently difficult to completely separate DINP and DIDP analytically when present in foods as a mixture. Therefore, it may be a pragmatic approach to also include DIDP in any resulting group restriction for migration from plastics, with the same relative potency factor as DINP (based on the similarity of the liver effects).

Having considered the limitations and uncertainties related to this assessment, the CEP Panel identified several recommendations that should be taken into account for a future re-assessment of these 5 phthalates:

- As regards the exposure assessment in general, and the question on contribution of plastic FCM to exposure and the TDI(s) of phthalates more specifically, a specific call for data should be launched, with the aim of gathering extensive data on occurrence of phthalates in food and of investigating the contribution of (plastic) FCM to the occurrence levels.
- As regards the hazard identification and characterisation,
    - endpoints other than reproduction, i.e. immunotoxic, metabolic and neurotoxic effects, also in relation to the endocrine disrupting properties, should be investigated in more depth, since they could be more sensitive (see also Appendix B).
    - for the derivation of PoD as the basis for setting TDI(s), instead of the NOAEL approach, the BMD approach should be used. Consequently, the raw data for each of the critical studies should be obtained, in order to allow the modelling of the benchmark dose.
    - the question on co-exposure to other phthalates either authorised or not authorised for use in plastic food contact materials, e.g. DIBP or di (2-propyl) phthalate, with potential reprotoxic/anti-androgenic and/or other relevant effects, should be included (see also Appendix C).
    - the CEP Panel is aware that DIBP is not authorised for use in plastic food contact materials, and therefore not within the scope of this assessment. However, noting the similar i) potency with regards to reprotoxic effects, and ii) intake estimates compared to DBP, the CEP Panel considers that DIBP substantially adds to the overall exposure of consumers to phthalates, from food and from other sources (see Appendix C). The risk manager may wish to take this into account when considering the legislation on plastic FCMs.

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Abbreviations

5OH-MEHP	Mono-(2-ethyl-5-hydroxyhexyl)phthalate
5-oxo-MEHP	Mono-(2-ethyl-5-oxo-hexyl)phthalate
AFC	EFSA Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food
AFD	Anofourchette distance
AGD	Anogenital distance
APD	Anopenile distance
ASD	Anoscrotal distance
BBP	Butyl-benzyl-phthalate
BMD	Benchmark dose
BMDL	Benchmark dose (lower confidence limit)
CAS	Chemical Abstracts Service
CEF Panel	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
CEP Panel	EFSA Panel on Food Contact Materials, Enzymes and Processing Aids
CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging
DBP	Di-butylphthalate
DEHP	Bis(2-ethylhexyl)phthalate
DEP	diethyl phthalate
DHEAS	Dehydroepiandrosterone sulfate
DIBP	Di-isobutyl phthalate
DIDP	Di-isodecyl phthalate
DINP	Di-isononyl phthalate
DNEL	Derived No Effect Level
DPB	Di-butyl phthalate
EC	European Commission
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
FCM	Food contact materials
FCs	Food categories
FLC	Fetal Leydig cells
FSH	Follicle-stimulating hormone
FUE	Fractional urinary excretion
GD	Gestational day
GLT4	Glucose transporter 4

HBGV	Health based guidance values
ICC	Intra-class correlation coefficients
IgE	Immunoglobulin E
LB	Lower bound
LCAs	Leydig cell aggregates
LDH	Lactate dehydrogenase
LH	Luteinising hormone
LOAEL	Lower observed adverse effect
LOD	Level of detection
LOQ	Level of quantification
MBP	Mono-butyl phthalate
MBzP	Mono-benzyl phthalate
MECPP	Mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MEOHP	Mono-(2-ethyl-5-oxohexyl) phthalate
MIBP	Mono-isobutyl phthalate
MNG's	Multinucleated gonocytes
MoA	Mode of action
NANs	National adult nutrition survey
NCFs	National children's food survey
NOAEL	No Observed Adverse Effect
NOS	Newcastle–Ottawa scale
PET	Polyethylene terephthalate
PND	Postnatal day
PNW	Postnatal week
PoD	Point of departure
PPARs	Peroxisome proliferator activated receptors
PVC	Polyvinyl chloride
PW	Penile width
RAC	Risk assessment committee
RCR	Risk characterisation ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
ROS	Reactive oxygen species
RP	Reference point
RPF	Relative potency factor
SC	Scientific committee
SD	Sprague Dawley

SDWH	Scientific data warehouse
SEA	Socio economic analysis
SHBG	Sex hormone binding protein
SML	Specific migration limit
SML (T)	Total specific migration limit
SSD	Standard sample description
SVHC	Substances of very high concern
T2	Second Trimester
TDI	Tolerable daily intake
TDS	Total diet studies
ToR	Terms of reference
UB	Upper bound
UF	Uncertainty factor
WG	Working group

Appendix A – Review of the epidemiological studies on reproductive toxicity

The focus of the evaluation is on epidemiological studies that investigated the role of phthalate exposure on reproductive outcomes since reprotoxicity was identified as the most sensitive endpoint (with robust underlying data) from the animal studies. However, the evaluation was mainly concentrated on prospective epidemiological studies investigating the role of *in utero* exposure to phthalates and AGD, a well-known early sexually dysmorphic marker for endocrine disrupting chemicals.

Studies on phthalate exposure and AGD in new-borns

AGD is thought to be a sensitive marker for androgen activity and it is used as a marker of reproductive toxicity. Prenatal phthalate exposure has been shown to shorten male AGD in rodents and some studies suggest the same effect in humans (ECHA, 2017b). ECHA (2017b) reported five epidemiological studies that investigated the association between prenatal exposure to phthalates and AGD were reviewed.

Studies which investigated AGD were conducted in USA, Mexico, Taiwan, Japan and Denmark and the sample size of the studies ranged from 73 to 753 subjects. All the studies adjusted for possible confounders and timing of exposure in two out of the fives studies reviewed by ECHA (2017b), was the first trimester of pregnancy (Huang et al., 2009; Swan et al., 2015). In all studies a single urine sample was collected, except for the study of Huang et al. (2009), where amniotic fluid was collected to characterise the subject's phthalate exposure. All the studies were conducted within large cohorts and metabolites of mainly DEHP were measured and reported. However, metabolites of other phthalates (e.g. DBP, BBP, DINP) were also measured.

In the study of Swan et al. (2005) urinary metabolites of e.g. DBP and BBP, but not of DEHP, were associated with a shorter AGD. In the study of Huang et al. (2009), no association was found between metabolites of DEHP in the amniotic fluid and AGD in both males and females. However, they found an inverse association between metabolites of DBP and AGD in female new-borns. In the study of Bustamante-Montes et al. (2013), DEHP prenatal exposure was not associated with AGD, but only total phthalates exposure (diethyl phthalate (DEP), DBP, BBP, DPHP) was found to be associated. Jensen et al. (2016) showed that high levels of metabolites of e.g. DINP, DEHP, and BBP were associated with short AGD, however without statistical significance. In the study of Suzuki et al. (2011), maternal urinary concentration of MEHP was inversely associated with anogenital index (i.e. AGD corrected by body weight) in males but not with other metabolites (MEHHP, MEOHP, MBzP). Swan et al. (2015) also showed an inverse association between maternal urinary concentration of MEHP, MEOHP, MEHHP and ∑DEHP, and AGD but not with other urinary phthalate metabolites (MBzP, MBP, Mono-carboxy-isooctyl phthalate).

Overall, there was little consistency between the five studies. Four (Swan et. al., 2005; Huang et al., 2009; Bustamante-Montes et al., 2013; Jensen et al., 2016) out of the five studies reviewed did not find a statistically significant inverse association between prenatal exposure of DEHP and AGD in newborns. However, all studies reviewed, except the study of Jensen et al. (2016), found a statistically significant association between prenatal exposure to among others BBP and DBP, and AGD.

<u>Studies on phthalate exposure, reproductive hormones and pubertal timing, semen quality and hypospadias</u>

Some studies on phthalate exposure and reproductive hormone levels and changes in pubertal timing and hypospadias were reviewed by ECHA (2017b) and are described below.

Main et al. (2006) studied the association between phthalates (e.g. DBP, BBP, DEHP, DINP) in breast milk and reproductive hormones in a population of new-born boys (n = 130) and showed that metabolites of DBP were positively correlated with sex-hormone binding globulin and with luteinising hormone (LH): free testosterone ratio, and metabolites of DINP with serum follicle-stimulating hormone (FSH). MIBP, a metabolite of DBP, was negatively correlated with free testosterone. In the same study, no association was found between phthalate exposure and cryptorchidism.

Pan et al. (2006) conducted a study in China to investigate the effect of high phthalate exposure (DBP and DEHP) at occupational level (n = 74 males) on free testosterone, LH, FSH and estradiol and found that high levels of urinary MBP (644.3 vs. 129.6 µg/g creatinine in non-exposed) and MEHP (565.7 vs. 5.7 µg/g creatinine in non-exposed) were associated with low serum levels of free testosterone.

Hauser et al. (2006) conducted a study on 463 males from sub-fertile couples and studied the association between phthalate exposure (e.g. DEHP, BBP) and sperm function (concentration and motility). High levels of urinary MBP was associated with decreased sperm concentration and motility with a dose-response relationship (P trend = 0.004). No association was found between semen function and other phthalates measured.

Meeker et al. (2009) collected urine and serum samples from 425 men in a USA infertility clinic and investigated whether phthalate exposure (urine levels of metabolites of e.g. DEHP, DBP, BBP) was associated with reproductive hormones. They showed that urinary metabolites of DEHP were inversely associated with inhibin B, testosterone and estradiol.

Fergurson et al. (2014) investigated the relationship between prenatal phthalate (e.g. DEHP, BBP) in the third trimester and sex hormones studied in 106 boys and showed an inverse association between exposure of some phthalates (e.g. DBP) and dehydroepiandrosterone sulfate (DHEAS) and inhibin B. Prenatal phthalate exposure and phthalate exposure in childhood were not associated with adrenarche and puberty.

Axelsson et al. (2015) showed (n = 112) that high prenatal exposure (first trimester) of DEHP and DINP in maternal serum was associated with high levels of reproductive hormones (FSH and LH) and low testicular and semen volume in adults. High prenatal exposure of DINP (MCIOP) was also associated with lower testicular volume.

Ormond et al. (2009) conducted a case-control study (471 cases; 490 controls) on endocrine disruptors in the workplace, hair spray, folate supplementation and hypospadias. Maternal exposure to phthalates was associated with a three times increased risk (OR=3.12; 95%CI: 1.04-11.46) of hypospadias.

Colon et al. (2000) investigated if serum phthalates (e.g. DBP, BBP, and DEHP) were associated with premature thelarche (n = 41) in Puerto Rico girls and 35 controls (median age 20 months) and found that cases have higher levels of metabolites of DEHP than controls. Lomenick et al. (2010) explored whether urinary metabolites and serum phthalate levels (DEHP, DBP, BBP) were associated with precocious puberty in girls (n = 28 girls with pre-pubertal puberty and 28 controls; 7 years) in USA and they found no association.

The studies reviewed on pubertal timing in children showed contradictory results and they have many limitations, such as small sample size and no control for confounding factors.

ECHA (2017b) reported that semen quality in populations in Europe varies according to geographic location. They stated that this variation could not be explained by genetics only and they suggested that environmental exposures might be playing a role. ECHA (2017b) also reviewed studies conducted in adult male population. Mendiola et al. (2011) conducted a study in 126 adult volunteers in USA and showed that AGD was associated with total sperm count, sperm concentration, motility and morphology. In the latter study, subjects with short AGD had 7.3-fold increased risk of having a low sperm concentration. Mendiola et al. (2012) pooled the data of two studies (n = 425) and showed that metabolites of DEHP (MEHP and MEOHP) were inversely associated with serum reproductive hormones testosterone/sex hormone binding protein (SHBG) and calculated free testosterone. Urinary concentrations of MEHP and MEOHP were also positively associated with SHBG. Cai et al. (2015) conducted a meta-analysis with 14 studies to study the association between phthalate exposure and human semen quality. The pooled results showed statistically significant associations between metabolites of DBP, BBP and decreased sperm production; metabolites of DBP, DEHP and decreased motility, and metabolites of BBP and DEP and motion parameters. Huang et al. (2014) conducted a study on 47 workers employed in two PVC pellet plants and 15 graduate students (non-exposed), and showed that high exposure, as indicated by urine DEHP metabolites, were associated with decreased sperm motility and increased apoptosis and reactive oxygen species (ROS) generation.

Epidemiological studies: prenatal exposure to phthalate and AGD in newborns

Sources of bias in observational studies are, among others, related to the study design and analytic methods. Using statistical adjustments in the models or matching procedures may decrease the risk of bias, which can increase confidence in the results. Bias can introduce an error in risk estimates in both magnitude and/or direction. The Newcastle–Ottawa Scale (NOS) is a scale to assess the quality of epidemiological studies (see Table 28). This scale uses a star system to assess the quality of a study in three domains: selection, comparability and outcome (cohort studies) or exposure (case–control studies). The NOS assigns a maximum of four stars for selection, two stars for comparability, and three stars for exposure/outcome. Nine stars reflect the highest quality. For the purpose of this evaluation, NOS was mainly used as guideline for describing and interpreting studies (Higgins, Green, Cochrane Collaboration, 2008).

Table 28: Quality assessment of epidemiological studies according to NOS

Study	**Population**	**Country**	**Timing**	**Precursor**	**Metabolites**	**β value**	**Quality score*** **
	(n)				**(μ/L)**	**(95% CI)**	**Score**
Swan et al., 2005	134 boys	USA	first, second, third trimester	DEP	MEP (>436.9) Q4 vs. Q1	4.7 (1.2 to 17.4)°	4
				DBP	MBP (>30.9)	10.2 (2.5 to 42.2)	
				BBP	MBzP (>23.5)	3.8 (1.03 to 13.9)	
				DIBP	MIBP (>5.1)	9.1 (2.3 to 35.7)	
Huang et al., 2009	64 males and females	Taiwan	first trimester	DBP	amniotic fluid MBP	-2.73 (P = 0.041)	4
Suzuki et al., 2011	111 males	Japan	first, second, third trimester	DEHP	MEHP	-0.226 (P = 0.017)	5
Bustamante-Montes et al., 2013	73 males	Mexico	third trimester	DEHP	MEHP	-0.0049 (P = 0.943)	4
					Total phthalates	-0.191 (P = 0.037)	
Swan et al., 2015	753 males and females	USA	first trimester	DEHP	MEHP	-1.12 (-2.16,-0.07)	5
				DEHP	MEOHP	-1.43 (-2.49,-0.38)	
				DEHP	MEOHHP	-1.28 (-2.29,-0.27)	
					ΣDEHP	-1.26 (-2.40,-0.13)	
Jensen et al., 2016	245 males	Denmark	third trimester	DEP	MEP (≥ 55)§	-1.37 (-3.27,0.54)	7
				DINP	DINPm (≥ 20)	-0.29 (-2.17,1.59)	
				DEHP	MEHP (≥ 34)	-1.16 (-3.08,0.77)	

° Ors AGI = AGDindex. ???, * Spearman correlation coefficient, § ng/mL.

Appendix B – Updated literature searches on effects of phthalates

As described under 2.2, searches of the recent literature (i.e. after the cut-off date for the ECHA (2017a)) were performed for effects of DBP, BBP and DEHP other than reproductive toxicity, i.e. immunotoxic, metabolic and neurotoxic effects. The aim of these searches was to obtain an overview of the recent research trends in these areas, as they had been addressed by the ECHA (2017a), who indeed indicated that, in addition to reproductive toxicity, these other effects could be associated with exposure to phthalates (and particularly to DEHP). As regards the effects on the immune system, the ECHA RAC concluded that those could even possibly occur at levels lower than reproductive toxicity. However, the available data did not allow to include these effects in a quantitative manner in the risk assessment. The outcome of the searches of the recent literature is reported in the following subchapters and besides that also some selected recent (i.e. after the cut-off date for the ECHA opinion (2017a)) papers on epidemiological studies investigating the reproductive effects of phthalates are described.

The impact of the below reported findings on the current TDIs should be assessed in an extensive review along with previously (before 2016) published literature. Such a review is outside the scope of the current ToR of the mandate.

Updated literature searches on neurotoxic effects of phthalates

Based on the retrieved data from reviews, epidemiological and experimental studies *in vivo* and *in vitro*, the CEP Panel noted that there are additional indications for phthalate-induced neurodevelopmental toxicity in humans, animals and in neuronal cells. For BBP however, no experimental studies on potential neurodevelopmental toxicity were retrieved. Some review papers report that several associations of adverse health outcomes with phthalate exposure are inconsistent in epidemiological studies (Vrijheid et al., 2016; Zarean et al., 2016; Tsai et al., 2017) and diverging outcomes might be due to methodological flaws or differences in exposure time or the time of effect assessment (Braun, 2017). Among the epidemiological studies, most of them have a cross-sectional design which does not make it possible to conclude on causality. However, four prospective cohort studies, which were positively associated with adverse neurodevelopmental effects, were also discussed (references in Braun, 2017, Precicados et al., 2016; Ponsonby et al., 2016). Neurodevelopmental toxicity is further supported by experimental animal studies with pre-, peri-, post-natal, pubertal, chronic or adult exposures to DEHP or DBP. While some authors (e.g. Basha and Radha, 2017; Ding et al., 2017; Kim et al., 2017a; Farzanehfar et al., 2016; Lee et al., 2016) reported adverse effects at doses above the lowest NOAELs for DBP and DEHP derived by EFSA (2005a, c), others claimed effects with oral doses at the NOAELs or below (e.g., Dombret et al., 2017; Komada et al., 2016; Quinnies et al., 2017 Luu et al., 2017; Wang et al., 2016a; Wang et al., 2016b; Yan et a., 2016).

Updated literature on metabolic effects of phthalates

Numerous studies on metabolic effects of phthalates and/or their metabolites have been published since the opinion of ECHA (2017a), with these including experimental animal studies, epidemiological studies and *in vitro* and *in vivo* mechanistic studies. In addition, there is a large number of reviews that have been published on the topic of obesogenic or diabetogenic chemicals and their effects, including phthalates.

In many of the experimental studies on metabolic effects of phthalates, the animals were not administered DEHP, DBP and BBP themselves but phthalate metabolites. In some of the studies, the authors claim that the results show non-monotonic dose-responses, such as inverted 'U' shaped curves, with opposite effects of lower versus higher doses. For instance, in a 13-week obesity study of DBP in rats, an increase in serum glucose and serum lactate dehydrogenase (LDH), a marker of cardiac function, was observed with 10, but not with 50 mg/kg bw per day (Majeed et al., 2017). However, very rarely the number of included doses was sufficient to solve the question as to whether the dose-response was monotonic or non-monotonic. In the external scientific report from EFSA published in 2016, at least five dose groups in addition to a negative control group were included in the evaluation of evidence for the non-monotonic dose-response hypothesis (Beausoleil et al., 2016).

These factors make it difficult to perform direct comparisons with the experimental doses in the reproductive toxicity studies, which were the basis for the determination of DNELs by ECHA (2017a).

Some newer studies published in 2016-2018 (mostly on DEHP) indicate that there may be effects of phthalates at lower concentrations than the NOAEL/LOAEL values from reproductive toxicity studies used to establish the present TDIs. For instance, administration of 0.05 mg/kg bw per day of DEHP to pregnant mice from gestational day GD1 to GD19 increased serum leptin, insulin, visceral fat pad weight, total triglyceride and total cholesterol levels and fasting serum glucose concentrations in the offspring of both genders at 9 weeks of age (Gu et al., 2016). In 3-week old rats given 5 mg/kg bw per day (lowest dose tested) of DEHP for four weeks, body weights were significantly increased, indicating this dose as the LOAEL (Jia et al., 2016). In adult rats, DEHP at 0.05 and 5 mg/kg bw per day for 15 weeks induced severe insulin resistance (Zhang et al., 2017). In the same study, the 5 mg/kg bw dose also significantly increased malondialdehyde and decreased superoxide dismutase in the liver, indicating oxidative stress, and both the 0.05 and 5 mg/kg bw doses significantly increased expression of PPARγ and decreased expression of insulin receptor and glucose transporter 4 (GLT4) proteins.

Several plausible mechanisms have been suggested for the potential effects of phthalates on metabolic endpoints, such as obesity and diabetes (Muscogiuri et al., 2017; Benjamin et al., 2017). The obesogens may increase the adipogenesis and/or the fat storage in existing fat cells, or they may act indirectly through change of the gut microbiota, or by altering basal metabolic rate and hormonal control of appetite and satiety. They may perturb the molecular signalling involved in lipid metabolism and its homeostasis through hypothalamic-pituitary-gonad/thyroid axis coupled with nuclear transcription factors such as the PPARs, which are master regulators of lipid and glucose homeostasis. Phthalates may also impart increased risk of diabetes through activation of PPARs, by disturbing the development and progression of pancreatic β cells.

A large number of human studies report statistical associations between one or several phthalates and/or their metabolites (very often including DEHP) measured in urine and increased risk of obesity or insulin resistance and/or type 2 diabetes. Obesity is measured as body mass index, abdominal obesity, waist circumference etc. (see for instance recent reviews by Song et al., 2016; Muscogiuri et al., 2017; Benjamin et al., 2017). However, in general, the epidemiological data on obesogens and diabetogens may be difficult to evaluate. In these human studies, exposure is mostly estimated from measurements of metabolites in the urine, often only from one spot urine sample per person. Many of these non-persistent chemicals, including phthalates, have short physiological half-lives, and, thus, a single measurement performed in most of the studies cannot provide information on the effects of long-term exposures. Especially for phthalates such as DEHP, having numerous oxidative metabolites, exposure should be estimated from the sum of all metabolites. Further, the various studies have measured different metabolites, therefore making it difficult to compare results across the studies. Most of the studies are small in size, limited in time period studied, of cross-sectional or retrospective design, and are based upon population-based surveys or pharmacovigilance studies, i.e. studies not designed to address specifically the effects of chemicals on obesity or diabetes. A commentary on general methodological shortcomings of epidemiological studies is described under 4.8.

Updated literature on immunotoxic effects of phthalates

From the search of the recent literature (see section 2.2), the CEP Panel noted subsequent reports on the immunotoxicity of phthalates. Epidemiological studies reported associations of several phthalates (DEHP, DBP, DIBP, DINP, DIDP) with respiratory allergy, asthma, and atopic dermatitis (Hu et al., 2017; Kim et al., 2017b; Li et al., 2017; Wang and Karmaus, 2017; Vernet et al., 2017; Soomro et al., 2018), but others (Bai et al., 2017) failed to identify such associations. Additional animal studies have further expanded the information on adverse effects of phthalates on the immune system, such as adjuvant activity of DEHP and BBP (You et al., 2016; Wang et al., 2018). Jahreis et al. (2018) found such effects even in the second (F2) generation after exposure to BBP of the parent mice. Enhanced antibody responses to thyroid globulin by exposure to DBP was observed by Wu et al. (2017), and enhanced skin sensitisation by DBP, DINP, DIDP were described by Kang et al. (2016, 2017); Shen et al. (2017) and Kurohane et al. (2017).

The recent literature lends further support to the notion indicated also in the ECHA RAC opinion (2017) that reproductive toxicity may not be the most sensitive endpoint for the effects of phthalates and that the current risk assessment may not be sufficiently protective for immunotoxic effects.

Updated literature on epidemiological studies investigating reprotoxic effects of phthalates

As regards epidemiological studies investigating reproductive toxicity effects of phthalates, no targeted search of the literature was conducted as for the other effects. However, the CEP Panel noted some recent papers, indicating ongoing research in this area of interest.

A recent systematic review (5 cohort studies and 19 animal studies) evaluated the effect of *in utero* exposure to DEHP on AGD. DEHP urinary metabolites were associated with a decreased AGD in boys. In male rats, a dose-response relationship was observed between DEHP and AGD (Dorman et al., 2018).

Martino-Andrade et al. (2016) conducted a study on 168 mothers to examine the effect of exposure timing on the action of prenatal phthalates, in particular DEHP, on male infant penile size and AGD. Penile width (PW) was inversely associated with second trimester (T2) DEHP metabolites, mono-2-ethyl-5-oxohexyl (MEOHP), MEHHP, mono-2-ethyl-5-carboxypentyl (MECPP). Concentrations of DEHP metabolite (MEHHP) in T1 urine samples were inversely associated with male AGD. However, no association was found between AGD and DEHP metabolites in the T2 and T3.

Wenzel et al. (2018) conducted a study on 380 pregnant African American and white women and their newborns, to study the role of race on the associations between prenatal phthalate exposure and AGD among a newborn population (171 boys and 128 girls). The outcomes of the study were anopenile distance (APD), anoscrotal distance (ASD), anoclitoral distance (ACD) and anofourchette distance (AFD). An association between second trimester gestational MEHP exposure and APD in boys was found. The effect was stronger for African Americans than for whites. Positive associations between prenatal exposure to the sum of DBP and ASD, with stronger associations for whites than for African Americans. No association was found between prenatal phthalate exposure and ACD or AFD in girls.

Appendix C – Considerations on DIBP

The CEP Panel notes that, besides the phthalates assessed in this opinion, consumers are exposed to a wider range of phthalates from other sources (Health Canada, 2015), among others also DIBP from FCM, e.g. recycled paper and board. Similarly as for DBP, BBP and DEHP, there is a harmonised classification for Reproductive toxicity (Category 1B) also for DIBP. Together with the 3 previously mentioned phthalates, DIBP was assessed in the ECHA opinion (2017a). The toxicological evaluation was based on read-across with DBP, for which a NOAEL of 2 mg/kg bw per day was identified based on reduced spermatocyte development at PND21, as well as mammary gland changes in adult male offspring (Lee et al., 2004; see also section 4.7.1). In a high dose study, both on DBP and DIBP, by Saillenfait et al. (2008), it was observed that DIBP exerted comparable effects (AGD, nipple retention, reproductive organ weights and reproductive tract malformations and puberty onset) to DBP when tested at a 25% higher dose (625 mg DIBP/kg bw per day vs. 500 mg DBP/kg bw per day). It was therefore concluded by ECHA RAC (2017a) that the NOAEL of DIBP should be 25% higher than the one of DBP, i.e. 2.5 mg/kg bw per day.

As regards exposure values to DIBP, the CEP Panel took note of the human biomonitoring data and estimates of exposure from modelling, as reported in the ECHA RAC opinion (2017a). For the human biomonitoring, two main data sources were used, as described under 1.3.3, i.e. the EU-wide DEMOCOPHES project and the study by Myridakis et al. (2015). ECHA RAC (2017a) combined the results of these studies and derived the intake estimates for mothers as reported in Table 29**Error! Reference source not found.**

Table 29: Intake estimates (μg/kg bw per day) for mothers from Myridakis et al. (2015) for Greece, in combination with DEMOCOPHES (Table adapted from ECHA, 2017a)

Substance	Median	P95	Number of samples
DBP	0.88	3.50	1586
DIBP	1.08	4.38	1586
BBP	0.12	0.83	2039
DEHP	2.37	10.33	2039
Sum DBP, BBP, DEHP (potency-adjusted)	6.8	n/a	
Sum all (potency adjusted)	12.2	n/a	

Comparing the intake estimates for DIBP with the ones for DBP, the CEP Panel noted that they are in the same range for median and P95 values. Due to the occurrence level of DIBP coupled with its high potency factor, adding it to the GroupPhthalates estimate almost doubles the estimate for medium exposure, from 6.8 up to 12.2 μg/kg bw per day, as DEHP equivalents.

In addition to the data from human biomonitoring, the ECHA RAC opinion (2017a) reports intake estimates from food, based on data from the literature (see Table 30).

Table 30: Intake estimates for food (μg/kg bw per day) (Table adapted from ECHA, 2017a)

	Infants[(b)]		Children[(a)]		Women[(a)]	
	Median	P95	median	P95	median	P95
DBP	0.70	1.24	0.20	0.30	0.08	0.16
DIBP	1.03	9.02	0.42	0.64	0.14	0.28
BBP	0.15	0.24	0.12	0.21	0.05	0.12

DEHP	4.66	7.09	3.50	5.38	1.49	2.86
Sum DBP, BBP, DEHP[(c)]	8.2	n/a	4.5	n/a	1.9	n/a
Sum all [(c)]	13.3	n/a	6.6	n/a	2.6	n/a

(a): Sioen et al. (2012),
(b): Fromme et al. (2013), except BBP where 30% of the estimate in Fromme et al. (2007) is used.
(c): Potency-adjusted
n/a: not applicable

Comparing the intake estimates from food for DIBP with the ones for DBP, the CEP Panel noted that values for DIBP (both median and P95) are slightly higher than those for DBP. The median GroupPhthalates exposure can be calculated as 8.2 for infants, 4.5 for children and 1.9 µg/kg bw per day, for women (see Table 30). If the [occurrence * relative potency] of DIBP are added to the GroupPhthalates there would be about a 50% increase in the exposure estimates, to 13.3, 6.6 and 2.6 µg/kg bw per day, respectively, expressed as DEHP equivalents.

The CEP Panel is aware that DIBP is not authorised for use in plastic food contact materials, and therefore not within the scope of this assessment. However, noting the similar i) potency with regards to reprotoxic effects and ii) intake estimates compared to DBP, the CEP Panel considers that DIBP substantially adds to the overall exposure of consumers to phthalates, from food and from other sources. This should be taken into account by the risk manager when considering the legislation on plastic FCMs.

Annex A – Dietary surveys in the EFSA Comprehensive Database and occurrence values in the EFSA Chemical Occurrence Database

Annex B – Occurrence data from the literature and results of exposure assessment based on EFSA Chemical Occurrence Database

Annex C – Results for exposure assessment based on occurrence data from the literature