Ministry of Environment of Denmark
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich (DTDP)

EC No 271-089-3

CAS RN 68515-47-9

Evaluating Member State(s): Denmark

Dated: 4 January 2022

Evaluating Member State Competent Authority

Danish Environmental Protection Agency (Danish EPA)
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Year of evaluation in CoRAP: 2014

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich (DTDP, EC number 271-089-3) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (reproductive toxicity evaluated only)
- Exposure/Lack of exposure assessment
- Lack of risk characterisation ratio (RCR)
- High (aggregated) tonnage

During the evaluation two additional end-points of concern were identified:

- Endocrine disruption
- PBT/vPvB

Background for CoRAP listing

The initial concern for reproductive toxicity of the substance DTDP was based on the classification of structurally related substances as reproductive toxicants. The Danish EPA had proposed C7-11 phthalates, branched and linear (1,2-Benzenedicarboxylic acid, di-C7-11 branched and linear alkyl esters (DHNUP; CAS RN 68515-42-4) for the candidate list, because the substance has a harmonised C&L as Repr. 1B and it was foreseen to be used as a substitute for other phthalate plasticisers already agreed for inclusion in Annex XIV (the authorisation list).

DHNUP was pre-registered but not registered in November 2010. However, a number of other individual phthalates with alkylchain lengths within the same range as DHNUP (i.e. in the C7-C11 range) were registered, including. DTDP. The Danish EPA was concerned that the registred substance may also be warrant classification as a reproductive toxicant. However, the registrant had not self-classified the substance.

Concerns on the lack of information on exposure and risk were also included in CoRAP for this high (aggregated) tonnage substance, should the concern for hazardous properties of the registered substance be confirmed.

In addition to the initial grounds for concern, a concern for endocrine disruption of sex- and thyroid hormones was identified during the evaluation due to effects on the endocrine system observed for structurally similar substances.

Furthermore, the additional concern on PBT/vPvB identified the substance fulfills some of the PBT screening criteria as specified in REACH, Annex XIII, section 2

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A targeted compliance check was performed in 2013.

A PBT assessment was concluded in 2019 with the publication of an hazard assessment outcome document in December 2019.

ECHA opened a new compliance check end of 2021 which is currently ongoing.

There is no other regulatory process currently ongoing.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level, but a Compliance check should be initiated.	X

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

No need for regulatory action is identified at this point in time. However, the outcome of the requested compliance check may entail a revised conclusion on possible regulatory action.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

No reproductive toxicity or developmental toxicity studies on the registered substance have been provided by the registrant. Instead, the Registrant proposed to use read-across from similar substances to fill in the data gaps on reproductive toxicity and repeated dose toxicity.

The eMSCA analysed the read-across justification applying the ECHA Read-Across Assessement Framework (RAAF) guidance. The eMSCA found the proposed read-across justification incompliant with several points of the RAAF. Therefore, the proposed read-across adaptation was rejected by the eMSCA. Rejection of the applied read-across leads to data gaps on standard information regarding repeated dose toxicity and reproductive toxicity for the registered substance.

There is a continued concern for reproductive toxicity and endocrine disruption. No conclusion can be reached for these endpoints due to data gaps in the standard information on reproductive toxicity and repeated dose toxicity in the registration of this substance.

In order to retrieve the missing standard information, the eMSCA has filed a hand-over-document to ECHA to request the initiation of a compliance check on the end-points of repeated dose toxicity and reproductive toxicity.

Further evaluation of exposure awaits the outcome of evaluation of the information to be provided under the requested compliance check.

The end-point of concern for PBT was clarified in an PBT asessement in which DTDP was concluded not to be a PBT or vPvB substance (ECHA, 2019).

5.2. Other actions

There is a continued concern for reproductive toxicity and endocrine disruption of sex- and thyroid hormones. No conclusion can be reached on these endpoints due to data gaps in the standard information on repeated dose toxicity and reproductive toxicity in the registration of this substance and an incompliant read across justification.

The missing standard information requirement data are expected to allow to evaluate and conclude on the two hazard endpoints raised under substance evaluation. Therefore, a Compliance Check is requested by the eMSCA to obtain the missing standard information and the substance evaluation is concluded at this point.

If warranted by the information provided as a results of the Compliance Check decision, elaboration of a RMOA might be considered.
Should the testing provided as an outcome of the Compliance Check decision not allow for conclusion on end-points of reproductive toxicity and endocrine disruption raised by the Danish EPA in the substance evaluation process, but indicate that further data are needed to clarify the concerns raised under SEv, initiation of a new SEv could be envisaged to conclude whether further regulatory action is needed for this substance.

Currently, no regulatory follow-up in foreseen at EU-level. However, conclusion on possible regulatory follow-up awaits the results of the compliance check.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Initiate Compliance Check	2021	ECHA
Possible RMOA	tbd	DK
Possible subsequent substance evaluation	tbd	DK

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich (DTDP, EC number 271-089-3) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (reproductive toxicity evaluated only)
- Exposure/Lack of exposure assessment
- Lack of risk characterisation ratio (RCR)
- High (aggregated) tonnage

During the evaluation two additional end-points of concern were identified:

- Endocrine disruption
- PBT/vPvB

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Suspected CMR (reproductive toxicity evaluated only)	Concern unresolved. Continued concern based on information from structurally similar substances. Read-across applied by REG to fill in data gaps not acceptable. No conclusion can be reached due to data gaps in standard information. Compliance check requested.
Exposure/Lack of exposure assessment	Concern unresolved. Evaluation awaits the outcome of the hazard assessment after compliance check.
Lack of RCR	Concern unresolved. Evaluation awaits the outcome of the hazard assessment after compliance check.
High (aggregated) tonnage	Concern unresolved. Evaluation awaits the outcome of the hazard assessment after compliance check.
Endocrine Disruption	Concern unresolved. Continued concern based on information from structurally similar substances. No conclusion can be reached due to data gaps in standard information. Compliance check requested.
PBT/vPvB	Concern refuted. The registered substance is concluded not to be a PBT or vPvB substance.

7.2. Procedure

The Substance DTDP was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014 due to initial grounds for concern relating to Human health/Supected CMR (reproductive toxicity); Exposure/Lack of exposure assessment, Lack of risk characterisation ratio, High (aggregated) tonnage. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of Denmark was appointed to carry out the evaluation.

In the course of the evaluation, the eMSCA identified additional concerns regarding PBT/vPvB and endocrine disruption, i.e. disruption of sex- and thyroid hormones.

The eMSCA reviewed available data in order to evaluate whether the concerns for reproductive toxicity, endocrine disruption and PBT/vBvB and on exposure could be clarified.

No studies on reproductive toxicity, repeated dose toxicity or endocrine disruption had been performed with the Substance. The Registrant proposed to use read-across from similar substances to fill in the data gaps on reproductive toxicity and repeated dose toxicity.

Based on the evaluation of the available information a draft decision was prepared by the eMSCA and sent through ECHA to the registration on 25 April 2015, asking for further information on the identify of the source and target substances used in the proposed read across.

The registrants comments were received June 2015.

The eMSCA analysed the read across justification proposed by the registrants applying the ECHA Read-Across Assessement Framework (RAAF) guidance. Interaction with the registrants was taken into account.

This evaluation concluded that the read across does not fulfil the criteria of the RAAF. Thus, there are standard information gaps on the end-points of repeated dose toxicity and on reproductive toxicity in the registration.

The eMSCA has consequently filed a Hand-over-Document requesting ECHA to launch a compliance check in order to retrieve the missing standard information.

The eMSCA further decided to conclude the substance evaluation with the present conclusion report not requesting further information.

The end-point of concern on exposure and risk characterisation was not addressed in this document, as it depends on the conclusion of hazard assessment and therefore its evaluation awaits the outcome of the Compliance Check.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich
EC number:	271-089-3
CAS number:	68515-47-9
Index number in Annex VI of the CLP Regulation:	No annex VI entry
Molecular formula:	C34H58O4 (representative constituent)
Molecular weight range:	530.8219
Synonyms:	Diisotridecyl phthalate, DiTP, DiTDP, DTDP

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☐ x UVCB

Structural formula:
Not applicable, as the substance is an UVCB.

Multiconstituent/UVCB substance/others

DTDP is a di-ester of phthalic anhydride and isotridecyl alcohol. It is a high purity di-ester (≥ 99.3 % (w/w)). The Registrant categorizes the registered substance as a multi-constituent substance in the CSR. However, it is referred to as an UVCB in other documents in the registration dossier. Based on the complexity and lack of knowledge on the constituents, the registered substance is here considered an UVCB.

According to the Registrant, it is not possible to assess branching directly. This is further discussed in the IUCLID registration (section 1.4) document "DTDP compositional information_2015": "*Due to the complexity of DTDP, with the presence of over 3000 isomers all present with boiling ranges very close to each other, analytical techniques (beyond GC, GC-MS, and NMR) are not yet available allowing the precise determination of the specific structure of each of these many isomers.*

Information about the exact composition of the registered substance is insufficient. Some information has been provided by the Registrant upon request from the eMSCA, but detailed specifications on branching are lacking.

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid Viscious Colour: 30 (Pt/Co) (Max 50) scale - Clear, colourless Odour: odourless
Vapour pressure	Value used for CSA: 10 Pa at 423.15 K Vapor pressure for Di-isotridecyl phthalate is 0.0000000363 Pa at 25 degrees C and below 0.01 Kpa at 150 degrees C.
Water solubility	Water solubility for Di-isotridecyl phthalate is 0.00000007 mg/L at 25 degrees C
Partition coefficient n-octanol/water (Log Kow)	Log Kow (Pow) for Di-isotridecyl phthalate is estimated at 12.06 at 25 degrees C.
Flammability	Value used for CSA: non flammable Di-isotridecyl phthalate has a very low degree of flammability
Explosive properties	Value used for CSA: non explosive Di-isotridecyl phthalate does not have explosion limits under standard conditions According to Reach Annex VII end point 7.11, the study does not need to be conducted if there are no chemical groups associated with explosive properties present in the molecule. This is the case for this substance.
Oxidising properties	Value used for CSA: Oxidising: no. Di-isotridecyl phthalate has no oxidizing properties.
Granulometry	Not relevant In accordance with REACH chapter R.7A Endpoint Specific Guidance, specifically R.7.1.14.1 Information requirments on granulometry, the granulometry study does not need to be conducted as the substance is marketed or used in a non solid or granular form.

Stability in organic solvents and identity of relevant degradation products	Di-isotridecyl phthalate is stable in organic solvents.
Dissociation constant	In accordance with REACH Chapter R.7A Endpoint Specific Guidance, specifically R.7.1.17.1 Information Requirements on Dissociation Constant, if the substance cannot dissociate due to a lack of relevant functional groups, the dissociation constant is irrelevant. Di-isotridecyl phthalate does not contain functional groups subject to dissociation, consequently a study is not justified.
Melting/freezing point	Value used for CSA: 237 K at 101 325 Pa Pour point for Di-isotridecyl phthalate is below -36 degrees C. Pour point is the measurement closest to freezing point and is defined as the lowest temperature at which a sample will continue to flow when cooled under specified conditions. Jayflex DTDP will not freeze at low temperature.
Boiling point	Value used for CSA: 785 K at 101 325 Pa Boiling point for Di-isotridecyl alcohol is above 400 degrees C. (> 673.15 K). Acording tot USEPA studies the boiling point for Di-isotridecyl alcohols is 512 º C.
Surface tension	Surface tension for Di-isotridecyl phthalate is 30.9 mN/m at 20 Degrees C.
Flash point	Value used for CSA: 547 K at 101 325 Pa Flash point for Di-isotridecyl phthalate is 274 degrees C at 1013.25 hPa
Self ignition temperature	Value used for CSA: 678 K at 101 325 Pa Autoflammability / Self-ignition temperature for Di-isotridecyl phthalate is 405 degrees C at 101325 Pa Autoflammability / Self-ignition temperature for Di-isotridecyl phthalate 678 kelvin at 101325 Pa.
Viscosity	Di-isotridecyl phthalate viscosity is 331 mPa.s at 20 degrees C. 338 mm²/s (static) at 20º C. - 338 cSt 84 mm²/s (static) at 40º C. - 84 cSt

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

No information available on production of articles covered by the specified use(s).

Table 7

USES	Use(s)
Uses as intermediate	This substance has an industrial use resulting in manufacture of another substance
Formulation	This substance is used in the following products: laboratory chemicals, adhesives and sealants, fuels, hydraulic fluids, inks and toners, lubricants and greases, metal working fluids, polishes and waxes, polymers and cosmetics and personal care products. (use of intermediates). Release to the environment of this substance can occur from industrial use: formulation of mixtures and formulation in materials.
Uses at industrial sites	DTDP is used primarily to impart flexibility in polyvinyl chloride (PVC) resins. DTDP applications can include wire and cable insulation (automotive cables), and automotive upholstery. Articles made with DTDP can also be used in construction. Products: polymers, lubricants and greases, hydraulic fluids, adhesives and sealants, inks and toners, metal working fluids and polishes and waxes. Manufacture of: machinery and vehicles, plastic products, rubber products and electrical, electronic and optical equipment. Activities or processes at workplace: transfer of chemicals, transfer of substance into small containers, closed, continuous processes with occasional controlled exposure, closed batch processing in synthesis or formulation, batch processing in synthesis or formulation with opportunity for exposure, mixing in open batch processes, production of mixtures or articles by tabletting, compression, extrusion or pelletisation and closed processes with no likelihood of exposure. Release to the environment of this substance can occur from industrial use: in the production of articles, of substances in closed systems with minimal release and in processing aids at industrial sites.
Uses by professional workers	Products: adhesives and sealants, fuels, hydraulic fluids and lubricants and greases. Manufacture of: plastic products, electrical, electronic and optical equipment, machinery and vehicles and rubber products. Activities or processes at workplace: transfer of chemicals, transfer of substance into small containers, roller or brushing applications, non-industrial spraying and treatment of articles by dipping and pouring. Other release to the environment of this substance is likely to occur from: indoor use in close systems with minimal release (e.g. cooling liquids in refrigerators, oil-based electric heaters), outdoor use in close systems with minimal release (e.g. hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids), indoor use as processing aid and outdoor use.
Consumer Uses	This substance is used in the following products: cosmetics and personal care products. Other release to the environment of this substance is likely to occur from: indoor use as processing aid.
Article service life	Release to the environment of this substance can occur from industrial use: of articles where the substances are not intended

	to be released and where the conditions of use do not promote release. Other release to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment). This substance can be found in complex articles, with no release intended: vehicles and machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines). This substance can be found in products with material based on: rubber (e.g. tyres, shoes, toys) and plastic (e.g. food packaging and storage, toys, mobile phones).

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonised classification for the Substance.

7.6.2. Self-classification

The Substance is not classified in the registration dossier.

One hundred and 10 notifiers do not classify the substance, whilst one notifiers self-classifies DTDP as Aquatic Chronic 2; H411 (toxic to aquatic life with long lasting effects).

7.7. Environmental fate properties

The Substance DTDP has been screened for its potential PBT properties since the substance fulfills some of the PBT screening criteria as specified in REACH, Annex XIII, 2. In that regard the PBT expert group was consulted on the 8th PBT meeting in December 2014. The expert group generally supported the conclusion that DTDP is not persistent (P) and bioaccumulative (B) or very persistent (vP) and very bioaccumulative (vB). The potential of DTDP for fulfilling the toxicity criterion (T) was not discussed at the meeting.

QSAR estimates have been used as supporting information for some environmental fate endpoints derived from a representative structure. The structure used for the QSAR calculations has a C13 backbone with some branching. This structure has been chosen since DTDP is predominantly composed of C13 alkyl side chains and since it was not possible to identify a "worst" case constituent based on available information. It should be noted that many of the model estimates are outside the applicability domain of the applied models due to the high log Kow of the constituents in DTDP. Hence, the model calculations for these properties are included as supporting information only and due to the general uncertainty in using these QSAR estimates for highly hydrophobic substances it was not considered necessary to extend the QSAR analysis to include all potential constituents in the registered substance.

7.7.1. Identity and composition of degradation products/metabolites relevant for the PBT assessment

The ester bonds in each of the side chains are prone to ester hydrolysis to form the monoester phthalate and corresponding alcohol. The monoester phthalate can subsequently be further degraded by a number of different routes depending on the conditions.

The microbial metabolism simulator in the OECD QSAR Application Toolbox has been used to identify potential degradation products for one representative C13 structure (C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCCCC)cccc1)OCCCC(C)CC(C)CCCCC).

This simulator predicts a decline in hydrophobicity of degradation products compared to the parent chemical due to attack on the ester bond and/or hydroxylation (a total of 183 degradation products have been estimated by the simulator – quantity and likelihood of formation is not reported) – see Annex 2. A decline in hydrophobicity and molecular dimensions compared to the parent compound could lead to higher bioavailability of the degradation products (Lipinski rule of five predicts that the parent compound is not bioavailable) and hence, potentially to higher toxicity and bioaccumulation potential.

Therefore, a monoester of the representative parent compound has been included in this assessment and is presented below. The alkyl side chain of the mono phthalate esters will consist of C11 to C14. A mono phthalate ester with branched C13 side chain has been chosen as representative for further analysis.

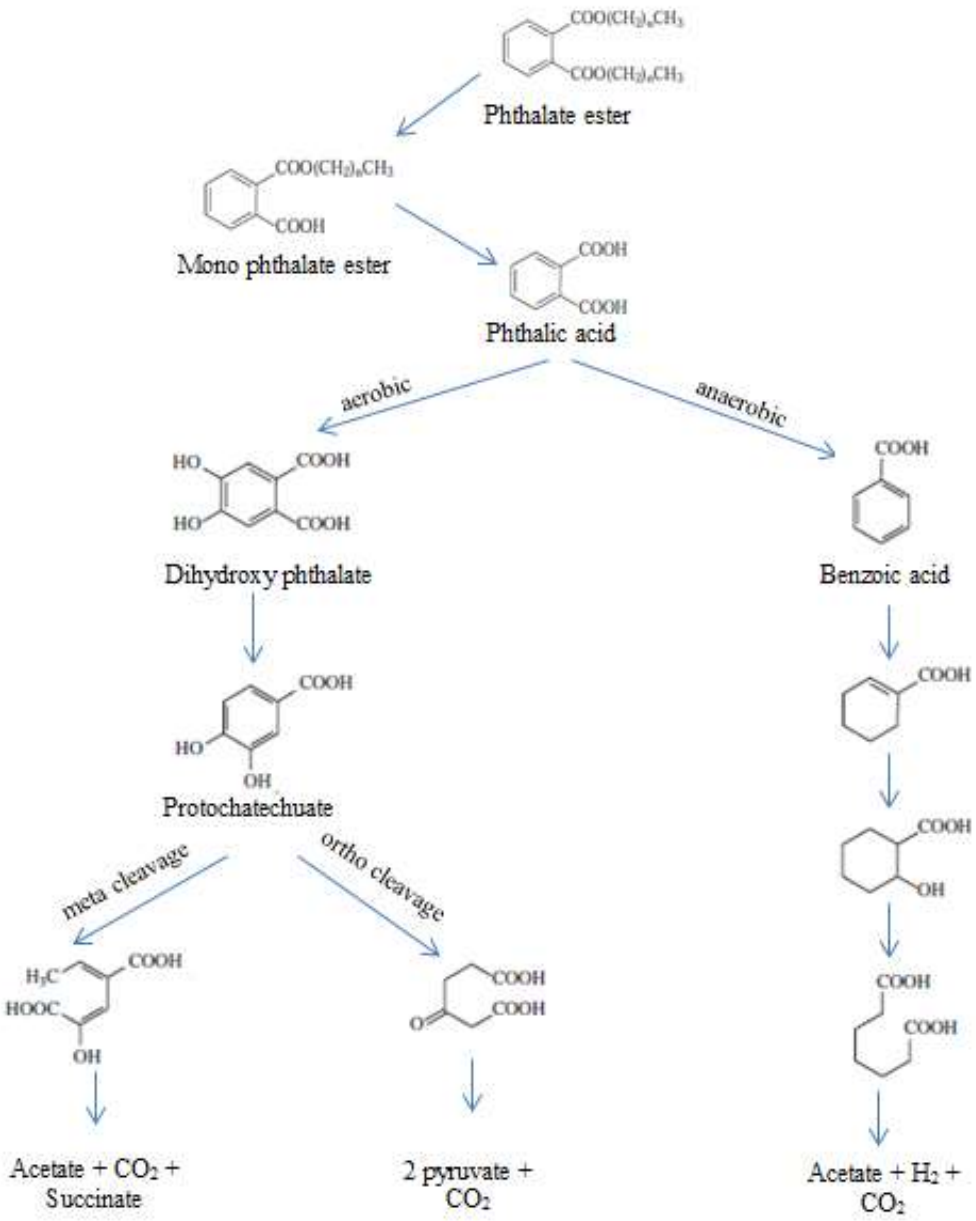
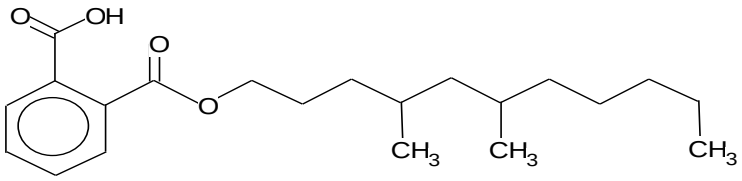


Figure 1. General biodegradation pathway for phthalate esters in the environment. For more information see Staples *et al. (1997); Liang* et al*. (2008) & Vamsee-Krishna & Phale (2008).*

Table 8

EC number:	N.A.
EC name:	N.A.
SMILES:	C(=O)(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)ccccc1
CAS number (in the EC inventory):	N.A.
CAS number:	N.A.
CAS name:	N.A.
IUPAC name:	N.A.
Index number in Annex VI of the CLP Regulation	N.A.
Molecular formula:	$C_{21}H_{32}O_4$
Molecular weight range:	348.5
Synonyms:	N.A.

Structural formula:



Indication of the process, organism and/or organ in which the formation takes place: Degradation of di-phthalate esters to mono phthalate esters is a well-known process and is generally believed to be the first step in the degradation pathway of phthalates in the environment under both aerobic and anaerobic conditions (Staples *et al.* 1997). This is also supported by the metabolic site predictor MetaPrint 2D (Figure 2) which predicts that reaction at the ester bonds is the most likely metabolism pathway for the representative structure.

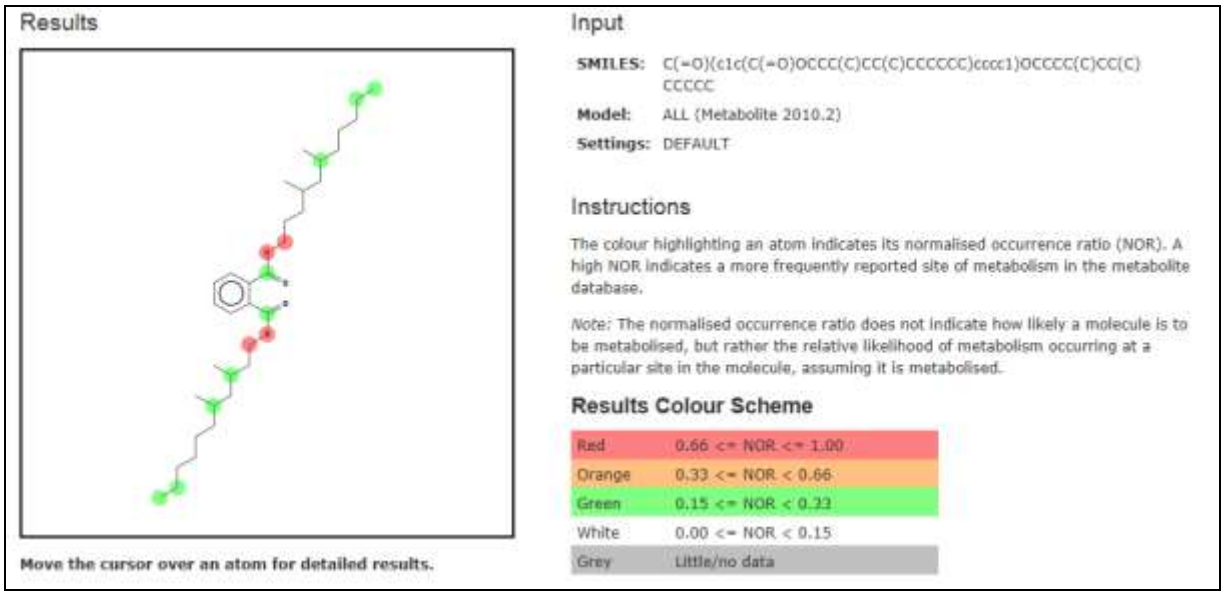


Figure 2: Screen dump from MetaPrint 2D

7.7.2. Degradation

DTDP is not expected to undergo significant abiotic degradation (based on predicted information and distribution modelling). The major route of degradation is therefore expected to be biotic.

DTDP is *not readily biodegradable*. However, when applying expert judgement and taking all available information into account it seems unlikely that the substance will persist in the environment under most environmental conditions (see in particular above the *-marked pieces of information). The rate of biodegradation may, however, be rather low due to strong sorption potential (high hydrophobicity) which may make the availability of the substance low to degrading microorganisms.

The degradation product (representative mono phthalate ester) is predicted to be readily biodegradable. This is further supported by test data on a structural analogue.

The eMSCA concludes that this degradation product does *not* meet the P criterion.

7.7.2.1. Abiotic degradation

7.7.2.1.1. Hydrolysis

Table 9

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
Calculated half-life:	Calculated half-life:
pH 7 = 3.4 years pH 8 = 125.2 days	pH 7 = 6.9 years pH 8 = 250.4 days
Hydrowin (v.1.67)	Hydrowin (v.2.00)
Calculation SMILES: O=C(c1ccccc1C(=O)OCCCCC(C)CCCCC(C)C)OCCC(C)CCC(C)CCC(C)C	Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)ccccc1

Based on the estimated values provided above hydrolysis is not expected to contribute significantly to the removal of the substance or its representative degradation product from the environment. Hydrowin (v.2.00) does not have a well-defined applicability domain and no specified applicability domain for log Kow. However, the model calculations for DTDP and its degradation product are judged to be within the applicability domain of the model which has a total of 124 ester substances in the training set.

7.7.2.1.2. Phototransformation/photolysis

7.7.2.1.2.1. Phototransformation in air

Table 10

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
Calculated half-life:	Calculated half-life:
4 hours	7 hours
AOPWIN (v.1.91)	AOPWIN (v.1.92)
Calculation SMILES: O=C(c1ccccc1C(=O)OCCCCC(C)CCCCC(C)C)OCCC(C)CCC(C)CCC(C)C	Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)ccccc1

Indirect photochemical degradation of the substance as mediated by OH- attack is estimated to have a half-life of 0.33 days or 4 hours based on a 12 -hour sunlight day, a rate of 3.27E-11 cm^3/molecule*sec, and an average OH- concentration of 1.5E6 OH-/cm^3 (AOPWIN v 1.91). A 12-hour day half-life value normalizes degradation to a standard day

light period during which hydroxyl radicals needed for photolysis are generated in the atmosphere. Although the substance has the potential to degrade rapidly by OH- attack, multimedia distribution modeling indicates that the substance is predicted to partition negligibly (0.1%) to the air compartment because it has a low vapor pressure (0.000000036 Pa) and a relatively short atmospheric oxidation half-life (4 hours). Therefore, this process is unlikely to contribute significantly to the loss of the substance from the environment (cited from registration dossier at ECHA website).

AOPWIN does not have a well-defined applicability domain and no specified applicability domain for log Kow.

7.7.2.1.2.2. Phototransformation in water

Direct photolysis will not contribute to the degradation of the parent compound in the aquatic environment because it does not absorb light at wavelengths >290 nm, i.e. the range that contribute to this process (cited from registration dossier at ECHA webpage).

No information is available for the degradation product.

7.7.2.1.2.3. Phototransformation in soil

Direct photolysis will not contribute to the degradation of the parent compound in terrestrial environments because it does not absorb light at wavelengths >290 nm, i.e. the range that contribute to this process (cited from registration dossier at ECHA webpage).

No information is available for the degradation product.

7.7.2.2. Biodegradation

7.7.2.2.1. Biodegradation in water

7.7.2.2.1.1. Estimated data

Table 11

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
Overall result: Not readily biodegradable Individual models: Biowin 1: Biodegrades fast (0.843) Biowin 2: Biodegrades fast (0.974) Biowin 3: Weeks to Months (2.31) Biowin 4: Days to weeks (3.54) Biowin 5: Not readily degradable (0.295) Biowin 6: Not readily degradable (0.145) Biowin 7: Does not biodegrade fast (-0.224) Biowin (v.4.10)	Overall result: Readily biodegradable Individual models: Biowin 1: Biodegrades fast (1.04) Biowin 2: Biodegrades fast (0.998) Biowin 3: Weeks (2.96) Biowin 4: Days (3.85) Biowin 5: Readily degradable (0.724) Biowin 6: Readily degradable (0.756) Biowin 7: Does not biodegrade fast (0.212) Biowin (v.4.10)
Calculation SMILES: O=C(c1ccccc1C(=O)OCCCCC(C)CCCCC(C)C)OCCC(C)CCC(C)CCC(C)C	Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)cccc1

The Biowin models do not have a well-defined applicability domain and no specifications of the applicability domain for log Kow. The fragments in both DIUP and the degradation product are well represented in the training sets of the various Biowin models and the estimates are judged to be reliable as supporting information.

In relation to screening criteria for persistency one of the following conditions has to be met to be designated "screening P":

1. Biowin 2: does not biodegrade fast (probability <0.5) and Biowin 3: ultimate biodegradation time frame ≥months (probability <2.2)
2. Biowing 6: does not biodegrade fast (probability <0.5) and Biowin 3: ultimate biodegradation time frame ≥months (probability <2.2)

Neither the parent compound nor the degradation product fulfils the screening criteria for P with regard to Biowin predictions.

According to the Biowin models the ester fragments are the quantitative most important molecular feature that contributes with a positive coefficient in the biodegradation calculations. This is in agreement with the general notion that enzymatic attack on the ester bonds is the primary degradation pathway of the substance. Since the ester bonds are placed close to the aromatic ring in the molecule, the length of the aliphatic chains of the different constituents (from C11 to C14) is not expected to play a major role with regard to biodegradation potential. However, longer aliphatic side chains will lead to greater hydrophobicity and thereby a higher potential for sorption to particular matter. This can result in lower bioavailability for organisms including degrading microorganisms.

7.7.2.2.1.2. Screening tests

A number of biodegradation studies (guideline and non-guideline) conducted on the registered substance, individual constituents, and a mono phthalate ester degradation product are presented in the registration dossier.

Screening tests for DTDP (UVCB)

Key study: An extended OECD TG 301 F (Ready Biodegradability: Manometric Respirometry Test) has been conducted with the registered substances (CAS RN 68515-47-9). Biodegradation was based on oxygen consumption and was measured at day 27, 28, 47, 53 and 56. The initial test substance concentration was 52 mg/l and the test was conducted with non-adapted activated sludge. Benzoic acid was used as reference substance.

Table 12

Day	27	28	47	53	56
% Degradation (O_2 consumption)	10.6	12.8	51.3	60	62.7

Reliability of the test: No further details than those cited above are available in the registration dossier and the study has not been published. Hence, it is difficult to check the validity of the study which has been rated as Klimisch 1 by the registrant. Important details are missing from the robust study summary such as the composition of the test substance, further specifications on the test setup, degradability of the reference substance, etc. However, the study follows an OECD test guideline (although not GLP) and the available information does not reveal issues that indicate low reliability. Therefore, the reliability of the study is assessed to be adequate for the purpose of this PBT assessment. It could be considered if the study reports should be requested.

Conclusion: The registered substance was *not readily biodegradable* (12.8 % degradation in 28 days, O_2 consumption, non-adapted sludge). The substance reached 63 % ThOD degradation after 56 days, i.e. the substance was completely mineralized. The percentage degradation in this study is quite low in comparison with observations from other phthalate esters (see later sections).

Supporting study: A Shake Flask Die-away Test (EPA OPPTS 835.3170) has been conducted with the registered substance (CAS RN 68515-47-9). The test was conducted with non-adapted acclimated inoculum and an initial test substance concentration of 20 mg/l. No reference substances were included.

Conclusion: 37 % ThOD was reached after 28 days based on CO_2 evolution while >50 % ThOD was recorded based on test material analysis.

Screening tests for individual constituents in the registered substance

Three screening studies are reported for constituents. However, two of these studies are based on adapted test media and are not further analysed here.

Key study: A biodegradability study has been conducted following a draft ISO guideline: BOD Test for Insoluble Substances. Only a trade name of the tested substance "Vestinol TD" is available in the registration dossier at the ECHA website. However, according to searches on the Internet, this trade name is a synonym for Diisotridecyl phthalate, CAS RN 27253-26-5, which is also reported as a C13 constituent in the registered substance subject to this PBT assessment.

The inoculum consisted of non-adapted, activated sludge which was prepared predominantly from a domestic sewage plant. The initial concentration of the test material was 6.9 to 7.2 mg/l and solubilising agents were not used. The test temperature ranged from 20.5 to 24.0 °C and the pH was 7.4.

The test was performed with 3 test vessels and 4 inoculum blanks. Samples were taken once a week on days 7, 14, 21 and 28. Diethylene glycol was used as reference substance.

Table 13

		% degradation at sampling time			
	Vessel No.	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Test substance	1	6	30	62	74
	2	-1	28	55	66
	3	1	30	64	73
	mean	**2**	**28**	**60**	**71**
Reference substance	1	53	75	81	84
	2	56	82	88	90
	3	56	76	83	84
	mean	**55**	**78**	**84**	**86**

Reliability of the test: The test is conducted according to a pre-guideline protocol but appears to be well conducted and is well described in the robust study summary. Furthermore, it is performed with GLP compliance. The remaining uncertainty relates to the identity of the test substance which is not well described in the robust study summary.

Conclusion: The study reports full mineralisation (71 % ThOD) after 28 days but without meeting the 10 day window.

Screening tests for degradation products

A single screening test (OECD TG 301B – CO_2 evolution test, GLP) is reported in the registration dossier as a supporting study, conducted with a mono phthalate ester with a slightly shorter alkyl side chain (C8 – C10) compared to the degradation product of the registered substance (C11 – C14). A unique identifier of the tested material such as CAS or EC number is not available but the substance is described as mono-n-octyl/n-decyl-phthalate with approximately a 1:1 distribution ratio between C8 and C10. The purity of the test substance was between 92 and 94 % with the remaining impurities composed of the diester, and the phthalic acid and C8 anols used in the esterification process.

The test was conducted with non-adapted activated sludge from domestic sources. No further information is available on the test design in the robust study summary.

Conclusion: This C8/C10 degradation product reached 90 % ThOD after 28 days (based on CO_2 evolution), and is hence readily biodegradable.

Screening tests for other phthalate esters

An overview of screening tests conducted with a number of C1-C13 phthalate esters are provided in Annex 1. Please note that the information is taken from the different REACH registration dossiers and has not been evaluated for reliability. Only key studies are included.

Far the majority of the conducted tests results in readily biodegradability, but there is a weak tendency for a slightly slower degradation for the long alkyl chain phthalate esters.

7.7.2.2.1.3. Simulation tests (water and sediments)

Guideline studies that simulate degradation under environmentally relevant conditions are not available for the DTDP.

Studies on degradation products

A non-guideline study on degradation of mono-alkyl phthalate esters is available in the public literature and is also cited in the registration dossier (Otton *et al*., 2008) measured the biodegradation kinetics in marine and freshwater sediments of eight mono phthalate esters with alkyl chain lengths ranging from C2 to C10. The higher (C9 and C10) alkylated substances in this study are similar to the mono phthalate ester degradation products of the registered substance which have alkyl chains ranging from C11 to C14.

The marine sediment samples were collected from two locations in an urbanized marine inlet in Vancouver and the freshwater sediment samples were collected from Buntzen Lake north of the city of Port Moody. The organic carbon content was 2.9 % and 10.8 % for the marine and freshwater sediments, respectively. The number of culturable bacteria was high in both sediments ($>10^8$/g sediment, wet weight). Samples from autoclaved sediment were used to determine loss of the substances by other processes than biodegradation.

The sediments were spiked with the mono phthalate ester to a final concentration of 2 µg/g sediment (wet weight) in triplicate samples. The spiked sediments were incubated at a temperature of 22 ± 1 °C for eight mono phthalate esters in marine sediments and for four in freshwater sediments. In addition, 5 of the substances were incubated at a temperature of 5 ± 1 °C in marine sediments.

The vials were incubated in the dark to avoid photolysis. The proportion of headspace air to sediment ratio was 4.5:1 at the beginning of the incubation. The sediments were not agitated or actively oxygenated during the incubations except when removing subsamples.

The kinetics ($t_{½}$) was determined from linear regression of the slope after the lag phase on a plot of the log substance concentration versus time. The lag phase was determined as the period of time were the concentration was <10 % of the concentration in the autoclaved control groups.

Chemical analysis was performed with GC/MS. Radiolabelling was not used in this study.

Results: The degradation half-lifes for the various mono phthalate esters can be seen in Table 14 below. The alkyl chain length of the mono phthalate ester did not appear to influence the degradation half-life in this study. At a temperature of 22 °C the half-life was below 40 hours for all of the mono phthalates in both marine and freshwater sediments. The half-lifes were approximately one order of magnitude longer at a temperature of 5 °C. However, they were still relatively rapidly degraded at this lower temperature with half-lifes below 10 days.

Validity of the test: It is difficult to compare this test with a guideline degradation simulation study. The test identifies only primary degradation of the parent compound (which in this case is actually degradation products of the di-phthalate esters). However, for these compounds, it is expected that initial degradation will result in degradation products with faster degradation rates compared to the parent compounds. Hence, the results of the test are still useful despite the fact that degradation kinetics is not followed all the way through to complete mineralization.

Conclusion: The mono phthalate esters displayed a rapid primary degradation half-life in marine and freshwater sediments under the conditions of the study.

Table 14. Primary degradation half-lifes ($t_{½}$) for various mono phthalate esters (from Otton et al. 2008)

Chemical	Alkyl chain length	Log Kow	$t_{½}$ (h) 22 °C	Lag phase (h) range	$t_{½}$ (h) 5 °C
Marine sediments					
Mono-ethyl phthalate	C2	1.86	35 ± 10	20-40	
Mono-butyl phthalate	C4	2.84	16 ± 2	24-50	150 ± 12
Mono-benzyl phthalate	C5	3.07	26 ± 12	18-50	188 ± 78
Mono-iso-hexyl phthalate	C6	3.85	26 ± 4	22-33	
Mono-ethylhexyl phthalate	C8	4.73	26 ± 9	18-50	215 ± 13
Mono-n-octyl phthalate	C8	5.22	18 ± 4	18-50	225 ± 50
Mono-iso-nonyl phthalate	C9	5.30	23 ± 5	20-70	200 ± 44
Mono-iso-decyl phthalate	C10	5.79	25 ± 6	22-30	
Freshwater sediments					
Mono-butyl phthalate	C4	2.84	30 ± 16	4	
Mono-benzyl phthalate	C5	3.07	34 ± 10	4	
Mono-ethylhexyl phthalate	C8	4.73	29 ± 9	50-140	
Mono-n-octyl phthalate		5.22	26 ± 7	50-70	
Mono-iso-nonyl phthalate		5.30	39 ± 6	4	

7.7.2.2.2. Biodegradation in soil

No information is available for the Substance. Information from a structural analogue with shorter alkyl side chains is available in the registration dossier. However, this study is not a simulation degradation study but an earthworm toxicity test (OECD TG 222) which is used to estimate the loss rate of the C9 phthalate DINP in soil over a 56-day period. According to the registrants the DT50 is 51 days based on a decrease of DINP from 982 to 441 mg/kg soil (wet weight).

7.7.3. Environmental distribution

7.7.3.1. Adsorption/desorption

Table 15

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
Experimental result	Calculated
Log Koc = 6.06	Log Koc = 3.9
EPA OTS 796.2750. Three sediments were used: EPA 8 (0.15% organic carbon), EPA 18 (0.66% organic carbon), and EPA 21 (1.88% organic carbon).	KOCWIN (v.2.00) Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)cccc1

The KOCWIN model does not have a specified applicability domain for log Kow. However, there is a specification of a maximum molecular weight of 504. The degradation product is within this domain.

Conclusion: 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich has high sorption potential.

7.7.3.2. Volatilisation

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
Calculated Henry's law constant H (unit less)	Calculated Henry's law constant H (unit less)
$8.21 \cdot 10^{-3}$	$8.56 \cdot 10^{-7}$
HenryWin, bond estimate (v.3.20)	HenryWin, bond estimate (v.3.20)
Calculation SMILES: O=C(c1ccccc1C(=O)OCCCCC(C)CCCCC(C)C)OCCC(C)CCC(C)CCC(C)C	Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)ccccc1

In the REACH registration, the same model calculations for the substance have been performed with manual input on vapor pressure and water solubility which results in a Henry's law constant of 275 Pa m^3/mol.

The following specifications are given for the applicability domain of the model:

Molecular Weight:

Minimum: 26.04

Maximum: 451.47

Henry's law constant (atm-m3/mole):

Minimum: $5.65x10^{-14}$

Maximum: $2.03x10^{+1}$

DTDP is outside the applicability domain for molecular weight whereas the degradation product is inside. This, however, does not influence the overall conclusion that DTDP has limited volatilization potential.

Conclusion: 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich has limited volatilization potential.

7.7.3.3. Distribution modelling

The distribution of 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich has been modeled with the EPIWIN 4.1. McKay Level III model using manual input parameters for log Kow, water solubility, VP and MP (as specified in the REACH registration dossier).

If equal and continuous release of the substance to soil, water and air is assumed the model predicts distribution to soil (60 %) and sediment (38 %) with limited distribution to water (2 %).

7.7.4. Bioaccumulation

7.7.4.1. Aquatic bioaccumulation

One bioconcentration study with dietary exposure in fish is available for the Substance (CAS RN 68515-47-9). In addition, the REACH registration includes a number of studies reported on structural analogues (see also Annex 1). Finally, calculated values are reported.

Calculated bioaccumulation values

1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	Degradation product (representative mono phthalate ester)
BCF (regression based): 13.9	BCF (regression based): 56.2
BCF (Arnot-Gobas, upper trophic level, including biotransf): 1	BCF (Arnot-Gobas, upper trophic level, including biotransf): 182
BCF (Arnot-Gobas, upper trophic level,	BCF (Arnot-Gobas, upper trophic level,

excluding biotransf): 1	excluding biotransf): 10,420
BAF (Arnot-Gobas, upper trophic level, including biotransf): 2.6	BAF (Arnot-Gobas, upper trophic level, including biotransf): 430
BCFBAF (v.3.01)	BCFBAF (v.3.01)
Calculation SMILES: O=C(c1ccccc1C(=O)OCCCCC(C)CCCCC(C)C)OCCC(C)CCC(C)CCC(C)C	Calculation SMILES: O=C(O)c1c(C(=O)OCCCC(C)CC(C)CCCCC)ccccc1

The BCFBAF models predict that the representative constituent of DTDP has no bioaccumulation potential. However, the log Kow is outside the applicability domain of the models and the results should therefore be used with caution.

The registered substance has a log Kow above 10 which is specified in the REACH Guidance Document on PBT Assessment (R.11) as the cut-off point, were substances may be assumed to have aquatic BCF values below the B criterion of 2,000. The BCFBAF models also predict the representative constituent as having no bioaccumulation potential.

The degradation product / metabolite mono phthalate ester is predicted to have a low potential for bioaccumulation except in the Arnot-Gobas model that assumes a biotransformation rate of zero. The Arnot-Gobas models use a calculated whole body primary biotransformation estimate for fish as input in those models that include biotransformation rate estimates. In this equation the ester fragment is the quantitative most important molecular feature that contributes with a negative coefficient in the calculations (meaning it is the most important fragment that reduces the calculated half-life in the fish body).

Experimental aquatic bioaccumulation values are presented below for the registered substance.

Chemical	Experimental result
Registered substance Based on the constituent Di-isotridecyl phthalate ester (C 13)	BCF (calculated) < 1 BMF = 0.004 Elimination half-life: 0.65 days OECD TG 305 with dietary exposure (draft version). Test organism: *Oncorhynchus mykiss*.

Due to the high log Kow and low water solubility, the test was conducted with dietary exposure of Rainbow trout (*Oncorhynchus mykiss*) following the draft OECD TG 305 guideline (non GLP) in 2007. Five fish samples were collected from each tank on day 9 of the uptake phase and four fish samples were collected from each tank on day 1 and 3 of the depuration phase. This is below the minimum specified number of sampling occasions in the OECD TG 305 guideline which is at least 5 occasions during the uptake period and at least 4 occasions during the depuration phase.

The test was conducted in a semi-static exposure system with five to six volume replacements in each test chamber per day. The test substance was added to the test feed in a single batch to achieve a nominal concentration of 500 µg/g. The treated and untreated diets were weighed and fed to the fish as a daily single feeding. After the 9 day exposure phase all fish were fed untreated food for the 3 day depuration period.

The test organism loading at the start of the test was 0.28 grams of fish per liter of dilution water per day. Length and weight measurements were recorded for a subsample at the beginning of the test and also on fish removed at each sampling period. However, these recordings are not provided in the robust study summary and the size and age (e.g. if juvenile or sexually mature fish were used) of the test organisms is therefore unknown. The mean lipid content in the fish was 4.25 %.

The following test conditions are reported:

- Hardness: 96 to 116 mg $CaCO_3$ /l
- Temperature: 13.4 (sd = 0.2)
- pH: 7.4 to 7.5
- Dissolved oxygen: above 60 % ranging from 8.8 to 10
- TOC: 0.234 to 0.743
- Light: diurnal with 16 hours light and 8 hours dark
- Test chambers: 38 l glass aquaria with aeration.
- Radiolabelling: No

A reference substance was not included in the test and hence it has not been demonstrated that the food spiking technique was adequate to ensure maximum homogeneity and bioavailability of the test substance.

The measured concentrations in the feed were 533 mg/kg in the pre-study and 588 mg/kg at day 9. No measured concentrations are provided for the test organisms in the robust study summary.

The following calculated values are reported by the registrant:

- Elimination rate constant: 1.06 µg/g day^{-1}
- Tissue elimination half-life: 0.65 days
- BMF: 0.004 (lipid normalized)
- BCF: <1

Reliability of the test: A number of issues make it very difficult to assess the reliability of the test. There is no information on the concentration of test substance in the sampled test organisms at the different sampling occasions. In combination with the lack of a positive control it puts a question mark to the ability of the test system to achieve adequate bioavailability of the test substance. In addition, there is no information on which equation that has been used to calculate the BCF (a number of different methods exist) and the number of sampling occasions is below the minimum number specified in the guideline. In addition it cannot be documented from the study summary if there was significant fish growth or changes in lipid content during the study. Therefore a Klimisch score of 4 is assigned to the study. Nevertheless, the BMF and elimination rate reported from the study is very low and does indicate that the substance has low bioaccumulation potential. It could be considered if the original study report should be requested.

7.7.4.2. Terrestrial bioaccumulation

No studies are available for the registered substance.

7.7.4.3. Summary and conclusion on bioaccumulation

Based on a dietary study with a constituent of DTDP, QSAR estimates, the high log Kow and considerations of biotransformation rates, eMSCA concludes the substance does not meet the criteria for B or vB.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

For human health, a concern regarding reproductive toxicity was raised initially and an additional concern regarding endocrine disruption of sex- and thyroid hormones were raised during the substance evaluation. No data are available on DTDP to inform about these endpoints (repeated dose toxicity or reproductive toxicity studies).

For repeated dose toxicity, diisodecyl phthalate (DIDP, CAS RN 68515-49-1 or CAS RN 26761-40-0) and diisononyl phthalate (DINP, CAS RN 68515-48-0) are used as read-across substances to provide toxicological information.
For reproductive toxicity, diisodecyl phthalate (DIDP, CAS RN 68515-49-1 and 26761-40-0), is used as a read-across substance to provide toxicological information (key studies). Additionally, supporting studies on ditridecyl phthalate (CAS RN 119-06-2, C13 linear) and C911P (CAS RN 68515-43-5, C9-11 branched and linear) were included regarding toxicity to fertility. Supporting studies on diundecyl phthalate (DUDP, C11 linear), C911P (CAS RN 68515-43-5, C9-11 branched and linear), dioctyl phthalate (CAS RN 117-84-0, C8 linear), ditridecyl phthalate (CAS RN 119-06-2, C13 linear) were included regarding developmental toxicity.

The available information has been reviewed by the eMSCA and it is concluded that there is a continued concern for reproductive toxicity (fertility and developmental toxicity) and endocrine disruption of sex- and thyroid hormones (see also section 7.10 for more detailed information about the evaluation of endocrine disruption).

Further, the read-across provided by the Registrant to fill in the data gaps on repeated dose toxicity and reproductive toxicity has been reviewed and is rejected by the eMSCA. The dossier has therefore several data gaps on standard information requirements.

The eMSCAs concern for reproductive toxicity leading to CORAP nomination and the additional concern for endocrine disruption of DTDP (see also section 7.10) cannot be resolved due to the lack of standard information requirements especially on repeated dose toxicity and reproduction toxicity studies with the registered substances.

7.9.1. Toxicokinetics

No toxicokinetic data on DTDP are available. However, the toxicokinetics of other high molecular weight phthalates, DINP and DIDP, have been studied and are included in the registration. It is suggested by the registrant(s) that these data can be used as read-across information relevant for the evaluation of DTDP.

The eMSCA finds it plausible that toxicokinetics of the registered substance is similar to that of other phthalates. However, the read across proposed by the Registrant has not been verified in detail.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated by the eMSCA.

7.9.3. Sensitisation

Not evaluated by the eMSCA.

7.9.4. Repeated dose toxicity

Repeated dose toxicity was not identified as an area of concern during substance evaluation. However, some repeated dose toxicity studies may in some cases inform about potential reproductive toxicity and endocrine disruption, which have been identified as concerns for DTDP.

No repeated dose toxicity data on DTDP is provided by the registrant, as diisodecyl phthalate (DIDP, CAS RN 68515-49-1 or 26761-40-0) and diisononyl phthalate (DINP, CAS RN 68515-48-0) are used as read-across substances to provide toxicological information.

This use of read-across is rejected by the eMSCA. Detailed information of the rejection is provided in section 7.9.8. Consequently, there is an information gap in the registration dossier for repeated dose toxicity, as further described in section 7.9.4.2.

However, during the substance evaluation, the available information on repeated dose toxicity of source substances was thoroughly reviewed be the eMSCA since it could provide information about potential reproductive toxicity and endocrine disruption of the Substance.

7.9.4.1. Review of repeated dose toxicity data used in eMSCA evaluation of continued concern for effects on reproductive toxicity and endocrine disruption

Three rat studies and a dog study on DIDP were included in the registration dossier. Two of the rat studies (by Barber et al., 1987 and Lake et al., 1991), were also included in the section on fertility of the registration dossier, and are therefore presented in section 7.9.7.1 of this document. The third rat study is presented here together with the dog study.

Table 16: Overview of endpoints relevant for reproductive toxicity and endocrine disruption in two oral repeated dose toxicity studies on the proposed read-across substance DIDP.

Method	Results	Remarks	Reference
Rat (Charles River), n= 10 males and 10 femalesSubchronic (oral:feed) 0.05%, 0.3% and 1% (approximately 35, 200 and 650 mg/kg/d, respectively). Exposure: 13 weeks	Results according to EU risk assessment report: Liver weights and liver/body weight ratios for the high-level males and females were significantly higher than those for the corresponding controls. A minimal increase in thyroid activity was observed at the highest-level dose (the activity was judged to be higher when the follicles were more uniform and smaller in size with a lighter colloid along with a tall cuboidal or columnar epithelium).	2(reliable with restrictions) Evidence form structural analogue Di-isodecyl Phthalate (DIDP)	Unpublished study report, 1968a, cited in EC 2003
dog (Beagle), n=3 male/female subchronic (oral: feed) 0.05, 0.3, 1% (approx. 15, 75 and 300 mg/kg/day) Exposure: 13 weeks (daily) Method: other: not specified	NOAEL: ca. 75 mg/kg bw/day (nominal) (male/female) LOAEL: ca. 265 mg/kg bw/day (nominal) (male/female) (Based on increased absolute and relative liver weights and the presence of swollen vacuolated hepatocytes from the high dose male and female dogs.)	3 (not reliable) supporting study read-across from supporting substance (structural analogue or surrogate) Test material (Common name): Di-isodecyl phthalate	Unpublished study report (1968b). 13-Week Dietary Administration - Dogs Plasticiser (DIDP)

In one of the rat studies with DIDP, a minimal increase in thyroid activity was observed at the highest dose level (the activity was judged to be higher when the follicles were more uniform and smaller in size with a lighter colloid along with a tall cuboidal or columnar epithelium) (Unpublished study report, 1968a, cited in EC 2003). In the EU risk assessment report, it was assumed from the above rat study with DIDP that the NOAEL is 0.3% (about 200 mg/kg/d) based on the fact that the highest dose leads to liver and thyroid effects. It is noted that only relative kidney weight is affected at the 0.3% dose, probably due to a lower body weight. This study indicates possible thyroid disrupting activity of DIDP.

The dog study revealed hepatic effects, whereas no effects on thyroid weights and histology were reported.

No effects were reported in an inhalation study with the structurally related substance DIDP (CAS no 68515-49-1) where Sprague-Dawley rats were exposed a total of 10 days

(5 days exposure, 2 days recovery, 5 days exposure), 6 hours/day to 500 mg/m^3. The study was attributed a liability score of 2. (Unpublished study report, 1981).

No systemic toxicity of DINP was reported in a 6 week dermal study in New Zealand White rabbits at 2.5 ml/kg/day. (Unpublished report).

The observed effect of DIDP on the thyroid in the rat study (Unpublished rerport, 1968a) raise a concern for endocrine disruption and is further discussed in the section 7.10.2.2. on evaluation of concern for thyroid disrupting properties of the registered substance.

7.9.4.2. Data gap on repeated dose toxicity due to rejection of read-across prodivided by the Registrant

As laid out in the previous sections, no repeated dose toxicity data on DTDP is provided by the registrant, as diisodecyl phthalate (DIDP, CAS RN 68515-49-1 or 26761-40-0) and diisononyl phthalate (DINP, CAS RN 68515-48-0) are used as read-across substances to provide toxicological information.

This use of read-across is rejected by the eMSCA. Detailed information of the rejection is provided in section 7.9.8.

Consequently, there is an information gap in the registration dossier for repeated dose toxicity.

7.9.4.2.1. Repeated dose toxicity, 90 days study

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. The registrant has not provided any study record of a sub-chronic toxicity study (90-day) in the dossier for the registered substance. Instead the registrant has sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. The applicant has provided a justification for read across to waive the requirement.

The following studies with dosing by the oral route were provided by the registrant in support of for the proposed read across:

- Oral: 21 days of exposure to Di-isodecyl phthalate (DIDP) in diet where DEHP served as study control (male and female rats, three exposure levels, n = 5/sex and exposure group), (Barber et al 1987) (key study).
- A 90 day oral study on DIDP from the Hazelton Laboratories (1968a) (male and female rats, three exposure levels, n = 10 / sex and group) (supporting study).
- Oral: 28 days of exposure to Di-ethylhexylpthalate (DEHP) (served as control) and DIDP administered in diet (male Fischer 344 rats, 42 days old, five exposure levels, n = 5 / exposure group) (Lake et al., 1991)(supporting study).
- A subchronic toxicity study on DIDP administered in diet (male and female beagle dogs, three exposure levels, n = 3 / sex and exposure group) (Unpublished study report 1968b) (supporting study).

Additional studies included for dermal/inhalation toxicity:

- Dermal: Six weeks dermal toxicity study to 24-hour daily application 5 times/week of di-isononyl phthalate, DINP (68515-48-0) on the abdominal skin (New Zealand White rabbits, two exposure levels) (Unpublished study report, 1969)
- Inhalation: 2 week exposure to DIDP (68515-49-1) by inhalation (male rats, n = 8 exposed, n =6 control, 1 exposure level, 6 hours / day, 5 days /week) (Unpublished study report 1981).

The eMSCA has analysed the read across justification applying the Annex XI point 1.5 elements and the ECHA Read-Across Assessement Framework (RAAF) guidance (see. Section 7.9.8). However, the proposed adaptation of the information requirement is incompliant with several points of the RAAF. due to:

i) insufficient information on identity and concentration of the constituents in target and source substance,
ii) insufficient information with respect to mechanistic explanations on why and how predictions are possible within the group, and
iii) no bridging studies are presented to allow side-by-side comparison of substances.
iv)

Therefore, the proposed adaptation is rejected, and thus, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement for sub-chronic toxicity study (90 day), Annex IX, Section 8.6.2.

In regards to substance evaluation, the 90-day study may provide information to help clarify the concerns for reproductive toxicity and endocrine disruption, e.g. through investigation of effects on the thyroid. Information from the 90-day study may further be used as supportive evidence to trigger the inclusion of the F2, DNT and/or DIT cohorts in the EOGRTS (OECD TG 443), for which a data gap is also identified (see section 7.9.7.1.1).

7.9.5. Mutagenicity

Not evaluated by the eMSCA.

7.9.6. Carcinogenicity

Carcinogencity was not evaluated in the present substance evaluation. However, some carcinogenicity studies may in some cases inform about potential reproductive toxicity and endocrine disruptive effects, which have been identified as concerns for the registered substance.

No data on carcinogenicity of the registered substance, DTDP, is provided by the registrant. Diisodecyl phthalate (DIDP, CAS RN 26761-40-0) is used as a read-across substance to provide toxicological information and a 2-year oral rat study on DIDP (Cho et al., 2008) is included in the registration dossier. According to the ECHA review (ECHA 2013), this study included examination of thyroid histology of DIDP. The incidence of c-cell hyperplasia was increased in females of the two lowest dose groups and reduced in males of the middle dose group. It cannot be concluded whether effects on c-cell hyperplasia are related to thyroid hormone disrupting properties. No long-term study of DIDP was available for the EU risk assessment from 2003 (EC 2003).

The study by Cho et al., 2008 is used in the discussion of possible thyroid disrupting properties of the registered substance, DTDP, in section 7.10.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

The initial concern for reproductive toxicity of DTDP was based on the harmonised classification of structurally similar substances, including 1,2-Benzenedicarboxylic acid, di-C7-11 branched and linear alkyl esters, EC no 271-084-6, CAS RN 68515-42-4 (C7-11P or DHNUP) which was classified as Repr. 1B for developmental effects and Repr. 2 for effects on fertility.

This concern was partly based on a concern for reproductive toxicity of phtalates with a carbon backbone of C7 or below. The registrant has informed the eMSCA that the shortest backbone of the registered substance is C9, but as described in section 7.9.8, this claim has not been substantiated. Furthermore, a concern for reproductive toxicity of substances with longer carbon backbones also remains (see section 7.9.7.1 and 7.9.7.3).

No data on reproductive toxicity of DTDP is provided by the registrant, as diisodecyl phthalate (DIDP, CAS RN 68515-49-1 and 26761-40-0) is used as a read-across substance to provide toxicological information (key studies). Additionally, supporting studies on ditridecyl phthalate (CAS 119-06-2, C13 linear) and C911P (CAS RN 68515-43-5, C9-11 branched and linear) were included regarding toxicity to fertility. Supporting studies on diundecyl phthalate (DUDP, C11 linear), C911P (CAS RN 68515-43-5, C9-11

branched and linear), dioctyl phthalate (CAS 117-84-0, C8 linear), ditridecyl phthalate (CAS RN 119-06-2, C13 linear) were included regarding developmental toxicity. For DIDP, two two-generation studies with oral exposure of rats, two short-term studies investigating testicular atrophy with oral exposure of rats, two prenatal developmental toxicity studies in rats, one prenatal developmental study in mice were presented in the registration dossier, and summary data are publicly available online through ECHAs homepage. No data from study reports were available for review, but published papers were available for the two-generation studies and developmental toxicity studies on DIDP (Hushka et al. 2001, Waterman et al 1999).

This proposed use of read-across is rejected by the eMSCA. Detailed information of the rejection is provided in section 7.9.8. Consequently, there is an information gap in the registration dossier for reproductive toxicity, as further described in section 7.9.7.4.

However, during the substance evaluation, the available information on reproductive toxicity of source substances was thoroughly reviewed be the eMSCA in order to evaluate whether there is a continued concern for reproductive toxicity of the substance under evaluation DTDP.

In addition to summary data from the registration dossier, discussions and conclusions from an ECHA review on DIDP from 2013 are included in the following sections. This review on DIDP includes a targeted evaluation of endpoints related to reproductive development, endocrine disruption of sex hormones and thyroid disrupting effects based on available data from in vivo and in vitro studies. The review builds upon the EU risk assessment of DIDP from 2003 and a previous review by ECHA from 2010. As this comprehensive review by ECHA is given substantial weight, the description of specific studies is focused on studies considered critical for reproductive effects by ECHA or relevant for the evaluation of possible endocrine disrupting effects of DIDP.

The ECHA review discussed a study on effects of DIDP on sperm count and –quality (Kwack et al 2009), a Hershberger study on possible anti-androgenic effects of DIDP (Lee and Koo, 2007), and a study on effects of DIDP on fetal testosterone production and steroid synthesis (Hannas et al., 2012). These studies are also presented and discussed in the following sections.

7.9.7.1. Review of information regarding the concern for effects on fertility

There are no data available on DTDP regarding effects on fertility.

Data on two two-generation studies in rats on DIDP as a read-across substance is presented below (based on data from registration dossier and the published paper by Hushka et al., 2001) together with data from a study on testicular toxicity of DIDP (based on data from registration dossier) as well as a study on the effects of DIDP on sperm count and sperm quality in rats (based on the published paper by Kwack et al., 2009). The registration also includes a combined repeated dose and reproductive/developmental toxicity screening study with another phthalate, CAS RN 119-06-2, which also includes up to 13 carbon atoms in the side chain, but with a different composition.(Japanese Ministry of Health and Welfare, 1997)

Table 17. Summary of some studies used to ealuate the concern for effects on fertility

Method	Results	Remarks	Reference
rat (Sprague-Dawley) male/female, N= 30/sex/group. 2 two-generation studies, equivalent to test method B35 oral: feed In study A 0.2, 0.4, 0.8% were target dietary concentrations	Both studies are presented together: There were no statistically significant differences in male mating, male fertility, female fertility, female fecundity, or female gestational indices between treated and control animals in the P1 or P2 generation. Mean days of gestation and mean litter size and of the treated and control groups were similar. Postnatal survival of F2 offspring was reduced at doses from 0.2% DIDP in both studies leading to an overall NOAEL	Study performed on structural analogue substance: DIDP, CAS RN 68515-49-1 This study is considered reliable without restrictions, score 1.	Hushka LJ, Waterman SJ, Keller LH, Trimmer GW, Freeman JJ, Ambroso JL, Nicolich MJ and McKee RH 2001

(corresponding to 131, 262 and 524 mg/kg bw/day during gestation). In study B the target concentrations were 0.02%, 0.06%, 0.2%, and 0.4% in diet (corresponding to 13, 39, 127 and 254 mg/kg bw/day during gestation) Vehicle: unchanged (no vehicle)	of 0.06% Up to the highest dose tested no overt signs of reproductive toxicity were reported and no effect was observed on fertility parameters. However, males of the P1 generation had significantly increased absolute weights of right cauda epididymis at 0.8 % (slight but NS increase of total epididymis weight in P1 and P2 at 0.8%). In females of the P1 generation, left ovary weights were significantly reduced at the high dose, and in P2 females both right and left ovary weights were significantly reduced at 0.8%. Oestrous cycle length was reduced slightly (<6%) at 0.8% in P1, but not in P2 females. Weights of liver and kidney were reduced in male and female parental animals at all several doses. In offspring, a small (1.2 days) delay in preputial separation in F2 males at 0.4% (high dose of study B) and an increase in age of vaginal patency (2 days) in F1 females at 0.4 and 0.8% (two highest dose of study A) were observed. As these effects were related to a decreased body weight at that age these findings were not considered biologically significant by the registrant. Anogenital distance and nipple retention were assessed in the second study (i.e. doses up to 0.4%). There were no statistically significant differences in F1 or F2 offspring mean PND 0 anogenital distance between treated and control animals of either sex. Nipple retention was similar between treated and control offspring of both sexes.		
rat (Fischer 344) male Investigation of testicular atrophy oral: feed 0.02-0.05-0.1-0.3 and 1% (approximately 25-57-116- 353- 1,287 mg/kg/d) DIDP in diet. Exposure: Exposure period: 28 days (daily)	Results according to EU risk assessment report for DIDP: No testicular atrophy was reported at the highest dose tested 1,287 mg/kg/d for DIDP.	Study performed on structural analogue: DIDP (CAS RN number: 68515-49-1) This study is considered reliable (1).	BIBRA (1990) Lake B, Cook W, Worrell N, Cunninghame M, Evans J, Price R, Young (1991)
rat (Fischer 344) male, n=5. oral: feed Exposure period: 21 days (daily) Doses: 0.3% (304 mg/kg/d (males) and 264	Results according to EU risk assessment report for DIDP: The absolute testis weights of the males given 2.5% DIDP were slightly but significantly lighter than the controls (2.31 g versus 2.59 g in controls). No atrophy was observed histologically. In comparison, DEHP showed marked testis weight reduction and atrophy at the	Test material DIDP (CAS number): 68515-49-1, 99.84% purity This study is considered reliable (1).	BIBRA (1986) Lington A, Gray T, Evans J, Lake B and Moran B (1993) (cited in EC,

mg/kg/d (females)), 1.2% (1,134 mg/kg/d (males) and 1,042 mg/kg/d (females)), 2.5% (2,100 mg/kg/d (males) and 1,972 mg/kg/d (females)).	same dose level. Comparable effects were seen for DEHP and DIDP regarding hepatic effects.		2003)
Rat (SD), juvenile male, n=6 Oral: gavage Exposure: 28 days (PND 35 to 77) Dose: 500 mg/kg bw/day DIDP, CAS RN 26761-40-0. Purity not described. Vehicle: corn oil	NOAEL: Not determined LOAEL: 500 mg/kg bw/day. DIDP did not affect sperm count after a 4-week exposure of juvenile rats at 500 mg/kg bw/day (oral gavage). DIDP did not significantly lower the sperm counts but reduced the motility, straight-line velocity, curvilinear velocity, straightness and linearity of the epididymal sperm motion.	Published in open literature, not discussed in registration dossier. This study is considered reliable with restriction (2), as only one dose group is included. Test material DIDP, CAS RN 26761-40-0.	Kwack et al., 2009
rat (Sprague-Dawley) oral: gavage Doses of 10, 50, and 250 mg/kg/day Vehicle: corn oil Exposure: Males 42 days and females 14 days prior to mating to day 3 of lactation OECD TG 422 (Combine repeat dose and reproductive/developmental toxicity screening)	NOEL (250 mg/kg/day) : Highest dose tested	2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) Test material (CAS number): 119-06-2 No further information available than what is listed in registration dossier.	Japanese Ministry of Health and Welfare (1997)
Rat, Sprague-Dawley, n=28 2-generation reproduction study (OECD TG 416). Doses were 0, 1000, 5000 and 20000 ppm in the diet. After six weeks of treatment, the highest dose was reduced to 10000 ppm. During gestation, the lowest dose group (1000 ppm) corresponded to 66-76 mg/kg/day, the middle dose group (5000 ppm) to 343-379 mg/kg/day and	In the F0 generation, a markedly lower body weight in males of the high dose group complicated the assessment of possible effects of treatment on organ weights. Absolute weights were decreased for adrenals, brain, epididymides, kidneys, prostate (86% of controls), seminal vesicles and spleen, whereas relative weights were increased for epididymides, kidneys, seminal vesicles and testes. Epididymal sperm count and sperm motility were unaffected. Testicular spermatid count was increased in all treatment groups, likely due to an unusually low control level. A few males in all groups exposed to C911P had small testis and/or small epididymis, whereas this was not seen among controls. Histological changes in liver were indicative of hepatotoxicity in both F0 and F1 males and females from the high dose group.	Klimish 1, reliable without restriction. Test material: C911P (CAS no. 68515-43-5)	Unpublished study report (2001) (referred in Willoughby et al., 2000)

the highest dose group (10000 ppm) to 724-787 mg/kg/day (after reduction of dose in high dose group). During lactation, the dose groups corresponded to 118-163, 593-867 and 1329-1760 mg/kg/day, respectively.	In female of the F0 generation, the absolute and relative weight of uterus and cervix was decreased in the highest exposure group and relative weight of female livers was increased down to 5000 ppm of C911P. Slight reductions in absolute ovary weight (11%) and relative ovary weight (8%) in the high dose group were not statistically significant. In dams, a decrease in body weight gain during the first week of gestation was seen in all dose groups in F0 and in the two highest doses in F1. Decreased body weight during lactation was also found in dams in the highest dose group in F0 and the two highest dose groups for F1 generations. A decreased gestation length was seen in the two highest doses in F0 and in the highest dose in F1. Treatment effects were not seen for the oestrous cycle before mating, number of implantation sites, litter size or pup survival. In offspring, a decreased body weight was observed in males and females in F1 generation in the 2 last weeks of lactation. At sacrifice on PND 25, liver weight was increased at 5000 and 10000/20000 ppm, but no other organs or body weight was affected. In males, a slight and not statistically significant delay of sexual maturation was observed in the high dose group (1.3 day delay of preputial separation; this was within historical control range and not associated with altered body weight at preputial separation). In adult offspring (F1), male body weight was reduced in both generations and female body weight was decreased at the highest dose level. Absolute organ weights were also decreased in the high dose group males for adrenals, epididymides, kidneys, seminal vesicles and spleen. These effects are most likely related to the low body weight, as these effects were not retrieved in the relative organ weights (except for epididymis weight, see discussion below). Relative but not absolute testis weight was increased. No significant effects on sperm parameters were seen, and a slight reduction (by 7%) in epididymal sperm count was not statistically significant. In high dose females, reduced absolute weights of adrenals, spleen and thymus were observed, but no reductions of relative organ weights were seen. In offspring, no significant effects on female sexual maturation, ovary weights or histology of other organs than the liver were seen. Slight reductions in absolute ovary weight (11%) and relative ovary		

	weight (5%) in the high dose group were not statistically significant		

The two studies by Hushka et al., 2001, showed no effects of DIDP on fertility of males or females. In females, a slight reduction in oestrous cycle length was only seen in P1 and not in P2 generation, and it is unclear whether this reflects a specific toxicity to reproductive organs.
In the EU risk assessment report, reductions of absolute testis weights were described for offspring exposed to 0.8% of DIDP in the first two-generation study (Hushka et al., 2001). This was suggested as being related to low body weight, but testis weights are generally not considered to be sensitive to body weight, it is unclear whether this is an indication of organ specific toxicity, i.e. a developmental effect on testicular development. In a 21-day study, a very high dose of DIDP also reduced testis weights (Lington et al., 1993, as cited in EC 2003). It is unclear whether reductions in ovary weights of F1 and F2 offspring is related to body weight changes or reflects organ specific toxicity of DIDP.
In the EU risk assessment report, a statistically significant decrease in mean percent normal sperm (sperm morphology evidenced by phase contrast microscopy) in all treated groups of P1 males compared with controls. This finding is not presented in the paper by Hushka et al., 2001, or in the CSR. It is concluded in the EU risk assessment report that the decrease was not dose-dependent and that in the P2 generation no statistically significant differences were noted in sperm data. According to the laboratory, these small differences (< 1.4%) were considered incidental and not related to treatment with DIDP. The EU risk assessment report concludes that no adverse effects on fertility can be anticipated based on these data.
Kwack et al, 2009, compared several phthalate esters for effects on sperm count and sperm motitily in the rat. Male rats were exposed from age 35 to 63 days to phthalate diesters at doses of 500 mg/kg bw/day. For DIDP, relative weight of liver was increased, while no effects were seen on relative weights of testis or epididymis. No effect on sperm count was observed, but the percentage of motile sperm was reduced to 52% of control levels, and other measures of sperm motility (straight-line velocity, curvilinear velocity, straightness, and linearity) were also reduced.
The applied dose in the Kwack study was comparable to the highest dose of the first two-generation study (Hushka et al., 2001), which showed no effect on sperm motility, but a slight reduction in sperm count (8%, not statistically significant). Another study showed effects on testis weights only at very high doses of DIDP (Lington et al 1993). A 90-day study in rats showed no effects on testis weight at doses up to 650 mg/kg bw/day of DIDP (Unpublished study report, 1968a) (see section 7.9.4.1).
Overall, the effect of DIDP on sperm motility and possible effects on testis weight at high doses indicates toxicity to fertility.
The supporting study on source substance ditridecyl phthalate (Japanese Ministry of Health and Welfare 1997) cannot be evaluated as no information is available.
Regarding the supporting study on source substance C911P (Willoughby et al 2000), indications of adverse effects on parental male and female reproductive organs lead to a minor concern for toxicity to fertility. Absolute weights of epididymis and seminal vesicles were reduced, but this is not considered reproductive toxic effects, as relative weights were increased, indicating that the changes were secondary to the markedly lower body weights. Epididymal sperm count and sperm motility were unaffected in parental animals and offspring. Testicular spermatid count was increased in all treatment groups of parental males, likely due to an unusually low control level, and no effects on fertility were observed. Parental males (F0) had a low, not statistically significant incidence of small testes and epididymis in all exposed groups, but not in controls, and this could indicate possible adverse effects on fertility.
Additionally, parental females (F0) from the high dose group had significantly reduced weights of uterus and cervix (absolute weight reduced by 23%; relative weight reduced by 20%), and slightly (absolute weights reduced by 11%, relative weights reduced by 8%, not statistically significant) reduced ovary weights that, however, could not be explained by the concomitantly reduced body weight at 5000 and 10000 ppm. An evaluation by United Satates Consumer Product Safety Commission (CPSC 2010a) concluded that in contrast to the organ weight changes in males, the observed decreases

in absolute and relative uterus + cervix weights in parental females do not appear to be a simple reflection of altered body weights. The CPSC applied these data to set a NOAEL for reproductive effects for the registered substance.
Overall, indications of adverse effects on parental male and female reproductive organs lead to minor concern for toxicity to fertility of source substance C911P.
Furthermore, the main arguments given by the Registrant for lack of reproductive and developmental toxicity of the registered substance is that it belongs to the group of High Molecular Weight Phthalate Esters (HMWPE). However, the proposed hypothesis that all HMWPE (phthalates with carbon backbones of C7 and above) show low reproductive toxicity has been challenged by studies pointing to reproductive and endocrine disrupting effects of certain HMWPEs (see also section 7.9.7.3).
The HMWPE category consists of phthalate esters with an alkyl carbon backbone with 7 carbon (C7) atoms or greater. The category is formed on the principle that substances of similar structure have similar toxicological properties (OECD 2004). Although available data indicate clear differences among the different phthalates of the HMWPE group, there are also similarlities due to the overlap in constituents of the registered substance with e.g. diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP). For these two substances there are indications of toxicity to fertility, as reduced reproductive organ weights were seen in males and females in repeated dose studies (Aristech 1995, Unpublished study report 1992, Lington et al., 1993) and parental males of two-generation studies (Waterman et al., 2000, Hushka et al., 2001). An oral repeated dose toxicity study of 4 weeks exposure of rats comparing effects of nine different phthalate diesters (C3-C11) showed significant changes in sperm counts and motility for several diesters including DEHP, DBP, BBP, DnOP, DINP, DIDP, and DUP[2] (Kwack et al 2009). In that study, male rats were exposed from age 35 to 63 days to phthalate diesters at doses of 500 mg/kg bw/day. This may indicate concern for adverse reproductive effects of phthalate esters with longer carbon backbones than C7.

Conclusion on review of information regarding the concern for effects on fertility
For proposed source substances DIDP and C911P, there are indications of toxicity to reproductive organs, as described above (Hushka et al., 2001, Willoughby et al., 2000, Kwack et al., 2009). The indications of effects on parental male and female reproductive organs of source substances lead to the conclusion that there is a concern for toxicity to fertility of the registered substance which cannot be dismissed.

Furthermore, the main arguments given by the Registrant for lack of reproductive and developmental toxicity of the registered substance is that it belongs to the group of High Molecular Weight Phthalate Esters (HMWPE) (phthalates with carbon backbones of C7 and above). However, the proposed hypothesis that all HMWPE show low reproductive toxicity has been challenged by studies pointing to reproductive and endocrine disrupting effects of certain HMWPEs.
The eMSCA concludes, based on the available data, that there is a continued concern for effects on fertility of the substance under evaluation, DTDP.

7.9.7.2. Review of information regarding the concern for developmental toxicity

There are no data available on DTDP regarding developmental toxicity.

Six developmental toxicity studies on source substances for read-across were presented in the registration dossier. Detailed information about studies conducted on DIDP (by Hushka et al 2001) and C911P (by Willoughby et al 2000) can be found in section 7.9.7.2. since they also provide information about effects on fertility. Results from other reproductive toxicity studies on source substances were also included in the evaluation of developmental toxicity by the registrant and are included in the table below. In addition,

[2] di(2-ethylhexyl) phthalate (DEHP), di(*n*-butyl) phthalate (DBP), butylbenzyl phthalate (BBP), di-*n*-octyl phthalate (DnOP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP), diundecyl phthalate (DUP)

a study on effects of source substance DIDP on fetal testosterone production is presented in the table below (Hannas et al., 2012).

Table 18: Summary studies relevant for evaluation of developmental toxicity.

Method	Results	Remarks	Reference
Rat (Sprague-Dawley), n=25 oral: gavage 100, 500, 1000 mg/kg (actual ingested) Exposure: Gd 6 through 15 (daily) equivalent or similar to EU Method B.31 (Prenatal Developmental Toxicity Study)	NOAEL (maternal toxicity): 500 mg/kg bw/day (LOAEL 1000 mg/kg bw/day for reduced maternal weight gain and food consumption) NOAEL (developmental toxicity): 500 mg/kg bw/day (LOAEL 1000 mg/kg bw/day for increased incidence of frequency of 7th cervical and rudimentary lumbar ribs)	1 (reliable without restriction) key study Study performed on the structural analogue substance DIDP CAS RN 68515-49-1	Waterman SJ, Ambroso JL, Keller LH, Trimmer GW, Nikiforov AI and Harris SB (1999) Nikiforov AI, et al (1995)
Rat (Wistar), n=7-10 oral: gavage 40, 200, 1000 mg/kg/day Exposure: day 6-15 of gestation (daily) EU Method B.31 (Prenatal Developmental Toxicity Study)	NOAEL (maternal toxicity): 200 (LOAEL 1000 mg/kg bw/day for increased liver weight) NOAEL (teratogenicity): 200 (LOAEL 1000 mg/kg bw/day for skeletal variations and soft tissue variations).	1 (reliable without restriction) supporting study Study performed on structural analogue: DIDP CAS RN 68515-49-1	Hellwig J, Freudenberger H and Jackh R (1997)
Mouse (CD-1), n=50 oral: gavage 9650 mg/kg/day (undiluted DIDP) Exposure: gestation days 6-13 (daily), sacrifice at PND 3. EU Method B.31 (Prenatal Developmental Toxicity Study)	NOAEL (maternal toxicity): > 9650 mg/kg bw/day NOAEL (teratogenicity): > 9650 mg/kg bw/day. No effects on maternal death, maternal weight, viable litters (until PND 3), birth weight.	1 (reliable without restriction) supporting study (screening study, no examination of malformations) read-across from supporting substance (structural analogue or surrogate) Test material Di-isodecyl Phthalate – no CAS RN indicated.	Harding BD, et al (1987), as cited in EC, 2003
Rat (SD), n=3-4. Oral: gavage 500, 750, 1000 or 1500 mg/kg bw/day. Vehicle: corn oil Exposure GD 14 to 18.	No effects on testicular testosterone production ex vivo at GD 18 and no effects on expression of genes related to steroid synthesis.	Small number of animals per group, Reliable with restrictions (2). Structural analogue substance tested:Di-isodecyl Phthalate CAS RN 26761-40-0	Hannas et al., 2012

Rat (Sprague-Dawley) oral: gavage 0, 250, 500, or 1000 mg/kg/day Vehicle: olive oil L11P, CAS 3648-20-2 (called DUDP in the article) Exposure: GD 6-20 (Dosing occurred once daily, in the morning, from GD 6 to 20. The dosing volume was 5 ml/kg. Initial doses were based on GD 6 weight and adjusted every 3 days throughout the treatment period. Concurrent control group received the vehicle under the same conditions.) OECD TG 414 (Prenatal Developmental Toxicity Study)	In dams, the number of implants was significantly decreased in groups exposed to 0.25 and 0.5 g/kg L11P, but not at 1 g/kg. In male fetuses, the anogenital index (AGDi, AGD adjusted to the body weight) was decreased in the group exposed to 0.5 g/kg L11P compared to controls, although AGD (not adjusted to the body weight) was not changed. At 1 g/kg AGDi was also slightly lower than controls, but this was not statistically significant (1.65±0.08, 1.59±0.05, 1.60±0.09 in controls, middle and high dose groups respectively). Moreover, an increased number of lumbar ribs were found in foetuses from the two highest dose groups. No effects were observed in mean maternal body weight, bodyweight gain throughout the study or food consumption. Treatment effects were not seen on the number of corpora lutea in the ovaries or the incidence of pre-implantation loss, post implantation loss, resorptions, live foetuses or fetal sex ratio. In the fetuses, no effects on body weight or positioning of the testis were observed. No other skeletal effects were observed in the foetuses besides the occurrence of lumbar ribs.	2 (reliable with restrictions) weight of evidence read-across from supporting substance (structural analogue or surrogate) Test material (CAS RN 3648-20-2) Form: >98% pure	Saillenfait A.M, Gallissot F., Sabaté J-P, Remy A. (2013a)

Data from the two-generation study on DIDP (see table in section 7.9.7.1) (Hushka et al., 2001) were also applied to evaluate effects on developmental toxicity. A small (1.2 days) delay in preputial separation in F2 animals and an increase in age of vaginal patency (2 days) related to a decreased body weight at that age was not considered biologically significant by the registrant. No effects were seen on anogenital distance or nipple retention. It may be noted that preputial separation, anogenital distance and nipple retention were only investigated in the second study, in which the highest dose was 0.4% corresponding to 254 mg/kg bw/day during gestation. This dose is relatively low compared to the dose levels showing adverse effects of other phthalates, e.g. DINP (Boberg et al., 2011).

The lack of effect on fetal testosterone production in rats (Hannas et al., 2012) support that DIDP has a different mode of action than e.g. DEHP and DBP. The data from Hannas et al., 2012, were also reported in a study by Furr et al., 2014, comparing effects of several phthalate esters on fetal testosterone production.

DIDP produced a small, statistically significant decrease in postnatal survival indices which was observed in the second generation of both of the two-generation studies leading to the NOAEL of 0.06% (33-76 mg/kg/d) (Hushka et al., 2001). These effects were found in association with maternal toxicity: reduced body weight, instances of increased kidney weight, and /or liver enlargement. It was concluded by the registrant that effects on post-natal survival could be a secondary rather than direct effect of DIDP on the rat pups. In contrast, the ECHA review on DIDP from 2013 found that the most critical effect for DIDP was the decreased survival of F2 pups observed in both two-generation studies with rats (Hushka et al 2001).

According to the registration dossier, developmental toxicity studies of DIDP conducted at doses of 100, 500, and 1000 mg/kg provided evidence of slight and transient signs of maternal toxicity at 1,000 mg/kg/d (significant reversible decrease of body weight gain and food consumption) suggesting a NOAEL of 500 mg/kg/d for maternal toxicity. The only statistically significant changes were skeletal variations (supernumerary cervical and rudimentary lumbar ribs) on a per litter basis at the high dose. It was noted in the CSR that rudimentary ribs are a common finding in rat fetuses and should not be regarded as associated with malformations, but may only be related to transient maternal stress. The CSR refers to the EU risk assessment report for DIDP, in which the finding of skeletal effects is applied to set a NOAEL of 500 mg/kg/d (EC, 2003).

In the ECHA review from 2013, this effect on skeletal variations of DIDP was considered critical and is used for NOAEL determination.

Overall, the effect of DIDP on skeletal effects and decreased survival of F2 pups raise a concern for toxicity to development.

Data from the 2-generation study on C911P (Willoughby et al., 2000) (see section 7.9.7.1) was also applied to evaluate developmental toxicity. Adverse effects on development were seen, as a reduction in absolute epididymis weight was seen in adult offspring of the high dose group. In the peer-reviewed paper discussing the full reproductive toxicity study, the reduction of epididymis weight is discussed as a possible specific effect of exposure (Willoughby et al., 2000). It is noted that absolute epididymis weight was significantly reduced by 7% in the high dose D911P group, and that this may be a direct effect of the test substance rather than being secondary to low body weight, as the epididymis is generally resistant to starvation (Willoughby et al., 2000). The epididymal sperm count in the high dose group offspring was reduced by 7%, but this was not statistically significant. However, the authors note that the variability in epididymis weight is less than the variability for sperm count, and that organ weight is more sensitive than sperm count to treatment-related toxicity (Willoughby et al., 2000).

In another study, source substance C911P showed no effects on developmental parameters investigated, except for an increased body weight in female foetuses in the highest dose group (1000 mg/kg) (Bottomley and Fulcher 2000). This is not considered to be a sign of developmental toxicity. Exposure to C911P resulted in the development of minor skeletal variants in pups, i.e. supernumerary 14th ribs and dilated renal pelves (Bottomley and Fulcher, 2000). The effect on dilated renal pelvis was mainly associated with a few litters and is not considered to be an effect of C911P. An increased percentage of foetuses with supernumery ribs was observed in the two highest dose groups but showing no dose-response relationship, and with a high percentage of supernumerary ribs also in the control group (14% of pups and 59% of litters in control group versus 28% and 77% in the most affected group (middle dose)). However, for DIDP the presence of supernumerary cervical ribs was the reason for concern, whereas the presence of supernumerary lumbar ribs (as in the study on C911P) is a common finding. Due to the small difference in percentage of supernumerary ribs between controls and exposed groups and the lack of effect on supernumerary cervical ribs, this effect is not considered to be a clear adverse effect of C911P.

<u>Conclusion on review of information regarding the concern for developmental toxicity</u>

Developmental effects (skeletal variations) observed for phthalate C7-11P (DHNUP), which is the basis for the initial concern, have also been observed for other phthalates with similar constituents as the registered substance , e.g. DIDP and C911P (both used as source substances), diundecyl phthalate, and DINP (ECHA 2013, Waterman 2000, Waterman 1999, Unpublished study report, 2000, Saillenfait et al., 2013a). For DIDP (CAS 68515-49-1), it was evaluated that these skeletal variations (supernumerary cervical and rudimentary lumbar ribs) could be applied to set a NOAEL according to the EU risk assessment report (EC 2003) and a recent ECHA review (ECHA 2013). For source substance C911P (CAS 68515-43-5) the effects on supernumerary ribs was less marked and seen for lumbar and not cervical ribs, and therefore the effect was not considered a clear adverse developmental effect. Overall, effects on skeletal development are seen for some members of the group of HMWPEs, and the initial concern for developmental toxicity of the registered substance cannot be rejected.

There are also indications of toxicity to the developing reproductive system for source substances DIDP and C911P, as reduced reproductive organ weights are seen in offspring (Hushka et al., 2001, Willoughby et al., 2000). It is unclear whether reductions in testis and ovary weights of offspring in the two-generation study on DIDP is related to body weight changes or reflects organ specific developmental toxicity (Hushka et al., 2001). For C911P, the observed reductions in epididymis weights of offspring does not appear to be related to body weight changes and may thus be considered a developmental effect on the male reproductive system (Willoughby et al., 2000).

Based on the available data, the eMSCA concludes that there is a continued concern for developmental toxicity of the registered substance.

7.9.7.3. Consideration of reproductive toxicity of phthalates in relation to phthalate ester backbone length

Phthalates with "intermediate" backbone lengths are commonly described as reproductive toxicants, as this group includes phthalates with backbone of 4 to 6 carbon atoms (C4-C6 plus extra carbon atoms as side chains) and thereby comprises the four reproductive classified phthalates (DEHP, DBP, DIBP and BBP). Phthalates with an alkyl carbon backbone with 7 carbon atoms or more are described as high molecular weight phthalate esters and are considered to have similar environmental and toxicological properties (OECD 2004).

However, the proposed hypothesis that all HMWPE (phthalates with (straight chain) carbon backbones of C7 and above) show low reproductive toxicity has been challenged by studies pointing to reproductive and endocrine disrupting effects of certain HMWPEs, though with differing potencies and possibly via other modes of action than the reproductive toxicity of phthalates with C4-C6 backbones (Furr et al. 2014, Saillenfait et al. 2011, Kwack et al. 2009).

Observed effects include skeletal malformations (Waterman et al., 1999, Hellwig et al., 1997), reduced anogenital distance and fetal testosterone production in rats after exposure to diheptyl phthalate (C7 backbone) (Saillenfait et al 2011, Furr et al 2014) and significant changes in sperm counts and motility after exposure to several phthalates with differing carbon backbones, including DEHP, DBP, BBP, DnOP, DINP, DIDP (diisodecyl phthalate, C10 branched), and diundecyl phthalate (C11 backbone) (Kwack et al 2009). The mode of action behind these effects is not well investigated, but for these endpoints no clear relationship with backbone length has been found.

As described above, developmental effects (skeletal variations and decreased survival of pups) have been found for DIDP, and DINP has comparable effects. It is conceivable that other phthalates including phthalates with long backbones can affect skeletal development and pup survival.

7.9.7.4. Data gap on reproductive toxicity due to rejection of read-across prodivided by the Registrant

As laid out in the previous sections, no reproductive toxicity data on DTDP is provided by the registrant, as diisodecyl phthalate (DIDP, CAS RN 68515-49-1 and 26761-40-0), is used as a read-across substance to provide toxicological information (key studies). Additionally, supporting studies on ditridecyl phthalate (CAS RN 119-06-2, C13 linear) and C911P (CAS RN 68515-43-5, C9-11 branched and linear) were included regarding toxicity to fertility. Supporting studies on diundecyl phthalate (DUDP, C11 linear), C911P (CAS RN 68515-43-5, C9-11 branched and linear), dioctyl phthalate (CAS RN 117-84-0, C8 linear), ditridecyl phthalate (CAS RN 119-06-2, C13 linear) were included regarding developmental toxicity.

This use of read-across is rejected by the eMSCA. Detailed information of the rejection is provided in section 7.9.8.

Consequently, there is an information gap in the registration dossier for reproductive toxicity. This data gap must be addressed in order to clarify the concerns for reproductive toxicity and endocrine disruption, as further described below.

7.9.7.4.1. Extended One-Generation Reproductive Toxicity Study (EOGRTS, EU B.56, OECD TG 433)

The standard information requirement under Annex X, 8.7.3 is an Extended One-Generation Reproductive Toxicity Study (EOGRTS, EU B.56, OECD TG 443). As laid down in column 1 of 8.7.3., Annex X the basic test design of this study includes Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation.Further, the study design needs to be expanded to include the extension of Cohort 1B to include the F2 generation, and Cohorts 2A/2B, and/or Cohort 3 if the conditions described in column 2 of Annex X, point 8.7.3 are met. Adequate information on this endpoint needs to be present in the registration dossier for the DTDP to meet this information requirement.

The registrant has not provided any study record of an extended one-generation reproductive toxicity study with the registered substance in the dossier that would meet the information requirement of Annex X, Section 8.7.3. Also no two-generation reproductive toxicity study (EU 8.35, OECD TG 416) with DTDP initiated before 13 March 2015 and which would be considerd appropriate to address this standard information requirement is included in the registration dossier. Instead an adaptation of this information requirement according to Annex XI, Section 1.5. of the REACH Regulation was sought. The applicant has provided a justification for read across to waive the requirement.

The following studies were provided for read across:

- Two 2-generation reproductive toxicity studies on DIDP (CAS RN 68515-49-1) administered in diet (key data published in Hushka et al. (2001)) (exposure range from approximately 15-600 mg/kg/day) (key study).
- Combined repeat dose and reproductive/developmental toxicity screening test on DTDP (CAS RN 119-06-2) via oral gavage (OECD TG 422, Japan Ministry of Health and Welfare, 1997, registrant does not have access to full study report) (Sprague-Dawley rats, three doses) (supporting study)
- A 2-generation reproductive toxicity study on a C9-11 phthalate ester (CAS RN 68515-43-5) at levels of 100-1000mg/kg/day (Willoughby et al. 2000) (supporting study).

Additional studies were included for testicular atrophy: Two supporting studies on DIDP (CAS RN 68515-49-1), exposure via diet for 28 and 21 days (Lake et al. 1991/BIBRA 1990 and Lington et al. 1993/BIBRA 1986) (supporting studies).

The eMSCA analysed the read across justification applying the Annex XI point 1.5 elements and the ECHA Read-Across Assessement Framework (RAAF) guidance (see section 7.9.8). The proposed adaptation of the information requirement is incompliant with several points of the RAAF. due to:

i) insufficient information on identity and concentration of the constituents in target and source substance,

ii) insufficient information with respect to mechanistic explanations on why and how predictions are possible within the group, and

iii) no bridging studies are presented to allow side-by-side comparison of substances.

Therefore, the proposed adaptation is rejected, and thus, the information provided on this endpoint for DTDP in the registration dossier does not meet the information requirement of Annex X, 8.7.3, Extended One-Generation Reproductive Toxicity Study. Consequently there is an information gap in the registration dossier for this endpoint.

In regards to substance evaluation, the information from the EOGRTS is necessary to clarify the concerns for reproductive toxicity and endocrine disruption.

In the design of the EOGRTS, inclusion of the DNT cohort should be considered, since it can be argued that the triggers in column 2 are fulfilled by existing information regarding effects on the thyroid hormonal system from structurally analogous substances (i.e. DIDP, DTDP, C9-11 phthalate ester). This information may further be supported by information from the sub-chronic toxicity study (90-day study), for which a data gap is also identified (see section 7.9.4).

7.9.7.4.2. Prenatal Developmental Toxicity Study (PNDT, EU B.31, OECD TG 414)

A "pre-natal developmental toxicity study (EU B.31, OECD TG 414)" for one species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

No study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2, for the registered substance is provided. Instead the registrant has sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. The applicant has provided a justification for read across to waive the requirement.

The following studies were provided for read across (weight of evidence studies):

- Equivalent to Prenatal Developmental Toxicity Study. Daily exposure GD6-15 (daily) to DIDP (CAS RN 68515-49-1) via oral gavage (Sprague-Dawley rats, three exposure levels) (Waterman et al 1999)
- Prenatal Developmental Toxicity Study. Daily exposure GD 6-15 (daily) to DIDP (CAS RN 68515-49-1) via oral gavage (Wistar rats, three exposure levels) (Hellwig et al 1997)
- Prenatal Developmental Toxicity Study. Daily exposure GD 6-16 (daily) via oral gavage to CAS RN 3648-20-2 via oral gavage (Sprague-Dawley rats, three exposure levels) (Saillenfait et al 2013a)
- Prenatal developmental toxicity study on CAS RN 68515-43-5 via oral gavage (Sprague-Dawley rats, three exposure levels) (Unpublished study report, 2000)
- Prenatal developmental toxicity study on CAS RN 117-84-0 via oral gavage (Sprague-Dawley rats, three exposure levels) (Saillenfait et al 2011)
- Prenatal developmental toxicity study, exposure GD 6-13 daily) on CAS RN 26761-40-0 via oral gavage (CD-1 mice, one exposure level) (Harding et al 1987 as cited in EC, 2003)

The eMSCA has analysed the read across justification applying the Annex XI point 1.5 elements and the ECHA Read-Across Assessement Framework (RAAF) guidance (see. section 7.9.8). The proposed adaptation of the information requirement is incompliant with several points of the RAAF due to:

i) insufficient information on identity and concentration of the constituents in target and source substance,

ii) insufficient information with respect to mechanistic explanations on why and how predictions are possible within the group, and

iii) no bridging studies are presented to allow side-by-side comparison of substances.

Therefore, the proposed adaptation is rejected, and thus, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement of Annex IX, Section 8.7.2 pre-natal developmental toxicity study, first species.

Consequently there is an information gap in the registration dossier for this endpoint.

In regards to the substance evaluation, the information obtained from the pre-natal developmental toxicity study is necessary to clarify the concern for reproductive toxicity

and it may provide information about endocrine disruption, which has been identified as an additional concern in the substance evaluation process.

7.9.7.4.3. Prenatal Developmental Toxicity Studies in a second species.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 2 of the REACH Regulation),

As explained above, the technical dossier does not contain information on a pre-natal developmental toxicity study on a first species with the registered substance and the adaptation provided is rejected. The technical dossier also does not contain an adaptation for the second species in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI for this standard information requirement.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

In regards to the substance evaluation, the information obtained from the pre-natal developmental toxicity study in the second species, if conducted, is necessary to clarify the concern for reproductive toxicity and it may provide information about endocrine disruption, which has been identified as an additional concern in the substance evaluation process.

7.9.8. eMSCA rejection of read-across provided by the Registrants to fill the data gaps on repeated dose toxicity and reproductive toxicity.

The Registrant(s) categorize the registered substance as a multi-constituent substance in the CSR, however, it is referred to as an UVCB in other documents in the registration dossier. Based on the complexity and lack of knowledge on the constituents, the registered substance is here considered a UVCB.

No studies were provided to address the standard information requirements related to reproductive toxicity (sub-chronic 90 day repeated dose toxicity, prenatal developmental toxicity, fertility and developmental toxicity) in accordance with REACH Annex IX 8.6.2 and REACH Annex X 8.7.2 and 8.7.3. Instead, the Registrant(s) use several substances) as read-across source substances (analogue substances) for the endpoints required, in an attempt to fulfil the standard information requirements.

7.9.8.1. Hypothesis provided by the Registrant

In order to support the suggested read across, the Registrant(s) has provided the following read across justification statement in the CSR including an Appendix (added to registration dossier in 2015) describing the read-across justification. The following hypothesis is proposed:

"*Several criteria justify the use of the read-across approach to fill data gaps for the registered substance using 1,2-Benzenedicarboxylic acid, di-C10-12-branched alkyl esters (DIUP), 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (L9-11P), 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (DIDP), and 1,2 Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (DINP) as analogue substances. Furthermore, the target and source substances belong to the High Molecular Weight Phthalate Ester (HMWPE) Category which was established based on structural similarity. As described in below, these substances are similar in molecular structure, physicochemical properties, use, and manufacturing processes. Based on these unifying considerations, the variation in carbon backbone length among these analogues is not expected to significantly impact toxicity. When possible data from the source substance(s) with a carbon backbone length closest to target substance was preferred and used to fulfill individual endpoints. Therefore, it is scientifically reasonable to predict the toxicological properties for the registered substance from the properties determined for the analogues*."

7.9.8.2. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

The Registrant has provided read-across justification in the Chemical Safety Report (CSR) in Section 11, Appendix 1, added in 2015.

The Registrant(s) presents an "Analogue approach justification" stating that there are a number of unifying considerations that, when taken together, justify the use of read across from the chosen source substances to the registered substance. These considerations include:

(A) Similarity of production methods
(B) Similarity of use
(C) Similarity of composition
(D) Similarity of physical/chemical properties
(E) Similarity of metabolism
(F) Similarity of mammalian toxicity
(G) Similarity of environmental toxicity and fate properties
(H) Similarity in health effects

The appendix to section 11 of the CSR from the registrants further describe these considerations. Some of these point are noted below:

Regarding (C) 'Similarity of composition' it is stated that: "*The read across substances cover the range of alkyl chains predicted to be present in the registered substance (Figure 1)*. Figure 1, presents an illustration of backbone length of a number of phthalate substances of which some are used for read-across]. *The presence and quantity of the alkyl chains in the read across [source, red.] substances are of a type to be able to predict the toxicity of the registered substance DTDP has a low probability of having significant ethyl branching and low levels of tetra-branched alkyl chains. For this specific substance we expect the backbone chain length to contain at least 9 carbon atoms*".

The main source substance DIDP is "*expected to have a similar level and type of branching as the registered substance with alkyls of a shorter chain length than the registered substance."* For other source substances it is noted that "*DIUP and D911P are more linear than the registered substance and are expected to have less branches. The presence of branching is a key component for the developmental and reproductive toxicity considerations and discussed in detail during the weight of evidence supplied by the registrant in the dossier, but the difference in branching does not generate structures of concern in the registered substance (see detailed substance ID portion of the dossier)."* (CSR, Appendix 1, p. 112).

According to the Registrant(s) it is not possible to assess branching directly. This is further discussed in the IUCLID (section 1.4) document "DTDP compositional information": "*Due to the complexity of DTDP, with the presence of over 3000 isomers all present with boiling ranges very close to each other, analytical techniques (beyond GC, GC-MS, and NMR) are not yet available allowing the precise determination of the specific structure of each of these many isomers. This document describes what is scientifically reasonably known and foreseeable on olefin and alcohol structure and what can be inferred on the plasticizer structure from industry practice and knowledge, analytical techniques (GC, GC-MS, NMR) and data.*" (IUCLID "DTDP compositional information_2015").

Regarding (H) similarity in health effects, the CSR (Appendix 1 on justification for read-across) states that: "*Based on the similarity in molecular structure, carbon number, manufacturing process, toxicokinetic behavior, and physicochemical properties between the target and source chemicals it is scientifically reasonable to predict the toxicological properties for the target substance from the properties of the source chemicals. A summary of the reproductive and developmental endpoints is provided in Figure 2.* [Figure 2, not shown in this paper, presents an illustration of backbone length of substances applied for read-across including information on availability of test data for developmental and reproductive toxicity for selected substances]. *It is the Registrants*

scientific opinion that the available read-across information demonstrating that ortho phthalates with carbon side chain backbone lengths of C7 and greater have a low potential for toxicity for developmental and reproductive endpoints is ample evidence to support a rational judgment regarding hazard identification, classification and labeling and risk assessment for the registered substance (with alkyl backbone side chains with a minimum of C9 and in the range of C9-C12).

The mammalian toxicity data available on the source chemicals supports that these substances are non-hazardous. The source chemicals are not acutely toxic via the dermal or oral routes and are not eye/skin irritants, sensitizers, or mutagens (Table 2, Table 4). The source substances are not mutagenic. Please refer to substance dossiers for complete information regarding individual endpoints. The registrant does not manufacture 68515-43-5 so please refer to endpoint information available on the ECHA portal" (CSR Appendix 1, p. 115).

7.9.8.3. Analysis of the read-across hypothesis

ECHAs "Read-Across Assessment Framework" (RAAF) from 2017 (referred in the following as ECHA 2017a) provides a framework and principles for scientific examination of a read-across case, as well as specification of the critical scientific elements necessary for assessment of a read-across case. In the RAAF, the scientific assessment is divided into scenarios to account for the most frequently applied read-across approaches observed in REACH registration dossiers (ECHA 2017a). The different scenarios are designed to distinguish analogue approaches from category approaches, and are based on the types of read-across hypotheses typically submitted to ECHA. In the present case (substance 'EC 271-089-3'), the read-across approach is related to RAAF scenario 2, which addresses the use of the analogue approach for which the read-across hypothesis is based on different compounds which have the same type of effect(s). Specific requirements are: *"For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on worst case."* (ECHA 2017a, Appendix B: Scenario 2)

The supplied information does not fulfill the requirements outlined in the RAAF document or the related "Read-Across Assessment Framework (RAAF) – Considerations on multi-constituent substances and UVCBs" also from 2017 (in the following referred as ECHA 2017b).

Three issues can be raised:

i) insufficient information on identity and concentration of the constituents in target and source substance,

ii) insufficient information with respect to mechanistic explanations on why and how predictions are possible within the group, and

iii) no bridging studies are presented to allow side-by-side comparison of substances.

Re: **i) insufficient information on identity and concentration of the constituents in target and source substance:**
With regards to substance identity, the RAAF specifies*: "A fundamental aspect of read-across is structural similarity. Chemical composition, including structural information should be well defined. In addition, other constituents of a substance (e.g. impurities) can have a significant impact on the hazard or fate of a substance. Unambiguous substance identity for both the target and the source substances is therefore a prerequisite for read-across assessment"* (ECHA 2017a, p. 10).

The need for substantial information on source substance identity and concentration is further described in the RAAF Considerations on multi-constituent substances and UVCBs: *"Detailed compositional information on the source substance (composition and concentrations of the constituents) and the test material used in the conducted source studies is fundamental to establish the relation to the target substance in terms of grouping and predictions. For the assessment of such cases, the detailed information on the composition of the source substances forms the basis for the evaluation of the proposed prediction. In comparison with (rather pure) mono-constituent substances, multi-constituent substances and UVCBs involve more than one (sometimes many) relevant chemical structures. Consequently, read-across approaches for such substances require additional justifications and assessments to account for the increasing complexity of the composition of the substances and its impacts on the predictions."* (ECHA 2017b, page 29).

For UVCBs it is stated that: *"For UVCBs, grouping on the basis of structural similarity may become even more complex, e.g. due to the presence of more constituents in the substances, potentially higher variations in the concentrations of the constituents and sometimes unknown constituents. Such grouping proposals also clearly require extensive explanations and justified criteria for group membership."* (ECHA 2017b, page 30)

Little information is provided from the registrants with respect to **source** substances. Instead, the registrant refers to information in the respective registration dossiers of sources substances. "*Refer to existing REACH registration dossier on source substances for the detailed compositional information*" (CSR, Section 11, Appendix 1). However, the available information on source substances is limited, and has not been included in the justification document in any detail. The eMSCA notes the complexity of these substances and consider this lack of knowledge important in the analysis of the proposed read-across hypothesis.

The registrant has provided some information on the identity of the **target** substance: "The plasticizer structure is derived from the alcohol structure: a complex isomeric structure with overlapping carbon numbers and over 3000 isomers. Currently, proton NMR can identify the average carbon number and average branching of olefins and alcohols, however, the type of side chain found in those chemicals (methyl vs ethyl vs propyl) cannot be determined directly using analytical techniques but can be assessed indirectly through knowledge on the plasticiser itself, alcohol raw material, olefin and related hydrocarbon components of the raw materials. Higher olefin reactivity in oxonation depends on the structure of the olefin, the more linear the more reactive the olefin will be. Very limited ethyl and higher side chains are expected to be present in the final plasticizer because higher branched olefins exhibit very limited reactivity and are more difficult to convert into alcohols during oxonation. Based on extensive industry practice and more than 30 years of experience of alcohol and plasticizer manufacturing, of plasticizer performance in flexible PVC, DTDP has shown no presence of C7 backbone and/or C8 backbone." ("DTDP compositional information_2015", IUCLID, p. 1).

Based on gas-chromatographic methods the alcohol carbon distribution number was determined: C11 isomers 4.6%; C12 isomers 22.5%; C13 isomers 71.6%; C14 isomers 1.3% (wt %, "DTDP compositional information" p.3, IUCLID). The registrant writes that more linear isomers have higher boiling points and higher retention times on a boiling-point column than the more branched isomers, which can cause an overlap between the different carbon numbers. However, it is concluded that the target substance is C13 rich with some C11, C12, C14 isomers.

The alcohol carbon number distribution has also been measured using Gas Chromatography – Mass Spectrometry in Chemical Ionization mode (GC/CI-MS): - C11-C11 0.4%; C11-C12 1.6%; C12-C12 (C11-C13*) 7.3%; C12-C13 34.5%; C13-C13 (C12-C14*) 50.3%; C13-C14 5.2%; C14-C14 0.7%. (wt %, presented in "DTDP compositional information_2015", IUCLID). *C11-C13 and C12-C12 as well as C12-C14 and C13-C13 homologue esters have the same molecular weight and cannot be segregated in the above results. The authors write that the method is applicable to 'pure' mixtures of phthalates, meaning that if impurities are present they are not accounted for.

Furthermore, the Registrant(s) presents data showing that the average carbon number in the starting material alcohol is 12.93 and the average number of branches is 3.07. They write that based on this the DTDP alkyl chains will each have an average of 3.07 branches per molecule and present a structure mix (simulated data) that is "statistically realistic" within a very large number of possibilities:

Table 19:

Simulation 1				Simulation 2				Simulation 3		
%	# of branches	Average		%	# of branches	Average		%	# of branches	Average
1	1			1	1			0.1	1	
5	2			1	2			1	2	
80	3			88	3			91	3	
14	4			10	4			8	4	
100				100				100		
		3.07				3.07				3.07

These simulations highlight that, *"based on experience, with a majority of tri-branched alkyl chains and with low levels of mono and di-branched, some tetra-branched chains will be present"* (IUCLID "DTDP compositional information_2015, p. 4".

To evaluate the effect of branching on length of the carbon backbone it is also important to know which type of branching is occurring (methyl, ethyl, propyl, butyl etc). It is stated that NMR cannot help determining branching type (IUCLID "DTDP compositional information_2015", p. 6). It is however noted that "*Branched olefins reactivity, alcohol reactivity, plasticizer neat properties, expected performance in flexible PVC and NMR data indicate a low probability of having significant ethyl branching in Jayflex DTDP and low levels of tetra-branched alkyl chains*." (IUCLID "DTDP compositional information_2015", p. 8).

Overall, the claim that the shortest backbone is C9 is not substantiated in the registration. Rather, from the supplied information from the registrant it seems plausible that constituents with a backbone shorter than C9 may be present to some extent, i.e. C7 or shorter in cases with 3-4 branches, if one or more of these branches are ethyl, propyl or butyl etc. For example, tri-branched C13 will have a *maximum* backbone of C10, and if branches are longer than methyl the backbone will be shorter, e.g. C7, C8 or C9. It has not been substantiated whether this is the case. Another example is tri-branched C12 which will have a *maximum* backbone of C9, and if branches are longer than methyl the backbone is likely shorter, e.g. C6, C7 or C8. It has not been substantiated whether this is the case.

To elaborate on this issue, the eMSCA has tried to specify what constituents may be present given these simulations are correct:

- If 72% of the substance constituents have a total carbon chain number of C13, and 14% are tetra-branched with methyl branches (simulation 1), this means that 0,72*14%=10% of the substance has a C9 backbone. If one or more of these branches are ethyl or longer, these constituents will have C8 backbone or shorter.

- If 5% of the substance constituents have a total carbon chain number of C11, and 91% are tri-branched (simulation 3), then this means that 0,046*91%=4% of the

substance has a C8 backbone. If one or more of these branches are ethyl or longer, these constituents will have C7 backbone or shorter.

- Collectively, this indicates that a fraction of the substance is likely to have a C7 backbone or shorter.

Thus, the claim that the shortest backbone is C9 is not substantiated in the registration. Knowledge on the possible content of constituents with C7 backbone is important, as there is some concern for reproductive and developmental toxicity of phthalate esters with C7 backbone.

As cited above, the chemical structures (in this case knowledge on backbone length) and concentration of constituents (including impurities and additives) should be well defined (ECHA 2017b). As this information does not exist for the target compound and no such information is presented for the source substances, the prerequisites to conduct solid read-across are not fulfilled.

Overall, the eMSCA evaluates the information on the exact backbone chain lengths of the target and source substances, respectively, to be insufficient, and detailed specifications on branching are lacking.

Re: **ii) insufficient information with respect to mechanistic explanations on why and how predictions are possible within the group**

With regard to mechanistic explanations on why and how predictions are possible within the group, the fundamental types of mechanistic explanations are explained in different scenarios of the RAAF. For multi-constituent substances and UVCBs *"several mechanistic explanations may have to be assessed which simultaneously address the variety of structures present in the substances and consequently also more than one RAAF scenario may be needed to assess the case."* (ECHA 2017b, p 31). The RAAF documents further outline the critical assessment points regarding how activity may be affected by the differences in composition between the target and source substances as well as variations in concentrations of constituents. Specifically, the prediction model needs to take into account: *"Variations in the concentrations of the structurally similar constituents (or pool of constituents) and the impact of these variations on the predicted type and the strength of effects. The variations in proportion of constituents may influence the assumed dose response of the substance. Consequently, the quantitative nature (i.e. magnitude of the effects) of the predicted effect is a further issue that has to be assessed, taking account of the precise proportion of constituents in the source substance, in relation to the precise proportion of constituents in the target substance."* (ECHA 2017b, p. 31)

To this end the registrant has provided very limited information. As also cited above, the "Read-across justification" in the CSR, Appendix 1, builds on an argument that "*available read-across information demonstrating that ortho phthalates with carbon side chain backbone lengths of C7 and greater have a low potential for toxicity for developmental and reproductive endpoints is ample evidence to support a rational judgment regarding hazard identification, classification and labeling and risk assessment for the registered substance (with alkyl backbone side chains with a minimum of C9 and in the range of C9-C12)."* (CSR, Appendix 1, p- 115). There are no references to further substantiate this argumentation, and no further documentation is found in the registration dossier. Specifically, no endpoint-specific comparisons are performed to determine whether effects of one source substance may or may not be predicted for the target substance. A table is presented listing all studies on source substances (CSR p. 116-117). This table presents NOAELs for repeated dose toxicity and carcinogenicity for some sources substances, but it is not explained whether similar effects may or may not be expected for the target substance. For developmental and reproductive toxicity there is reference to figures listing backbone length of source substances together with information on classification (Fig. 1) and performed testing for developmental and reproductive toxicity (Fig. 2). These figures provide no information on effects observed in the listed studies on source substances. Instead it is noted: "*Please refer to substance dossiers for complete information regarding individual endpoints. The registrant does not manufacture 68515-*

43-5 so please refer to endpoint information available on the ECHA portal." (CSR, Appendix 1, p. 115). This information is not considered sufficient for read-across.

Re: **iii) no bridging studies are presented to allow side-by-side comparison of substances:**
With regards to bridging studies, the RAAF document notes*: "The test results obtained with a test material containing several constituents do not provide information on the individual contribution of the constituents to the observed toxicity or their possible interactions. The assessment of the read-across approach needs to evaluate what further information is presented by bridging studies and/or mechanistic explanations to explain why and how the results from the source substance are used to predict the properties of the target substance taking into account also possible interaction between constituents in the target substance. Bridging studies are comparable studies on the source and target substance, and these bridging studies allow side-by-side comparison of the substances for a particular property (e.g. properties as determined in a 90-day study). Bridging studies may enable the demonstration that two multi-constituent substances or UVCBs have similar properties for a particular endpoint, and thus play a key role in a read-across justification. In the absence of such an empirical demonstration, read across may be difficult to justify for complex compositions."* (ECHA 2017b, p. 31)

To this end the registrant has provided no information on bridging studies.

During its analysis of the proposed read-across hypothesis, the eMSCA noted the insufficient description of substance identity of the target substance, limited mechanistic explanation, lack of bridging studies and lack of evaluation of variations in the concentrations of the structurally similar constituents (pool of constituents) and the impact of these variations on the predicted type and the strength of effects. In addition, it is necessary that a registrant can provide detailed information on the substance identity for the proposed source substances, but this is not provided in the current case.

Overall, these points have not been sufficiently addressed in the supplied read-across documentation. The pre-conditions for scientifically sound read-across have therefore not been fulfilled.

In conclusion, the eMSCA rejects the proposed read-across. This leads to a data gaps for the standard information requirements on repeated dose toxicity and for reproductive toxicity.

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated by the eMSCA.

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The eMSCA cannot be perform due to data gaps described above.

7.9.11. Conclusions of the human health hazard assessment and related classification and labelling

The eMSCA cannot draw a conclusion due to the data gaps described above.

7.10. Assessment of endocrine disrupting (ED) properties

No discussion on endocrine disrupting properties of the substance under evaluation, DTDP was provided by the registrant. However, an additional concern for endocrine disruption was raised during substance evaluation due to information about endocrine disruptive properties of structurally related substances.

The available information was thoroughly reviewed by the eMSCA and it was concluded that the concerns for endocrine disruption (disruption of sex- and thyroid hormones)

could not be clarified due to the identified data gaps on reproductive toxicity and repeated dose toxicity.

7.10.1. Endocrine disruption – Environment

Not evaluated by the eMSCA.

7.10.2. Endocrine disruption - Human health

7.10.2.1. Review of information regarding the concern for effects on the sex hormonal system (anti-androgenecity)

No data on anti-androgenecity of DTDP is provided by the registrant.

However, data on the proposed read across substances for reproductive toxicity DIDP and C911P and other HMWPEs raise a concern for possible endocrine disrupting properties (antiandrogenecity) of DTDP.

As described in section 7.9 on reproductive toxicity, Willoughby et al., 2000_investigated reproductive toxicity of C911P. In the offspring from two two-generation studies performed with C911P, only subtle indications of reproductive toxicity and endocrine disrupting properties were observed. Indications of adverse effects on male and female reproductive organs and possibly age of male sexual maturation were however present in the two-generation studies (Willoughby et al. 2000), including effects on epididymal development. Effects on epididymal development have been described for other phthalates and may be related to an anti-androgenic mode of action (Barlow and Foster 2003). It should be noted that the two generation studies were conducted with the OECD TG 416 before its revision in 2001 and hence that several important endpoints in relation to endocrine disruption have not been investigated for C911P. No assessment of anogenital distance or nipple retention in male offspring has been performed with C911P to clarify whether this effect on the developing male reproductive system could be associated with an anti-androgenic effect on these markers.

For DIDP, endocrine disruption (anti-androgenecity) was discussed in the EU Risk assessment report from 2003 (EC 2003): *In the first two-generation reproductive toxicity study (Hushka et al. 2001]), some alterations in male reproductive development were found to be possibly indicative of a tendency of disturbance of masculinisation through an endocrine-mediated mechanism (change in sex ratio at the lowest dose, decreases of absolute but not relative testes weight in F1 and F2 offspring, cryptorchidism possibly related to delayed body weight gain). In a newer two-generation reproductive toxicity study (Hushka et al. 2001), there were no changes in developmental landmarks sensitive to hormonal disturbance at lower doses.* It was concluded that on the whole, no overt effect related to endocrine disruption of the reproductive system has been observed with DIDP. It should be noted that the high dose of the first two-generation studies showed minor indications of reproductive toxicity (altered weights of testis, epididymis and ovaries in some generations). No overt maternal toxicity was observed at the highest dose in either of the studies, supporting that the tested doses were too low, as according to OECD TG 416 the highest dose level should be chosen with the aim to induce some maternal toxicity.

Further, ECHA 2013 concluded that "*DIDP did not induce substantial anti-androgenic activity in available studies; in particular it did not reduce fetal testicular T levels or affect gene expression levels related to masculinization during critical time window during development. However, DIDP was anti-androgenic in the Hershberger assay, with a lower potency than DEHP. Thus, 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*" (ECHA 2013). ECHA concluded that DIDP did not induce substantial anti-androgenic activity in available studies; in particular it did not reduce foetal testicular testosterone levels or affect gene expression levels related to masculinization during critical time window during development, although DIDP was anti-androgenic in the Hershberger assay, with a lower potency than DEHP (ECHA 2013). If DIDP has endocrine disrupting

effects on the reproductive system, these are probably induced by other modes of action than DEHP, DBP and DINP.

For di(2-propylhexyl) phthalate the two-generation study and a 90-day repeated dose study showed no clear indications of toxicity to reproductive organs of adult rats (CPSC 2010b).

Furthermore, in an earlier version of the registration dossier, data were presented on the effects of DINP in studies on the estrogenic activity in vitro and in vivo and on effects of DINP on fetal testosterone production. Information on DINP was therefore included in the evaluation of possible effects of the registered substance on the sex hormonal system.

The earlier version of the registration dossier presented data from two studies on DINP: One in vitro study for estrogenic activity (Harris et al., 1997) showed inconclusive results, and another showed no effects in binding assays (Zacharewski et al., 1998). In vivo studies showed no estrogenic effects of DINP (Zacharewski et al., 1998). These conclusions are in general agreement with the conclusions in a recent review on DINP by ECHA stating that: *"In vitro studies indicate that DINP has a low potency to elucidate oestrogenic and/or antioestrogenic effects as measured by ER receptor assays (Akahori et al. 2005; 2008; Takeuchi et al. 2005)." (…) "In in vivo uterotrophic assay, DINP did not show oestrogenic properties (Akahori et al. 2008), but some anti-androgenicity was observed in the Hershberger assay (Lee and Koo 2007)"* (ECHA 2013).

Also, the registrant had reviewed (some of) the available studies on the influence of DINP on steroid synthesis and concluded that:*"Collectively, the data for anti-androgenicity of DINP are based on limited study designs with no or only minor effects being observed at very high doses with no dose-response observed. Based on the comprehensive 2-generation reproductive, sub-chronic, and chronic studies it can be concluded that DINP is not an endocrine disruptor as defined by the Weybridge, IPCS and REACH guidance definitions. Since DINP is a surrogate for DTDP, it can be concluded that DTDP will not have antiandrogenic properties."*

However, the registrant did not include data from a recent study published by Clewell et al., 2013b (sponsored by the registrant). This is a large dose-response study showing that DINP reduced fetal testicular testosterone concentration in a dose-response pattern with a NOAEL of 50 and a LOAEL of 250 mg/kg bw/day.

Effects on DINP on steroidogenesis in fetal testis have been examined in several studies described below. Reductions in fetal testosterone production were seen in the studies in which measurement of testosterone production and/or expression of factors involved in steroid synthesis were performed on the last day of dosing (Boberg et al., 2011; Borch et al., 2004; Hannas et al., 2011; Clewell et al., 2013b; Furr et al., 2014). In one study, a recovery period of two days was included between the last dosing and the time of examination, and this study did not show reductions in fetal testosterone production (Adamsson et al., 2009).

Key findings in animals studies on reproductive effects of DINP are a) dose-dependent long-lasting decrease in sperm motility in rats exposed perinatally (Boberg et al., 2011), b) increased nipple retention and decreased anogenital distance in male rats exposed perinatally (Boberg et al., 2011; Gray et al., 2000), c) increased incidence of permanent changes (permanent nipples, malformations of testes and epididymis) in rats exposed perinatally (Gray et al., 2000), d) a comparable pattern of adverse effects and of mode of action as the reproductive toxicants DEHP, DBP, DIBP and BBP. In fetal testes, several studies describe presence of multinucleated gonocytes and reduced testosterone production, as also described for DEHP, DBP, DIBP and BBP (Boberg et al., 2011; Borch et al., 2004; Hannas et al., 2011; Clewell et al., 2013a,b).

A large dose-response study sponsored by the registrant (Clewell et al., 2013b) showed that DINP induced changes in fetal testes on PND 2, and reduced anogenital distance on PND 14. DINP did not alter AGD, nipple retention or reproductive tract malformations on PND 49. In that study, no examination of sperm parameters was performed.

Table 20: Summary of some studies relevant for evaluation of endocrine disruption.

Method	Results	Remarks	Reference
Rat (Wistar), n= 8 litters Oral: gavage 750 mg/kg bw/day CAS RN 28553-12-0, purity >99% Vehicle: peanut oil Exposure: GD7 to GD 21	NOAEL: Not determined LOAEL: 750 Decreased testicular testosterone content GD 21	One dose only.	Borch et al., 2004
rat (SD), n=7-8 oral: gavage 250, 750 mg/kg/day Vehicle: corn oil Exposure: GD 13 to GD 17	No effect on testosterone production on GD 19	No examination of testosterone production at end of dosing (GD 17) but after 2 days recovery period (GD19)	Adamsson et al., 2009
rat (Wistar), n=9-10 litters oral: gavage 300, 600, 750, 900 mg/kg/d CAS RN 28553-12-0, purity 99% Vehicle: corn oil Exposure: GD 7 to PND 17	NOAEL: 300 LOAEL: 600 Reduced sperm motility and histological changes in foetal testis	Effects on pup body weights, male AGD, nipple retention, and female behaviour at higher doses. Satelite study examined foetal testes (n=3-4 litters)	Boberg et al., 2011
rat (Harlan SD), n= 3-6 litters oral: gavage 500, 750, 1000, 1500 mg/kg/d Two formulations of DINP= CAS RN 28553-12-0, a gift from BASF; and CAS RN 68033-90-2 purchased from Aldrich. Vehicle: corn oil Exposure: GD 14 to 18	NOAEL: Not determined LOAEL: 500 Reduced testis testosterone production GD 18	Similar effects of two different CAS numbers of DINP	Hannas et al., 2011
rat (SD), n=8-9 oral: gavage 50, 250, 750 mg/kg/day CAS RN 68515-48-0 Vehicle: corn oil Exposure: GD 12 to 19	NOAEL: 50 LOAEL: 250 Decreased testis testosterone content GD 19 and presence of multinuclear gonocytes	Effects on Leydig cell clustering at 750 mg/kg bw/day	Clewell et al., 2013a
Rat (SD), n=3-4 per group Oral: gavage 750 mg/kg/day CAS RN 28553-12-0, 98,8% and 68515-48-0, 99% Exposure: GD 14 to GD 18	Inhibition of testosterone synthesis, testosterone production significantly reduced at 750 mg/kg/day	Short-term in vivo One dose only. Similar effects of two different CAS numbers of DINP DINP is weak positive.	Furr et al. 2014
Rat (SD), n=19 in control group, n=14 in DINP group. Oral: gavage	NOAEL: Not determined LOAEL: 750 mg/kg bw/day Increased number of areolas in males, increased incidence of malformations of male	One dose only.	Gray et al., 2000

750 mg/kg/d CAS RN 68515-48-0. Vehicle: corn oil Exposure: GD 14 to PND 3	reproductive organs		
rat (SD), n=24 (controls), n=20 (DINP groups). oral: diet 760, 3800, 11400 ppm CAS 68515-48-0, 99.9% diester phthalates primarily with alkyl chains of isononyl alcohols (C9H19) with different branching structures Exposure: GD 12 to PND 14	NOAEL: 56 (760 ppm) LOAEL: 288 (3800 ppm) Increased number of animals with multinuclear gonocytes	At next dose effects on: maternal weight and weight gain, male pup weight at PND 2, anogenital distance and anogenital index at PND 14, testis histology on PND 2, and weight of the levator ani/bulbucavernosus muscle on PND 49-50. DBP used as positive control. Measurements of blood metabolites.	Clewell et al., 2013b

In a study by Borch et al., 2004, pregnant Wistar rats were exposed from GD 7 to GD 21 with DINP (750 mg/kg bw/day), DEHP (300 mg/kg bw/day) or a combination of DINP (750 mg/kg bw/day) plus DEHP (300 mg/kg bw/day). Testicular testosterone production and testicular testosterone content was reduced in DINP exposed male foetuses at GD 21.

Adamsson et al., 2009, examined the influence of DINP on testicular testosterone production, testicular mRNAand protein levels for steroidogenesis, and testicular histology in SD rats exposed during gestation from GD 13 to 17. Three groups of 7-8 pregnant dams were exposed by gavage from GD 13 to GD 17, and male foetuses were examined on GD 19. They found no change in testosterone production of foetal testes at GD 19 after exposure to 250 and 750 mg/kg bw per day of DINP. DINP did not alter the histology of steroidogenic cells in the foetal testes or adrenals. Adamsson et al. found increased mRNA levels of P450scc and Insl3, genes that are known to be reduced by other phthalates and that are likely involved in the anti-androgenic effects of these compounds. The discrepancy between other studies on phthalate effects on sterodiogenic factors and the results reported by Adamsson et al., 2009, may be due to the fact that their study included a recovery period of two days between the last dosing and the time of examination. As the authors describe in their discussion, it is possible that the detected increase in P450scc and Insl3 is a "rebound effect" due to low testosterone production at the time of dosing a few days earlier. The study did not include any examination of testosterone production or levels at the end of dosing at GD 17.

Hannas et al., 2011, describes a study in which pregnant Sprague-Dawley rats were exposed to 0, 500, 750, 1000, or 1500 mg/kg bw/day of DINP from GD 14 to 18 by gavage (in parallel with other phthalates). The study included three blocks of animals exposed to two different CAS numbers for DINP: CAS RN 28553-12-0 from BASF was administered to 3-6 dams per dose group across two separate blocks, and CAS RN 68033-90-2 was administered to 3 dams per dose group in a single block. DINP did not affect mortality, maternal body weight or litter size at any dose. Testicular testosterone production ex vivo was assessed by incubation of testes of 18 day old foetuses for 3 hours and testosterone measurement in the media. Dose-related decreases in testosterone production were seen for DINP from 500 mg/kg bw/day and for the other tested phthalates (DEHP, DiBP and DiHP (diisohexyl phthalate)) from 300 mg/kg bw/day and above. No NOAEL could be obtained for DINP, as effects were seen at all dose levels, whereas the other phthalates were tested in lower doses and showed a NOAEL of 100 mg/kg bw/day. DINP was 2.3 fold less potent than DIBP DIHP, and DEHP in reducing

foetal testicular T production (studied with a similar test set up) and 18-fold less potent that DPeP. The mean expression of mRNA for the steroidogenic factors StAR and CYP11a was reduced at all doses of DINP, though this was only statistically significant at 1000 and 1500 mg/kg bw/day. Overall, no differences were seen for the two different DINP formulations.

Clewell et al., 2013a (designated Clewell et al 2011a by ECHA 2013), performed a study on foetal exposure (GD 12 to 19) of rats to DINP with examination of metabolite disposition as well as anogenital distance (AGD) measurement, testicular testosterone measurement, and testicular histopathology. Dams (9 controls and 8 DINP exposed dams) were dosed from GD 12 to 19 and caesarean sections were performed 24 hours after last dosing (GD 20). Three doses of DINP were administered by gavage: 50, 250 or 750 mg/kg bw/day. Another subset of animals (9 controls and 8 DINP exposed dams) was similarly dosed from GD 12 to 19 and caesarean sections were performed 2 hours after last dosing. Though not clearly described in the paper, the actual number of litters in the control group was possibly 25 and 27 litters at 2 and 24 hours after dosing, respectively. The animals sacrificed 2 hours after dosing were applied for measurement of testicular testosterone and metabolite disposition, whereas the animals sacrificed 24 hours after dosing were applied for anogenital distance measurement, testicular testosterone measurement, testicular histopathology, and metabolite disposition. Other animals were sacrificed 0.5, 1, 6, and 12 hours after dosing and applied for metabolite disposition only, and these analyses will not be discussed in detail here.

DINP exposure by gavage did not alter maternal body weight or weight gain during pregnancy and did not alter foetal body weight at sacrifice. In the foetuses exposed to 250 and 750 mg/kg bw/day of DINP an increased number of multinuclear gonocytes in testes was seen, and testicular testosterone production 2 hours after dosing was decreased. At the highest dose of 750 mg/kg bw/day also the incidence of Leydig cell aggregates was increased. The potency of DINP (internal and external dose) on reducing testicular testosterone content was compared with the potencies of DEHP and DBP (internal and external dose). For the parent compound it appeared that DINP was 2.5 and 6 times less potent than DEHP and DBP, respectively. For the calculated foetal plasma concentration it was calculated that the DINP metabolite MINP was 7 and 4 times less potent than MEHP and MBP, respectively.

A study by Furr et al 2014 was designed to develop and validate a short-term in vivo protocol to detect phthalate esters (PEs) and other chemicals that disrupt foetal testosterone synthesis and testis gene expression in rats. Pregnant rats were dosed from gestational day (GD) 14 to 18 at one dose level (750 mg/kg) with one of 27 chemicals including PEs, PE alternatives, pesticides known to inhibit steroidogenesis, an estrogen and a potent PPARα agonist. Ex vivo testis testosterone production (T Prod) was measured on GD 18. Dose-response studies were conducted with 11 of the chemicals to determine their relative potencies. DINP was tested for two different CAS numbers (CAS RN 28553-12-0 and 68515-48-0). DINP inhibited the testosterone synthesis and the testosterone production was significantly reduced by DINP exposure at 750 mg/kg/day.

In the study by Gray et al., 2000, pregnant rats were gavaged daily with DEHP, BBP, DINP, DEP, DMP and DOTP at single dose of 750 mg/kg/d in corn oil as vehicle from GD 14 through postnatal day 3. Males in the DEHP and BBP groups displayed a reduced anogenital distance at PND 2 and males with areolas were observed in the DEHP, BBP and DINP dose groups at PND13 but without details on the incidence of affected male pups in treated and control animals. Adult males exposed perinatally to DEP, DMP and DOTP were unaffected while males in the DEHP, (91%, $p< 0.0001$), BBP (84%, $p< 0.0001$) and DINP (7.7%, $p<0.04$) treatment groups had malformations of testis, epididymis, accessory reproductive organs and external genitalia.

Clewell et al., 2013b, performed a dietary study on the developmental effects of DINP on the male reproductive system. Dams were exposed through diet to 0, 760, 3800 or 11400 ppm of DINP from GD 12 to PND 14. DBP was used as a positive control at a dose of 7600 ppm. The target doses for these dietary concentrations were: 0, 50, 250 and 750 mg/kg bw/day of DINP and 500 mg/kg bw/day of DBP. The control group included 24 dams, each DINP group contained 20 dams and the DBP group contained 21 dams.

At 250 mg/kg the presence of multinucleated gonocytes in testes was increased on PND 2. At the high dose of 750 mg/kg bw/day several endpoints were affected: maternal weight and weight gain, male pup weight at PND 2 (88% of control weight), anogenital distance and anogenital index ("scaled AGD"; AGD divided by cube root of body weight) at PND 14, presence of Leydig cell aggregates in testis on PND 2, and reduction of absolute, but not relative, weight of the levator ani/bulbucavernosus muscle on PND 49-50. No change in anogenital distance or anogenital index was seen at PND 2. No changes in the number of nipples were seen at PND 14 or 49-50. The reduction in maternal body weight was related to a significantly reduced food intake, which may be related to food palatability according to the authors. Male pup birth weight was significantly reduced in the high dose group, but no (significant) change in AGD was seen at PND 2. The positive control DBP showed more marked effects on these endpoints. No examination of sperm parameters was performed and no examinations were performed on offspring older than 49 days of age.

Considerations on effects of phthalates on the sex hormonal system in relation to phthalate ester backbone length

In addition to the phthalates DEHP, DBP, BBP and DIBP, a number of other phthalates have also been identified as being able to reduce fetal testosterone production in rats and thereby induce anti-androgenic effects such as reduced anogenital distance. Anti-androgenic effects (decreased prenatal testosterone production and reduced anogenital distance) are seen with di-n-heptyl phthalate (CAS RN 3648-21-3) which has a C7 backbone (Saillenfait et al. 2011, Furr et al., 2014). In addition, anti-androgenic effects (decreased prenatal testosterone production and reduced anogenital distance) are seen with fetal exposure to source substance diisononyl phthalate (DINP, mainly of C7 backbone with dimethyl branching, and some C8 backbone with methyl branching) (Clewell et al., 2013a, Clewell et al. 2013b, Furr et al. 2014, Hannas et al. 2011, Boberg et al 2011). As no sperm parameters were examined in the larger guideline studies for DINP, the potential association between the observed fetal testicular effects and possible late-life adverse effects has not been clearly examined. In contrast, di(2-propylheptyl) phthalate (CAS RN 53306-54-0) containing a C7 backbone has shown no effect on anogential distance or nipple retention of males in a two-generation study, thus pointing to lack of anti-androgenic mode of action of this phthalate (CPSC, 2010b). No effects on fetal anogenital distance were found in studies on DnOP and ditridecyl phthalate, which have backbones of 8 carbon atoms or more (Saillenfait et al, 2011; Saillenfait, 2013a).

However, the possible steroid synthesis disrupting ability of phthalate esters with C8 backbones has not been fully elucidated, and an in vitro study has shown that mono-n-octyl phthalate was able to reduce testosterone production in mouse Leydig tumor cells (Clewell et al 2010), indicating a possible anti-androgenic effect of a phthalate with C8-backbone.

Additionally, a study comparing effects of 4 weeks exposure of rats to nine different phthalate diesters (C3-C11) showed significant changes in sperm counts and motility for several diesters including DEHP, DBP, BBP, DnOP, DINP, DIDP (diisodecyl phthalate, C10 branched), and DUP (Kwack et al 2009). This may indicate adverse reproductive effects of phthalate esters with longer chain lengths than C7, although the mode of action is not clear.

A sharp division into low, intermediate and high molecular weight phthalates may thus be misleading with regards to expected toxicity including the endocrine disrupting mode of action. As numerous registered phthalates are multi constituent substances and include compounds with backbone lengths around 7 carbon atoms, it appears important to perform individual toxicity evaluations for each compound.

Collectively, available information suggests that not only phthalates with straight chain carbon backbones of C3-C6, but also phthalates with the shortest carbon backbones being C7 may cause anti-androgenic effects such as decreased prenatal testosterone production and reduced anogenital distance following fetal exposure (Saillenfait et al. 2011, Furr et al., 2014 , Clewell et al. 2013, Hannas et al. 2011, Boberg et al 2011). These effects are indicative of an endocrine disrupting mode of action that is often

associated with reproductive toxicity later in life, e.g. reduced sperm quality and impaired male and female fertility.

Conclusion on review of information regarding the concern for effects on the sex hormonal system

No discussion on endocrine disrupting properties of the registered substance was provided by the registrant.

There are minor indications of toxicity to the developing reproductive system for proposed source substances for read across in regards to reproductive toxicity, DIDP and C911P, as reduced reproductive organ weights are seen in offspring (Hushka et al., 2001, Willoughby et al., 2000). For C911P, the observed reductions in epididymis weights of offspring does not appear to be related to body weight changes and may thus be considered a developmental effect on the male reproductive system (Willoughby et al., 2000). In contrast, it is unclear whether reductions in testis and ovary weights of offspring in the two-generation study on DIDP is related to body weight changes or reflects organ specific developmental toxicity (Hushka et al., 2001). There are no indications of anti-androgenic effects on anogenital distance and nipple retention in the two-generation study (Hushka et al., 2001), but it should be noted that preputial separation, anogenital distance and nipple retention were only investigated in the second of two 2-generation studies, in which the highest dose was lower than applied in the first two-generation study.

In addition, there are indications of anti-androgenic properties of other structurally similar substances, including DINP.

It is well known that the phthalates DEHP, DBP, BBP and DIBP have anti-androgenic properties. In addition to these phthalates, a number of other phthalates have also been identified as being able to reduce fetal testosterone production in rats and thereby induce anti-androgenic effects such as reduced anogenital distance (including DINP, DNuP and DUP). Further, there are indication of adverse reproductive effects of phthalate esters with longer chain lengths than C7, although the mode of action is not clear. Thus, a sharp division into low, intermediate and high molecular weight phthalates may thus be misleading with regards to expected toxicity including the endocrine disrupting mode of action.

All in all, there is a concern for anti-androgenecity of the registered substance. In order to address this concern, the data gaps on repeated dose toxicity and reproductive toxicity needs to be filled (see section 7.9.4.2 and 7.9.7.4).

7.10.2.2. Review of information regarding the concern for thyroid disruption

An additional concern for endocrine disrupting activity (thyroid disrupting effect) and developmental neurotoxicity is raised due to several other phthalates including high molecular weight phthalate esters (HMWPEs) found to alter thyroid hormone balance in experimental studies.
No data on possible thyroid disruption of DTDP is provided by the registrant.
Thyroid toxicity, e.g. thyroid follicular hyperplasia, has been observed for phthalates with carbon backbones C6 to C8 (Bhat et al., 2014, Howarth et al 2001, Poon et al 1997, Hinton et al 1986, CPSP 2010c), but as e.g. thyroid hormone levels are rarely registered, it is not clear whether thyroid toxicity is related to certain backbone lengths. This concern for thyroid disrupting ability of phthalates is relevant for the HMWPE group also, including the registered substance, DTDP.

The following examples address the concern for interference with the thyroid hormone system by phthalates with carbon backbone length at or above C7:

- Diisononyl phthalate (DINP): No effects of DINP on thyroid weight or histology were seen in a 90-day subchronic toxicity study or a 2-year chronic toxicity study in rats according to the EU risk assessment report (EC, 2003). In another 2-year chronic toxicity study on DINP, relative and absolute thyroid weights were elevate in all doses and in both sexes after 12 months, but not after 24 months and no histological changes in thyroids were reported (Biodynamics 1986 as described in EC, 2003).

In the EC review it was concluded that DINP may increase thyroid activity because it enhances iodide uptake in a rat thyroid cell line mediated by sodium/iodide symporter (NIS) (Wenzel et al. 2005; Breous et al. 2005). DINP inhibits TH-dependent rat pituitary GH3 cell proliferation with and without T3 (Ghisari and Bonefeld-Jorgensen 2009). The effects of phthalates are rather weak in conditions mimicking the natural availability of the endogenous T3.

- Di-n-octyl phthalate (DnOP): According to US Consumer Product Safety Commission (CPSC 2010c), substantial evidence of DnOP-induced thyroid toxicity in experimental animals and in vitro has been presented in studies reviewed. Structural alterations such as reduced thyroid follicle size and decreased colloid density were reported in rat studies, as were alterations in thyroid hormones T3 and T4. In addition, ToxCast data show that DnOP is active in TPO assay, whereas other HMWPE are not currently tested (ToxCast accessed August 2018).
- Di(2-propylheptyl)phthalate: In a 90-day study changes in thyroid histology (hypertrophy of the follicular epithelium of the thyroid glands) were seen in both sexes. In a two-generation study, follicular hypertrophy/ hyperplasia was seen in the thyroid glands of 16 males and 18 females of the 600 mg/kg dose group as well as in 13 male and 6 female animals of 200 mg/kg dose group (F1 generation). Increases in thyroid weights were observed (information from CPSC link to robust study summaries provided by the registrant in IUCLID) (CPSC 2010a).
- Diisododecyl phthalate (DIDP): A 3-month study indicated thyroid disrupting effects of DIDP in vivo (see also section 7.9.4.1 on repeated dose toxicity) (Unpublished study report 1968a). However, a 2-year study in mice (Cho et al., 2008) reported c-cell hyperplasia in thyroids of some dose groups, but no histological changes related to possible thyroid disrupting properties of DIDP. A study on 90 days exposure of dogs to DIDP revealed no effects on thyroid weights and histology.

  DIDP and other phthalates: The ECHA review (ECHA 2013) discussed the possible influences of DIDP on thyroid hormone disruption, and found that DIDP may affect the sulphate supply pathway leading to increase in the availability of free hormones and decreased capacity for detoxification via sulphate conjugation (Harris et al. 1997; Turan et al. 2005). In addition, DIDP enhanced iodide uptake in thyroid cell line and had TH-like effects in pituitary cells (Wenzel et al. 2005; Breous et al. 2005; Ghisari and Bonefeld- Jorgensen 2009). DIDP had a similar potency to induce iodide uptake than DINP, DEHP being more potent.

  No clear conclusions regarding possible effects on the thyroid system were made in the ECHA review, but it was noted that "*In case of the thyroid, weak effects have been reported on iodide uptake for certain phthalates. DINP, DIDP, DEHP and DOP significantly enhanced iodide uptake, whereas BBP augments the uptake but that at toxic concentration and DBP had no effect (Wenzel et al. 2005; Breous et al. 2005). The molecular mechanisms may differ: DIDP, BBP and DOP enhanced transcriptional activity of promoter N3, whereas DEHP and DINP had no effect and DBP even reduced the activity. In addition, phthalates enhanced promoter and enhancer (N3 + NUE) activity in the following order: DIDP, BBP, DEHP, DOP and DINP, and DBP had a decreasing effect. Only DIDP, BBP and DOP seem to increase the mRNA levels of rNIS, and DEHP, DINP and DBP had no effect*." Chronic and subchronic toxicity studies on these substances showed no clear effects on thyroid weight or histology.

The data presented above, lead to a concern for thyroid toxicity of the registered substance. Due to the central role of the thyroid hormone system in brain development, the concern for effects on the thyroid hormone system is related to a concern for developmental neurotoxicity.

Conclusion on review of information regarding the concern for thyroid disruption

The eMSCA raised a concern for interference of the registered substance with the thyroid hormone system during substance evaluation based on a concern for thyroid toxicity of other HMWPEs.

No discussion on thyroid disrupting properties of the registered substance was provided by the registrant.

No conclusion regarding this concern can be drawn by the eMSCA due to the identified data gap on repeated dose toxicity and reproductive toxicity (see section 7.9.7.4). Further studies on DTDP are necessary. The data gaps on repeated dose toxicity and reproductive toxicity needs to be filled (see section 7.9.4.2 and 7.9.7.4).

7.10.3. Conclusion on endocrine disrupting properties

The eMSCA raised a concern for endocrine disruption of sex- and thyroid hormones during the substance evaluation. Due to the central role of the thyroid hormone system in brain development, the concern for effects on the thyroid hormone system is related to a concern for developmental neurotoxicity.

No conclusion regarding this concern for endocrine disruption (i.e. anti-androgenecity and thyroid disruption) can be drawn by the eMSCA due to the identified data gap on repeated dose toxicity and reproductive toxicity (see section 7.9.4.2 and 7.9.7.4). In order to address the concern, these data gaps needs to be filled.

The data gap in the standard information requirelements on reproductive toxicity includes the extended one-generation reproductive toxicity study (OECD TG 443) (section 7.9.7.4.1). In order to address the concern for thyroid disruption, inclusion of examination of thyroid hormones and thyroid histology as well as triggering of the Developmental Neurotoxicity cohort should be considered when the study is requested.

7.11. PBT and VPVB assessment

7.11.1. Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

7.11.1.1. Persistency assessment

The registered substance (CAS RN 68515-47-9) is *not readily biodegradable*. Low biodegradation rates are in particular likely occurring in ready biodegradation like tests employing environmentally unrealistic high concentration of the test substance due to the strong sorption potential (high hydrophobicity) of the substance which may decrease significantly the unavailability of the substance to the degrading microorganisms. Nevertheless a prolonged ready biodegradability test with non-pre-adapted inoculum and other ready biodegradability test data indicate that the substance and its degradation products (metabolites) based on screening level information should not be regarded as being persistent in surface water (adequate information is currently not available about the persistency of the substance in sediments and in soil).

The degradation product (representative mono phthalate ester) is predicted to be readily biodegradable. This is further supported by test data on a structural analogue. Therefore, this degradation product is concluded to *not* meet the P criterion.

7.11.1.2. Bioaccumulation assessment

The registered substance (CAS RN 68515-47-9) is concluded not to meet the criteria for bioaccumulation.

7.11.1.3. Toxicity assessment

Not assessed.

7.11.1.4. Summary and overall conclusion on PBT and vPvB properties

The parent substance (CAS RN 68515-47-9) is concluded to not fulfil criteria for bioaccumulation (B) and is *likely* to not fulfil criteria for persistency (P).

The degradation product is concluded not to fulfil criteria for persistency (P) and is *likely* not fulfil criteria for bioaccumulation (B).

Hence, overall the substance is concluded not to be a PBT or vPvB substance.

This conclusion does not necessarily cover additives which were not included in the PBT assessment.

7.12. Exposure assessment

Not evaluated by eMSCA as there was insufficient information in registration.

7.13. Risk characterisation

Not evaluated by eMSCA as there was insufficient information in registration.

7.14. References

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