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-C10-12-branched alkyl esters (D1012P)

EC No 700-989-5

(Previously registered as diundecyl phthalate (DIUP), branched and linear, EC No 287-401-6, CAS No 85507-79-5)

Evaluating Member State(s): Denmark

Dated: 4 December 2021

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

Danish Environmental Protection Agency (Danish EPA)
Tolderlundsvej 5
5000 Odense C
Denmark
Tel: +45 7254 4000
Email:mst@mst.dk

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-C10-12-branched alkyl esters (List no. 700-989-5) was originally included on CoRAP and selected for substance evaluation 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 additional points of concern were identified:

- Endocrine disruption
- PBT/vPvB

Background for CoRAP listing and for the identified additional concern

The initial concern for reproductive toxicity of the registered substance 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 classification 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).

Furthermore, DHNUP was included in the list of pre-registered substances with an anticipated registration deadline by end of November 2010. Following the registration deadline, it appeared that DHNUP had not been registered. However, several other individual phthalates with alkyl chain lengths within the same range as DHNUP (i.e., in the C7-C11 range) had been registered. The Substance, 1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters, List No 700-989-5 was one of these substances.

The Danish EPA was concerned that the Substance may also warrant classification as a reproductive toxicant. However, the registrant had not self-classified the substance.

A concern on the lack of information on exposure was also included in CoRAP as no assessment of exposure (including exposure scenarios) or evaluation of risk or calculation of RCRs were included in the registration despite the high (aggregated) tonnage registered, which may entail a risk should the concern for hazardous properties of the 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 related substances.

Furthermore, PBT/vPvB was identified as an additional concern during the substance evaluation since the registered substance fulfils some of the PBT screening criteria, as specified in REACH, Annex XIII, section 2.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A PBT assessment was concluded in 2019 with the publication of a hazard assessment outcome document in December 2019 (ECHA, 2019).

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

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information 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; a compliance check should be initiated.	X

4. FOLLOW-UP AT EU LEVEL

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

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Currently, no regulatory follow-up in foreseen at EU- level. However, the outcome of the requested compliance check may entail a revised conclusion on possible regulatory action, after a further evaluation of exposure and risk.

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 to an incompliant read-across justification.

The standard information which will be provided through the Compliance Check process is expected to enable to conclude on the concerns regarding reproductive toxicity and endocrine disruption and no further requests for testing beyond the missing standard information requirements are expected to be necessary. Therefore, the substance evaluation is concluded at this point.

Currently, no regulatory follow-up in foreseen at EU- level. However, the outcome of the requested compliance check may entail a revised conclusion on possible regulatory action, after a further evaluation of exposure and risk.

Should the testing provided as an outcome of the Compliance Check decision not allow for conclusion on the endpoints of reproductive toxicity and endocrine disruption, and further data are needed to clarify the concerns raised under SEv to evaluate whether further regulatory action is needed for this substance initiation of a new SEv could be envisaged.

Further evaluation of exposure awaits the outcome of the hazard assessment and a possible voluntary update of the registration with exposure information on this high tonnage chemical.

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-C10-12-branched alkyl esters (List no. 700-989-5) was originally selected for substance evaluation to clarify concerns about:

- Suspected CMR (reproductive toxicity only)
- Exposure/Lack of exposure assessment
- Lack of Risk Characterisation Ratio (RCR)
- High (aggregated) tonnage

During the evaluation additional points of concern were identified:

- Endocrine disruption
- PBT/vPvB

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Suspected CMR (reproductive toxicity 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.
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 of sex- and thyroid hormones	Concern unresolved. Continued concern based on information from structurally similar substances. No conclusion can be reached due to data gaps in standard information.
PBT/vPvB	Concern refuted. The registered substance is concluded not to be a PBT or vPvB substance.

7.2. Procedure

The Substance D1012P 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/Suspected 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.

During the evaluation, the evaluating MSCA identified additional concerns regarding PBT/vPvB and endocrine disruption, i.e., disruption of sex- and thyroid hormones.

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

No studies on reproductive toxicity or endocrine effects have been performed with the Substance D1012P. The registrant presents data for diisodecyl phthalate (DIDP), and other High Molecular Weigh Phthalic Acid Esters (HMWPEs) based on a category approach using read-across data to characterize endpoints regarding reproductive toxicity. For other endpoints including repeated dose toxicity, the registrant presents data for DIDP and diisononyl phthalate (DINP) as read-across substances.

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 identity of the source and target substances used in the proposed read-across.

The registrants' comments were received June 2015.

The eMSCA analyzed the read across justification proposed by the applicant and qualified by information provided by the registrant(s), applying the ECHA Read-Across Assessment Framework (RAAF) guidance. For use in this analysis, the eMSCA requested and received additional information from the Registrant about the composition of the registered substance and proposed read across substances.

This evaluation concluded that the read across does not fulfil the criteria of the RAAF. Thus, there are standard information gaps on the endpoints 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 eMSCA decided that the evaluation of exposure and risk characterisation would await the results of the hazard assessment, which in turn depend on the provision and the results of standard information data that are expected to be required once a compliance check is performed.

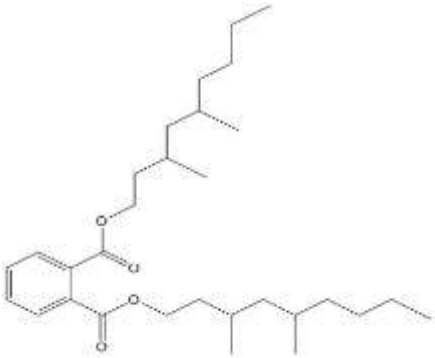
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	1,2-benzenedicarboxylic acid, di-C10-12-branched alkyl esters
List number	700-989-5
Previously registered as EC number:	287-401-6
Previously registered as CAS number:	85507-79-5
Index number in Annex VI of the CLP Regulation:	No annex VI entry
Molecular formula:	C30H50O4
Molecular weight range:	475.0
Synonyms:	Di-isoundecyl phthalate , D1012P

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

Structural formula:



Multiconstituent/UVCB substance/others

The registered substance is a di-ester of phthalic anhydride and isouncedyl alcohol.

The Registrant(s) categorize the registered substance as a multi-constituent substance in the CSR, however, it is referred to as a 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.

Information about constituents, impurities and additives is confidential.

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 (see also section 7.9.8).

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid Viscous Colour : 9 (Pt/Co) (max 30) scale, Colourless Odour: odourless
Vapour pressure	Vapor pressure for Di-isoundecyl phthalate is 0.000000497 Pa at 25 degrees C and below 0.01 Kpa at 150 degrees C.
Water solubility	Water solubility for Di-isoundecyl phthalate is 0.00000441 mg/L at 25 degrees C
Partition coefficient n-octanol/water (Log Kow)	Log Kow (Pow) for Di-isoundecyl phthalate is estimated at 10.3 at 25 degrees C.
Flammability	Non flammable Di-isoundecyl phthalate has a very low degree of flammability
Explosive properties	Nonexplosive Di-isoundecyl phthalate does not have explosion limits under standard conditions, due to the lack of flammability as indicated by the high flash point and boiling range.

Oxidising properties	Not oxidizing Di-isoundecyl phthalate has no oxidizing properties
Granulometry	n.a. In accordance with REACH chapter R.7A Endpoint Specific Guidance, specifically R.7.1.14.1 Information requirements 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-isoundecyl phthalate is stable in organic solvents
Dissociation constant	n.a. 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-isoundecyl phthalate does not contain functional groups subject to dissociation, consequently a study is not justified.
Melting/freezing point	Pour point for Di-isoundecyl phthalate is below -39 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 D1012P will not freeze at low temperature.
Boiling point	Boiling point for Di-isoundecyl alcohol is above 400 degrees C. (> 673.15 K). According to USEPA studies the boiling point for Di-isoundecyl alcohols is 466 º C.
Surface tension	Surface tension for Di-isoundecyl phthalate is 30.9 mN/m at 20 Degrees C.
Flash point	Flash point for Di-isoundecyl phthalate is 254 degrees C at 101325 Pa. 527 Kelvin at 101325 Pa
Self-ignition temperature	Auto flammability / Self-ignition temperature for Di-isoundecyl phthalate is400 degrees C at 101325 Pa Auto flammability / Self-ignition temperature for Di-isoundecyl phthalate 673 kelvins at 101325 Pa
Viscosity	Di-isoundecyl phthalate viscosity is 151 mPa.s at 20 degrees C. 180 mm²/s (static) at 20º C. - 180 cSt 52 mm²/s (static) at 40º C. - 52 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

Table 7

USES	Use(s)
Uses as intermediate	-
Formulation	-
Uses at industrial sites	1. Manufacture of substance Manufacture of the substance or use as an intermediate or process chemical or extraction agent including recycling/recovery, material transfers, storage, maintenance, and loading (including marine vessel/barge, road/rail car) Sectors of Uses (SU): Industrial SU8 Process Category (PROC): PROC1, PROC2, PROC3, PROC4, PROC8a, PROC8b, PROC15 Environmental Release Category (ERC): ERC1, ERC2 2. Polymer Processing Processing of formulated polymers including material transfers, additives handling (e.g., pigments, stabilisers, fillers, plasticisers, etc.), moulding, curing and forming activities, material re-works, storage and associated maintenance Sectors of Use (SU): Industrial (SU12) Process Category (PROC): PROC5, PROC6, PROC7, PROC8, PROC9, PROC13, PROC14 Environmental Release Category (ERC): ERC3, ERC10A, ERC11A 3. Use in coatings Covers the use in coatings (paints, inks, adhesives, etc) including exposures during use (including materials receipt, storage, preparation, and transfer from bulk and semi-bulk, application by spray, roller, spreader, dip, flow, fluid Sectors of Use (SU): Industrial (SU10) Process Category (PROC): PROC1, PROC2, PROC3, PROC4, PROC5, PROC7, PROC8a, PROC8b, PROC10, PROC13 Environmental Release Category (ERC): ERC2, ERC8C, ERC8F
Uses by professional workers	-
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classifications available.

7.6.2. Self-classification

No self-classifications in the registration dossier.

- There are no further hazard classes notified among the aggregated self-classifications in the C&L Inventory.

7.7. Environmental fate properties

D1012P have been screened for its potential PBT properties since the substance fulfils 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 D1012P is not persistent (P) and bioaccumulative (B) or very persistent (vP) and very bioaccumulative (vB). The potential of D1012P 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 C11 backbone with some branching. This structure has been chosen since D1012P is predominantly composed of C11 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 D1012P. 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 extent 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 several 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 C11 structure (SMILES: CCCC(C)CC(C)CCCOC(=O)c1ccccc1c(=O)OCCC(C)CC(C)CCCC).

In general, the 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 177 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 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 C10 to C12. A mono phthalate ester with branched C11 side chain has been chosen as a representative structure for the mono phthalate ester degradation products and is used for model calculations presented in the following sections.

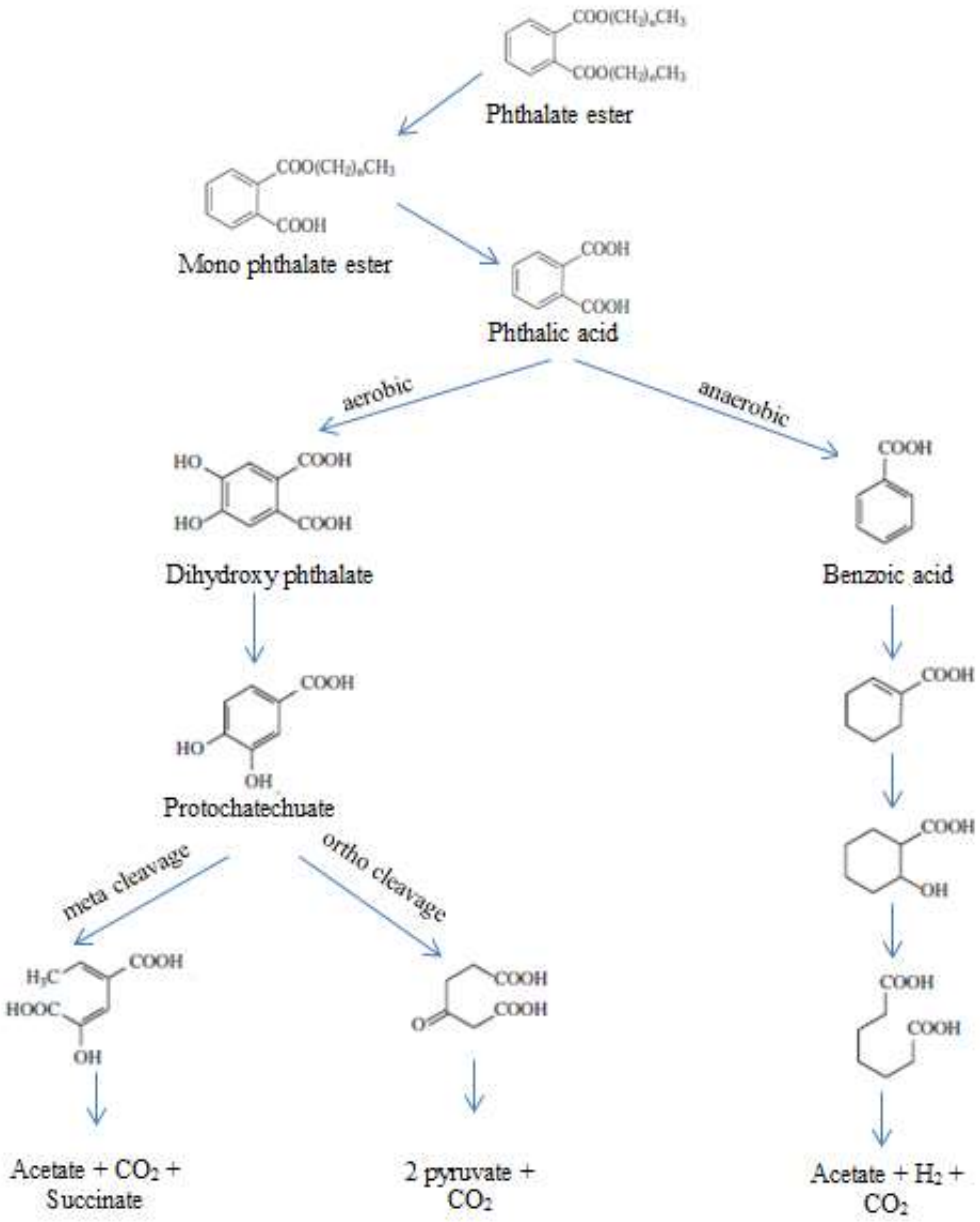
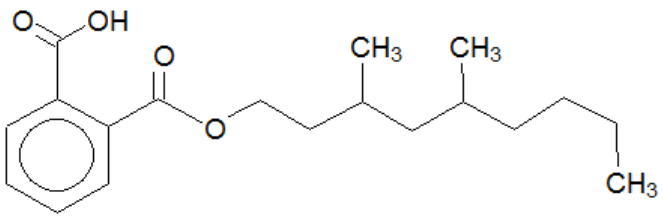


Figure 1. General biodegradation pathway for phthalate esters in the environment. For more information see Staples *et al. (1997); Liang* et al*. (2008)* & *Vamsee-Krishna & Phale (2008).*

Table 8 : Degradation (transformation) product/metabolite

EC number:	N.A.
EC name:	N.A.
SMILES:	C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1
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:	$C_{19}H_{28}O_4$
Molecular weight range:	320.43
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.

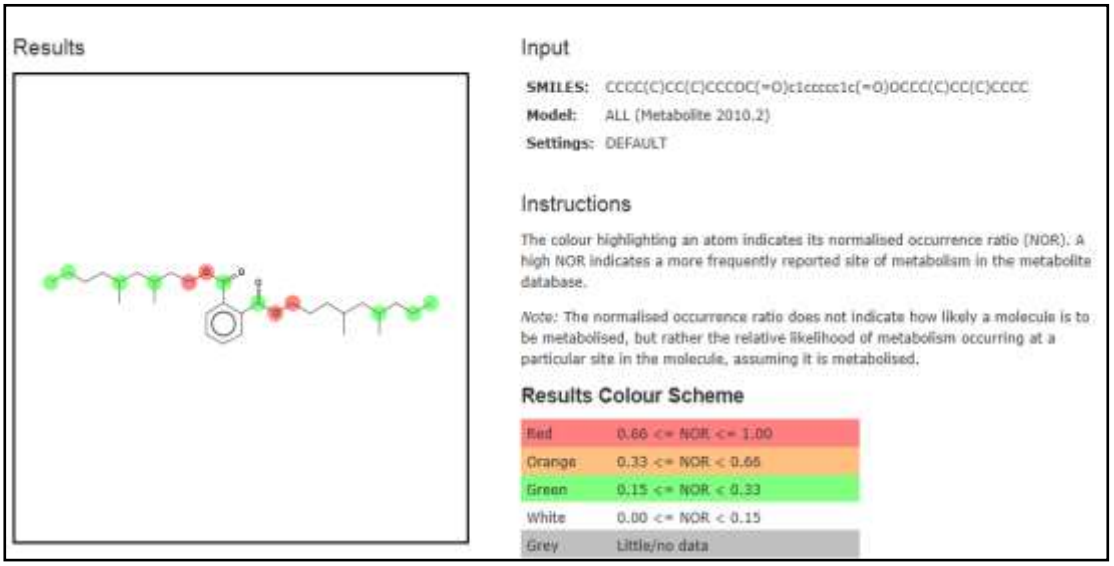


Figure 2. Screen dump from MetaPrint 2D

7.7.2. Degradation

7.7.2.1. Abiotic degradation

7.7.2.1.1. Hydrolysis

Diisoundecyl phthalate	Degradation product (representative mono phthalate ester)
Calculated half-life:	Calculated half-life:
pH 7 = 3.4 years	pH 7 = 6.9 years
pH 8 = 125 days	pH 8 = 250 days
Hydrowin (v.2.00)	Hydrowin (v.2.00)
Calculation SMILES:	Calculation SMILES:
C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1

Hydrolysis is not expected to contribute significantly to the removal of the substance or its representative degradation product from the environment. The model calculations are within the applicability domain of the model which has a total of 124 ester substances in the training set. Hydrowin (v.2.00) does not have a specified applicability domain for log Kow.

7.7.2.1.2. Phototransformation/photolysis

7.7.2.1.2.1. Phototransformation in air

Diisoundecyl phthalate (D1012P)	Degradation product (representative mono phthalate ester)
Calculated half-life:	Calculated half-life:
4.26 hours	8.17 hours
AOPWIN (v.1.92)	AOPWIN (v.1.92)
Calculation SMILES:	Calculation SMILES:
C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1

Photodegradation half-life has been calculated for the parent compound (D1012P) and degradation product (representative mono phthalate ester). The parent compound is estimated to have a half-life of 4.26 hours or 0.36 days based on a standard day with 12 hours of light. The degradation product is estimated to have a half-life of 8.17 hours or 0.68 days based on a standard day with 12 hours of light. Thus, both parent compound and degradation product have the potential to degrade rapidly by OH attack in the atmosphere. However, this degradation pathway is considered as unlikely to contribute significantly to the overall loss of the substances from the environment, since the substance is predicted to have negligible partitioning to air (see Section on environmental distribution).

AOPWIN does not have a specified applicability domain for log Kow.

7.7.2.1.2.2. Phototransformation in water

Photolysis will not contribute to the degradation of D1012P in the aquatic environment because it does not absorb light at wavelengths >290 nm, in the range that contribute to this process. 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 D1012P in terrestrial environments because it does not absorb light at wavelengths >290 nm, i.e. the range that contribute to this process. 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

Diisoundecyl phthalate, (D1012P)	Degradation product (representative mono phthalate ester)
Overall result:	Overall result:
Not readily biodegradable	Readily biodegradable
Individual models:	Individual models:
Biowin 1: Biodegrades fast (0.978) Biowin 2: Biodegrades fast (0.998) Biowin 3: Weeks to Months (2.729) Biowin 4: Days (3.890) Biowin 5: Not readily degradable (0.413) Biowin 6: Not readily degradable (0.282) Biowin 7: Does not biodegrade fast (-0.349) Biowin (v.4.10)	Biowin 1: Biodegrades fast (1.055) Biowin 2: Biodegrades fast (0.999) Biowin 3: Weeks (3.018) Biowin 4: Days (3.891) Biowin 5: Readily degradable (0.709) Biowin 6: Readily degradable (0.747) Biowin 7: Does not biodegrade fast (0.160) Biowin (v.4.10)
Calculation SMILES:	Calculation SMILES:
C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)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 D1012P 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 must 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 D1012P nor the representative mono phthalate degradation product fulfils the screening criteria for P regarding Biowin predictions.

7.7.2.2.1.2. Screening tests

Two screening studies OECD TG 301F (ready biodegradability: manometric respirometry test, non GLP) have been conducted with D1012P.

Test 1, OECD TG 301F conducted in 1995

Fresh activated non-adapted sludge was used as the inoculum. Biodegradation was based on oxygen consumption and the theoretical oxygen demand was calculated using results of an elemental analysis of the test substance. The ThOD calculation of the test and positive control substances was based on Annex IV of the OECD TG 301F.

Activated sludge and test medium were combined prior to test substance addition. Test medium consisted of glass distilled water and mineral salts (phosphate buffer, ferric chloride, magnesium sulfate, calcium chloride).

One litre glass flask vessel was used and were placed in water baths and monitored electronically for oxygen consumption. Test substance was tested in triplicate, controls and blanks were tested in duplicate.

Test substance concentration was approximately 50 mg/l. The positive control (sodium benzoate) concentration was approximately 50 mg/l. Test temperature was 22 +/- 1 °C.

All vessels were stirred constantly for 28 days using magnetic stir bars.

Day	12	13	14	23	28
Degradation (ThOD)	3.4 %	8.8 %	14.7 %	49.6 %	57.4 %

The positive control (sodium benzoate) degraded to >60% ThOD (no further details given in the robust study summary).

Conclusion: The test substance reached 57 % ThOD after 28 days and is therefore just below the cut off criteria for readily biodegradability (>60 %).
Validity of the test: The test appears to be reliable from the information provided in the robust study summary. No deviations from the guideline are reported. The Klimisch score of 2 designated by the registrant seems therefore to be appropriate.

Test 2, OECD TG 301F conducted in 2009

Fresh activated on-adapted sludge was used as the inoculum. Biodegradation was based on oxygen consumption and the theoretical oxygen demand of the test substance as calculated using results of an elemental analysis of the test substance. The ThOD calculation of the test and positive control substance was based on Annex IV of OECD TG 301F.
The total suspended solids of the activated sludge were 4.73 g/l, and the microbial count was 10^5 CFU/ml. The sludge supernatant was added at a 1% loading volume of to test medium. Test medium consisted of glass distilled water and mineral salts (phosphate buffer, ferric chloride, magnesium sulfate, calcium chloride). One litre of test medium and activated sludge, which was aerated for 24 hours with carbon dioxide free air, was added to each one litre respirometer flask.

One litre glass flask test vessel were used and were placed in water baths and monitored electronically for oxygen consumption. The test substance, positive control, and blanks were tested in triplicate.

Test substance concentration was 49.3 mg/l. The positive control (sodium benzoate) concentration was 53.2 mg/L. Test temperature was 22 +/- 1 °C. All vessels were stirred constantly for 28 days using magnetic stir bars.

Day	11	12	19	22	28
Degradation (ThOD)	7.9 %	12 %	50.8 %	60.8 %	70.9 %

The positive control (sodium benzoate) degraded to >60 % ThOD by day 4.

Conclusion: The test substance was readily biodegradable with >60 % ThOD in 28 days and meeting the 10-day window.

Validity of the test: The test appears to be reliable from the information provided in the robust study summary. No deviations from the guideline are reported. The Klimisch score of 2 designated by the registrant seems therefore to be appropriate.

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 D1012P (C10 – C12). 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 several 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.

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

7.7.2.2.1.3. Simulation tests (water and sediments)

Not available.

7.7.2.2.2. Biodegradation in sediment

Guideline studies that simulate degradation under environmentally relevant conditions are not available for D1012P.

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 for D1012P. 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 like the mono phthalate ester degradation products of D1012P which have alkyl chains ranging from C10 to C12 (branched and linear).

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 where 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-life for the various mono phthalate esters can be seen in Table 5. 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 the mono phthalates in both marine and freshwater sediments. The half-life was 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-life 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 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 even though 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 9. Primary degradation half-life ($t_{½}$) 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	

7.7.2.2.3. Biodegradation in soil

No information is available for D1012P. Information from a structural analogue di-isononyl phthalate (DINP) 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).

7.7.2.3. Summary and discussion on degradation

The eMSCA concludes that the Substance D1012P 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.

Two readily biodegradation studies are available for D1012P with one showing readily biodegradability and the other one being just below the cut-of criteria of >60 %. It is not

unusual to have somewhat differing results in different biodegradation screening tests since the bacterial composition in the activated sludge can influence the degradation rates of the substance. When also considering the results from Biowin predictions (not fulfilling the PBT screening criteria) and the results from a non-guideline study in sediments with the mono phthalate ester, it seems reasonable to conclude that D1012P is not persistent in surface water and in sediment.

7.7.3. Environmental distribution

7.7.3.1. Adsorption/desorption

Diisoundecyl phthalate, (D1012P)	Degradation product (representative mono phthalate ester)
Calculated	Calculated
Log K_{oc} = 10.5	Log K_{oc} = 3.4
KOCWIN (v.2.00)	KOCWIN (v.2.00)
Calculation SMILES: C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	Calculation SMILES: C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)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. Both D1012P (C11) and the degradation product are within this domain.

No test data for adsorption is available for D1012P. However, sediment partition coefficients have been measured for the structural similar phthalate esters, diisodecyl phthalate (DIDP) and diisotridecyl phthalate (DTDP) which has similar alkyl chain lengths as D1012P (C10). The experimental procedure was based on the US EPA Test Guideline 796.2750, "Sediment and Soil Adsorption Isotherm." Three sediments were used: EPA 8 (0.15% organic carbon), EPA 18 (0.66% organic carbon), and EPA 21 (1.88% organic carbon). The organic carbon-normalized sediment/water partition coefficients (Koc) averaged 2.86 *10^5 and 1.20 *10^5 for DIDP and DTDP, respectively. By interpolation, the log Koc of D1012P is estimated at approximately 5.8.

Conclusion: D1012P has a high sorption potential.

7.7.3.2. Volatilisation

Diundecyl phthalate, branched and linear (D1012P)	Degradation product (representative mono phthalate ester)
Calculated Henry's law constant H (unit less)	Calculated Henry's law constant H (unit less)
4.79 *10^{-3}	2.75 *10^{-7}
HenryWin, bond estimate (v.3.20)	HenryWin, bond estimate (v.3.20)
Calculation SMILES: C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	Calculation SMILES: C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1

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}

D1012P is just outside the applicability domain for molecular weight whereas the degradation product is inside. This, however, does not influence the overall conclusion that D1012P has limited volatilization potential.

7.7.3.3. Distribution modelling

Environmental distribution of D1012P has been estimated using the Mackay Level III fugacity model (in Episuite,v.4.1), under the default emission scenario (1000 kg/h into each of air water and soil compartments):

Relative distribution when released:

Air	0.23 %
Soil	83.9 %
Water	15.5 %
Sediment	0.37 %

7.7.3.4. Summary and discussion of environmental distribution

The eMSCA concludes, that the Substance has a low potential for long range environmental transport. The conclusion is based on the molecular size, strong sorption and low volatilisation potential and based on the above-mentioned environmental partitioning modelling.

7.7.4. Bioaccumulation

7.7.4.1. Aquatic bioaccumulation

Calculated bioaccumulation values

Diisoundecyl phthalate, (D1012P)	Degradation product (representative mono phthalate ester)
BCF (regression based): 30	BCF (regression based): 56
BCF (Arnot-Gobas, upper trophic level, including biotransf): 1.0	BCF (Arnot-Gobas, upper trophic level, including biotransf): 283
BCF (Arnot-Gobas, upper trophic level, excluding biotransf): 6.4	BCF (Arnot-Gobas, upper trophic level, excluding biotransf): 21,000
BAF (Arnot-Gobas, upper trophic level, including biotransf): 7.7	BAF (Arnot-Gobas, upper trophic level, including biotransf): 297
BCFBAF (v.3.01)	BCFBAF (v.3.01)
Calculation SMILES: C(=O)(c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1)OCCCC(C)CC(C)CCC	Calculation SMILES: C(=O)(O)c1c(C(=O)OCCC(C)CC(C)CCCC)cccc1

The BCFBAF models predict that the representative constituent of D1012P 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 degradation product / metabolite mono phthalate ester is within the applicability domain of the models and 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 tests

A pre-guideline dietary bioaccumulation study in fish (*Oncorhynchus mykiss)* conducted in 2005 is available in the registration dossier.

The study consisted of a 9-day uptake period followed by a 3-day depuration phase.

The age of the fish was not recorded in this study and the robust study summary does not mention the size (e.g., if juvenile or sexually mature fish were used). The lipid content was recorded as 3 % and did not vary significantly from the beginning to the end of the test. Thirty fish were used in the exposure group and in the control group, respectively. 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.

Fish feed was spiked with D1012P to a concentration of 1000 µg/g. The fish were fed at a level of approximately 3 % of their wet body weight per day. The amount of feed was adjusted at each fish-sampling period to account for the growth of the fish during the experiment and the reduced number of fish in the test chambers. The initial feed amount was calculated based on weights of a subsample of the stock population.

Chemical analysis was performed with GC/MS and radiolabelling was not used. Hence, bioaccumulation of metabolites of D1012P is not addressed in this study.

Hexachlorobenzene was used as a positive control. However, the robust study summary does not mention any details of the performance of the test system to characterize the bioaccumulation potential of the positive control.

The following calculated values are reported by the registrant:

- Elimination rate constant: 3.74 µg/g day [1]
- Tissue elimination half-life: 0.19 days (growth corrected, whole body)
- BMF: 0.0045 (lipid normalized)
- BCF: < 1

The eMSCA concludes that the BMF and elimination rate reported from the study is very low and does indicate that the substance has low bioaccumulation potential. However, several 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 addition, there is a lack of details on how the test system responds to the positive control. Together, this 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 (several different methods exist) and the number of sampling occasions is below the minimum number specified in the guideline. Therefore, a Klimisch score of 4 is assigned to the study. It could be considered if the original study report should be requested.

7.7.4.2. Terrestrial bioaccumulation

The registrant has included information from an earthworm acute toxicity test (OECD TG 207) to characterize the bioaccumulation potential in terrestrial organisms. The test is conducted with the analogous substance DIDP (1,2-benzenedicarboxylic acid, di-C9,C10 and C11 branched alkyl ester, C10 Rich, CAS RN 68515-49-1). It should be noted, however, that this test differs substantially from the OECD TG 317 guideline (bioaccumulation in terrestrial oligochaetes) not least regarding the test duration in OECD TG 317 which consist of a 21-day uptake period (unless it has been demonstrated that steady state occurs earlier) followed by a 21-day depuration period. This contrasts with the conducted OECD TG 207 which has a 14-day uptake period and no depuration phase. In addition, the exposure concentrations are expected to be much higher in the acute toxicity test compared to the bioaccumulation test.

Soil samples were dosed with 10,000 mg test substance/kg soil. Analysis of soil DIDP concentrations was performed at test initiation and termination. The temperature ranged from 18.2 to 20.6 °C and soil pH ranged from 6.9 to 7.2.during the duration of the test.

A radiolabel is not used, and the result of the test therefore only relates to the parent compound and not to metabolites. No mortality was observed in the test. Although not clearly stated in the robust study summary, it appears that the concentration in earthworm was only analysed at one sampling occasion (day 14). Hence, it would not be possible to assess if a steady state has been achieved between substance concentration in the test organisms vs the test medium.

The registrant concludes that the biota-soil accumulation factor (BSAF) was 0.015 based on a DIDP concentration in the earthworm of 120 mg/kg (wet weight) and in soil of 7829 mg/kg (dry weight).

Validity of the test: Due to the limitations described in the beginning of this section, the test is considered as having a low relevance to adequately characterize the bioaccumulation potential for terrestrial organisms. However, the study may be used as supporting information.

7.7.4.3. Summary and discussion on bioaccumulation

The data package on bioaccumulation consists of calculated values, a dietary bioaccumulation study in fish which has some uncertainties regarding validity and supporting information from an acute earthworm toxicity study on an analogue substance for terrestrial bioaccumulation. These pieces of information may be inadequate on their own for concluding on the bioaccumulation potential of D1012P. However, when taken together and considering information from other phthalate esters (see Annex 1) and the structural features of D1012P (ester bonds that are predicted to be metabolised), the eMSCA concludes that D1012P does not meet the B or vB criteria.

7.7.5. Secondary poisoning

Not evaluated.

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 D1012P 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 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 the registered substance (see also section 7.10) cannot be resolved due to the lack of standard information requirements on repeated dose toxicity and reproduction toxicity studies with the registered substance.

7.9.1. Toxicokinetics

The toxicokinetics of D1012P have not been examined. However, the toxicokinetics of other high molecular weight phthalates, DINP and DIDP, have been studied and it is suggested by the registrant that these data can provide an assessment for D1012P as read-across information.

The eMSCA finds it plausible that toxicokinetics of the registered substance is like 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.

7.9.3. Sensitisation

Not evaluated.

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 disruptive effects, which have been identified as concerns for the registered substance.

No data on D1012P 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 registered 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 were also included in the section on fertility of the registration dossier and are therefore presented in section 7.9.7.
- The third rat study is presented here together with the dog study.

Table 10: 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 females Subchronic (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 (DIDP)	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 that the NOAEL is 0.3% (about 200 mg/kg/d) since 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.

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 RN 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 Study Report, 1969).

The observed effect of DIDP on the thyroid in the rat study (Unpublished Study Report, 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 provided by the Registrant

As laid out in the previous sections, no repeated dose toxicity data on D1012P 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 challenged 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 were provided for read across:

- A 90-day oral study on Di-isodecyl phthalate (DIDP) from Unpublished Study Report (1968a) (male and female rats, three exposure levels, n = 10 / sex and group).

- 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))

Additional studies included for oral/dermal/inhalation toxicity:

- Oral: 21 days of exposure to 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)
- 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)
- Dermal: Six weeks dermal toxicity study to 24-hour daily application 5 times/week of DINP on the abdominal skin (New Zealand White rabbits, two exposure levels, n = 2 / group (one group with closely clipped intact fur and one group with abraded fur) (Unpublished Study Report, 1969)
- Inhalation: 2-week exposure to DIDP 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 Assessment Framework (RAAF) guidance. 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.

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.

Regarding 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.

7.9.6. Carcinogenicity

Carcinogenicity 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 D1012P 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 in section 7.10.

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

The initial concern for reproductive toxicity of the Substance 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.

No data on reproductive toxicity of D1012P is provided by the registrant. 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. 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 this endpoint, 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 to evaluate whether there is a continued concern for reproductive toxicity of the registered substance, D1012P.

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. ECHA has published a review on DIDP toxicity including 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. This 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 discuss 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 foetal 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 D1012P 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 11. Summary of some studies used to evaluate the concern for effects on fertility

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male/female, N= 30/sex/group. 2 two-generation studies oral: feed In study A 0.2, 0.4, 0.8% were target dietary concentrations (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)	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 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	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

Vehicle: unchanged (no vehicle)	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 68515-49-1) The sample of DIDP used was made up of equal part by weight of Hexaplas (ICI), Jayflex DIDP (Exxon) and Palatinol Z (BASF). 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 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)).	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 same dose level. Comparable effects were seen for DEHP and DIDP regarding hepatic effects.	Test material DIDP (CAS RN: 68515-49-1) 99.84% purity This study is considered reliable (1).	BIBRA (1986) Unpublished Study Report (1993) (cited in EC 2003)
Rat (SD), juvenile male, n=6 Oral: gavage Exposure: 28 days (PND 35 to 77) Dose: 500 mg/kg bw/day DIDP, CAS 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 RN 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 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 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 D911P 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. 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 D911P. 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	Klimisch 1, reliable without restriction.	Unpublished Study Report (2001) Willoughby *et al.,* 2000

	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 (Unpublished Study Report*,* 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 is reported. 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 motility 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 (Unpublished Study Report, 1993). A 90-day study showed no effects on testis weight at doses up to 650 mg/kg bw/day of DIDP (Unpublished Study Report 1968a).

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 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 States 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 (HMPWEs). 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 similarities 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 (Unpublished Study Report 1992; 1993; 1995) 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.

In conclusion, based on the available data, there is a continued concern for effects on fertility of the registered substance.

7.9.7.2. Review of information regarding the concern for developmental toxicity

There are no data available on the Substance, D1012P, 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, a study on effects of source substance DIDP on foetal testosterone production is presented in the table below (Hannas *et al.,* 2012).

Table 12: Summary of some studies relevant for evaluation of developmental toxicity

rat (Sprague-Dawley), n=25 oral: gavage 100, 500, 1000 mg/kg (actual ingested) Exposure: Gd 6 through 15 (daily) equivalent or like 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 number): 68515-49-1**:**	Waterman SJ, Ambroso JL, Keller LH, Trimmer GW, Nikiforov AI and Harris SB (1999) Nikiforov AI, et al (1995)

[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)

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 the structural analogue substance 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. Reliable with restrictions (2). Structural analogue substance tested: Test material: 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	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 foetuses, 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	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. (2013b)

the vehicle under the same conditions.) OECD Guideline 414 (Prenatal Developmental Toxicity Study)	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 foetal sex ratio. In the foetuses, 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 lumber ribs.		
Rat, Sprague-Dawley, n=22 Prenatal developmental toxicity study with termination on GD 20 (OECD TG 414). Pregnant rat dams were exposed by oral gavage with 0, 250, 500 or 1000 mg/kg bw/day of D911P from GD1-19.	No effects on maternal weight gain, food consumption, number of implantations, gravid uterus weight or macroscopic foetal malformations (skeletal or visceral) was observed. An increased body weight in foetuses in the highest dose group (1000 mg/kg) was observed but this effect was only statistically significant in females and was not considered of toxicologic relevance. Organ weights were not assessed, except for the weight of the gravid uterus with cervix.	Key study Klimisch 1, reliable without restriction.	Unpublished Study Report (2000) Fulcher et al. (2001)
rat (Sprague-Dawley) oral: gavage 0, 250, 500 and 1000 mg/kg/day Vehicle: olive oil OECD TG 414 (Prenatal Developmental Toxicity Study)	DnOP had no adverse effect on maternal feed consumption and body weight gain, or on the incidence of post-implantation loss and foetal body weight. There was no increase in the incidence of foetal malformations or external and visceral variations. A significant increase in rudimentary lumbar ribs was observed at all doses of DnOP. No effect of DnOP was seen on the anogenital distance of the male foetuses. Diheptyl phthalate showed the same effects as DnOP, except that male anogenital distance was significantly decreased at the highest dose of DHPP.	2 (reliable with restrictions) weight of evidence read across from supporting substance (structural analogue or surrogate) Test material: CAS RN 117-84-0	Saillenfait 2011

Data from the two-generation study on DIDP (see table in section 7.9.7.1) (Huska 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 foetal 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 foetal testosterone production.

DIDP produced a small, statistically significant decrease in postnatal survival indices which was observed in the second generation of both 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 foetuses 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 of DIDP on skeletal variations was considered critical and was 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 were also reviewed by the eMSCA 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 C911P 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) (Unpublished Study Report 2000/Fulcher et al., 2001). 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 pelvis. 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.

Conclusion on review of information regarding the concern for developmental toxicity:

Developmental effects (skeletal variations and decreased survival of pups) observed for phthalate of initial concern (C7-11P, DHNUP) have also been observed for other phthalates with similar constituents used as read across source substances, e.g., DIDP and DINP (ECHA 2013, Waterman 2000, Waterman 1999). Effects on skeletal variations (supernumerary ribs) were also seen for C911P (Unpublished Study Report, 2000), and diundecyl phthalate (Saillenfait et al., 2013b). For DIDP, it was decided 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 C911P the effects on supernumerary ribs were 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 frequently seen for 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, 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 HMWPEs (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 foetal 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 provided by the Registrant

As laid out in the previous sections, no reproductive toxicity data on D1012P is provided by the registrant. Diisodecyl phthalate (DIDP, CAS RN68515-49-1 and 26761-40-0) is used as a read-across substance for toxicological information (key studies). Additionally, supporting studies on ditridecyl phthalate (CAS RN 119-06-2, C13 linear) and C911P (CAS RN68515-43-5, 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 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. In addition to the basic test design of this study includes Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3, as laid down in column1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X, point 8.7.3 are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. 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 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 the registered substance initiated before 13 March 2015 and which would be considered 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 administered in diet (key data published in Hushka et al. (2001) (exposure range from approximately 15-600 mg/kg/day).
- Combined repeat dose and reproductive/developmental toxicity screening test on Di-tridecyl phthalate (DTDP, CAS RN 119-06-2) via oral gavage (OECD 422, Japan Ministry of Health and Welfare, 1997, registrant does not have access to full study report) (Sprague-Dawley rats, three doses)
- A 2-generation reproductive toxicity study on a C9-11 phthalate ester at levels of 100-1000mg/kg/day (Willoughby et al. 2000).

Additional studies included for testicular atrophy:

- Two supporting studies on di-C9-11-alkyl phthalate, C10-rich, CAS RN 68515-49-1, exposure via diet for 28 and 21 days (Lake et al. 1991/BIBRA 1990 and Unpublished Study Report 1993/BIBRA 1986).

The eMSCA has analysed the read-across justification applying the Annex XI point 1.5 elements and the ECHA Read-Across Assessment Framework (RAAF) guidance (see. attachment 1 'Analysis of read-across approach'). 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 X, 8.7.3, Extended One-Generation Reproductive Toxicity Study. Consequently, there is an information gap in the registration dossier for this endpoint.

Regarding 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" for a first 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:

- A 90-day oral study on DIDP from the Unpublished Study Report (1968a) (male and female rats, three exposure levels, n = 10 / sex and group).

- Daily exposure GD6-15 (daily) to CAS RN 68515-49-1 via oral gavage (Sprague-Dawley rats, three exposure levels) (Waterman et al., 1999).
- Daily exposure GD 6-15 (daily) to CAS RN: 68515-49-1 via oral gavage (Wistar rats, three exposure levels) (Hellwig et al., 1997).
- 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)
- EPA OPPTS 870.3700 (Prenatal developmental toxicity study) on CAS RN: 68515-43-5 via oral gavage (Sprague-Dawley rats, three exposure levels) (Fulcher et al., 2001).
- OECD TG 414 (Prenatal developmental toxicity study) on CAS RN: 117-84-0 via oral gavage (Sprague-Dawley rats, three exposure levels) (Saillenfait et al., 2011).
- EU Method B.31 (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).

The eMSCA has analysed the read across justification applying the Annex XI point 1.5 elements and the ECHA Read-Across Assessment 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.

Regarding 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.

Regarding 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. The eMSCA challenge of the read-across provided 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 a UVCB in other documents in the registration dossier. Based on the complexity and lack of knowledge on the constituents, the registered substance here is 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 for the endpoints required, to fulfil the standard information requirements.

7.9.8.1. Hypothesis provided by the Registrant

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-C11-14-branched alkyl esters, C13-rich (DTDP), 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 substance 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 several 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 further describes these considerations.

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 –not shown in the present paper - 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 substances are of a type to be able to predict the toxicity of the registered substance. Branched olefins reactivity, alcohol reactivity, plasticizer neat properties, expected performance in flexible PVC and NMR data indicate a low probability of having highly branched isomers in DIUP or significant ethyl branching. In the case of DIUP, a tri-branched C12 alkyl chain is resulting in respectively a C9 or C8 backbone. For this specific substance we expect the backbone chain length to contain at least 7 carbon atoms, with the majority being 9 carbon atoms and higher ".*

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 "*DTDP (CAS RN 27253-26-5) is more linear but related to CAS RN 68515-47-9 and is expected to have a similar level and type of branching as the registered substance with alkyls of a longer chain length than the registered substance. The presence of branching is a key component for assessing the developmental and reproductive toxicity and discussed in detail during the weight of evidence developmental and reproductive endpoints supplied by the registrant, 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. 104).

Information on the exact backbone chain length of the target and source substances is insufficient, and detailed specifications on branching are lacking. According to the

Registrant(s) it is not possible to assess branching directly, as further discussed in the IUCLID document "DIUP compositional information_2015": "*Due to the complexity of DIUP, with the presence of over two hundred 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, NMR) and data.*" (IUCLID "DIUP compositional information_2015").

Likewise, the available information on source substances is limited. The eMSCA notes the complexity of these substances and consider this lack of knowledge important in the analysis of the proposed read-across hypothesis (Section 1.3, see below).

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 the present 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 C7 and in the range of C8-C9**)**.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 – not shown in the present paper). 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).

During the analysis of the proposed read-across hypothesis (Section 1.3, see below) 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 source substances, and this is not provided in the current case.

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 700-989-5'), 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 of the registered substance, 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 based on 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 however 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).

The registrant has provided some information on the identity of the target substance in a document entitled "DIUP compositional information_2015" (IUCLID):

"The plasticizer structure is derived from the alcohol structure: a complex isomeric structure with overlapping carbon numbers and over 200 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, it is expected that DIUP (D1012P) will have some limited C7 backbone and with a large portion of C9 backbones present." ("DIUP compositional information_2015", IUCLID, p. 1).

However, it is noted that Figures 1 and 2 in the CSR (Appendix 1, Read-across justification) do not show the presence of any C7 backbone in the registered substance.

Based on gas-chromatographic methods the alcohol carbon distribution number was determined: C10 isomers 8.3%; C11 isomers 86.2%; C12 isomers 5.5% wt %, ("DIUP compositional information_2015" p.2, 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 C11 rich.

The alcohol carbon number distribution in the phthalate has also been measured using Gas Chromatography – Mass Spectrometry in Chemical Ionization mode (GC/CI-MS): C11-C11 (C10-C12*): 63.7%; C10-C11: 19.3%; C11-C12: 12.6%; C10-C10: 3.5%; C12-C12: 0.8% wt %, (presented in "DIUP compositional information_2015", IUCLID). It is noted that *C11-C11 and C10-C12 homologue esters have the same molecular weight and cannot be segregated in these results. Results are based on one single measurement made on commercial sample of DIUP (VE 8/13). 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 predictions showing that the average carbon number in the starting material alcohol is 11.08 and the average number of branches is 2.24. They write that based on this the DTDP alkyl chains will each have an average of 2.24 branches per molecule and present a structure mix that is "statistically realistic" within a very large number of possibilities:

Simulation 1

%	# of branches	Average
1	1	
76	2	
21	3	
2	4	
100		
		2.24

Simulation 2

%	# of branches	Average
1	1	
74	2	
25	3	
0	4	
100		
		2.24

Simulation 3

%	# of branches	Average
0.1	1	
76	2	
23.9	3	
0	4	
100		
		2.24

These simulations highlight that, *"based on experience, with most di-branched alkyl chains and with low levels of mono and tetra-branched, some tri-branched alkyl chains will be present"* ("DIUP compositional information_2015", IUCLID p. 3).

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 ("DIUP compositional information_2015", IUCLID p. 5). 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 highly branched isomers in D1012P or significant ethyl branching*." ("DIUP compositional information_2015", IUCLID p. 7).

Overall, the claim that the shortest backbone is C7 is not substantiated in the registration. Rather, from the supplied information from the registrant it seems plausible that constituents with a backbone shorter than C7 may be present to some extent, i.e., C6 or shorter in cases with 3 branches, if one or more of these branches are ethyl, propyl, or butyl etc. For example, tri-branched C11 will have a *maximum* backbone of C8, and if branches are longer than methyl the backbone is likely shorter, e.g., C5, C6 or C7. 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 86% of the substance constituents have a total carbon chain number of C11, and 2% are tetra-branched with methyl branches (simulation 1), this means that almost 2% of the substance has a C7 backbone. If one or more of these branches are ethyl or longer, these constituents will have C6 backbone or shorter.

- If 8% of the substance constituents have a total carbon chain number of C10, and 25% are tri-branched (simulation 2), then this means that 0,25*8%=2% of the substance has a C7 backbone. If one or more of these branches are ethyl or longer, these constituents will have C6 backbone or shorter.

- Collectively, this indicates that up to 4% of the substance is likely to have a C7 backbone or shorter.

Thus, the claim that the shortest backbone is C7 is not substantiated in the registration. There is concern for reproductive and developmental toxicity for constituents with backbone shorter than C7. Also, the concentrations of constituents with C7 backbone are important, as there is some concern for reproductive toxicity of phthalate esters with C7 backbone (see section 7.9.7.3).

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.

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

With regards 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 consider: *"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 must 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"* (CSR, Appendix 1, p- 107). 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. 108-110). 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. 107). This information is not considered sufficient for read across.

Furthermore, as noted above there is discrepancy between the information in the "DIUP compositional information_2015" document (IUCLID) and the CSR regarding presence or absence of C7 backbone in the registered substance. In contrast to information that "*it is expected that DIUP (now D1012P) will have some limited C7 backbone and with a large portion of C9 backbones present* (DIUP compositional information_2015), the figures of the CSR do not show the presence of any C7 backbone in the registered substance (CSR, Appendix 1, Read-across justification). The presence of absence of C7 backbone is important in an endpoint-specific read-across justification due to reproductive and developmental toxicity of some substances with a C7 backbone (see Section 7.9.7.3).

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 considering 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 the 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.

Therefore, the eMSCA challenges the proposed read across for several standard information requirements.

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated.

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

An evaluation cannot be conducted due to data gaps described above.

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

The eMSCA cannot conclude due to the data gaps described above.

7.10. Assessment of endocrine disrupting (ED) properties

No discussion on endocrine disrupting properties of the registered substance 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.

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-androgenicity)

No data on anti-androgenicity of D1012P is provided by the registrant.

However, data on read across substance DIDP and other HMWPEs raise a concern for possible endocrine disrupting properties (anti-androgenicity) of the registered substance.

ECHA review conclusions on endocrine disrupting properties on the reproductive system

The ECHA evaluation of DIDP from 2013 included summaries of risk assessment reports from different international organizations including the EU risk assessment. Regarding endocrine disruption, the EU risk assessment report concluded that no overt effect related to endocrine disrupting effect on the reproductive system was observed despite indications of effects on reproductive organs in a two-generation studies presented by Hushka et al., 2001.

Some *in vivo* studies on endocrine disruption were presented in the ECHA evaluation: A study by Kwack et al., 2009 showed effects of DIDP on sperm motility in young adult rats (Section 7.9.7.1, table 10), a study by Hannas et al., 2012 showed no effect of DIDP on testosterone production in foetal rats (Section 7.9.7.2, table 11), and a Hershberger study in castrated rats showed indications of anti-androgen effects (Lee and Koo, 2007). In an in vivo uterotrophic assay DIDP was not oestrogenic or anti-oestrogenic (Akahori et al. 2008; Lee and Koo, 2007).

Table 13: Overview of some in vivo studies used to evaluate the concern for endocrine disruption (anti-androgenecity)

Method	Results	Remarks	Reference
Hershberger assay in castrated male rats, n= Oral gavage 20, 100, 500 mg/kg bw/day 10 days exposure	Reduced weights of seminal vesicle and ventral prostate at 500 mg/kg bw/day. No effects on weights of glans penis, levator ani/bulbocavernosus muscle.	According to test guideline changes in weights of two tissues is sufficient to conclude that a compound is positive, i.e., has anti-androgenic effects. Effect of DIDP is less marked than effects	Lee and Koo, 2007

		of DEHP or DINP in the same study.	
Uterotrophic assay in immature rats, n=6. OECD TG 440, GLP.	No effects on uterine weight.	Information on doses is unclear. Comparison of several compounds, no effects of DINP or DEHP.	Akahori et al 2008

The ECHA evaluation also presented in vitro studies on DIDP. According to the ECHA review, *in vitro* studies showed that DIDP was involved in progesterone release in granulosa cells, was not oestrogenic and showed contradictory results for anti-oestrogenicity (Mlynarcikova et al. 2007; Akahori et al. 2008; Takeuchi et al. 2005; Ghisari and Bonefeld-Jorgensen 2009). DIDP did not affect AR but had a weak agonistic AhR activity (Kruger et al. 2008; Takeuchi et al. 2005).

There are minor indications of toxicity to the developing reproductive system after exposure to 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, 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.

Endocrine disruption (anti-androgenicity) was discussed in the EU Risk assessment report for DIDP from 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 overall, no overt effect related to endocrine disruption of the reproductive system has been observed with DIDP.

Further, ECHA 2013, concluded that "*DIDP did not induce substantial anti-androgenic activity in available studies; it did not reduce foetal 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). If DIDP has endocrine disrupting effects on the reproductive system, these are probably induced by other modes of action than DEHP, DBP and DINP.

<u>Considerations on effects in relation to phthalate ester backbone length:</u>

In addition to the phthalates DEHP, DBP, BBP and DIBP, several other phthalates have also been identified as being able to induce antiandrogenic 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 diisononyl phthalate (DINP, mainly of C7 backbone with dimethyl branching, and some C8 backbone with methyl branching) (Clewell et al. 2013, 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 anogenital 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 tumour 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 anti-androgenicity

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

It is well known that the phthalates DEHP, DBP, BBP and DIBP have anti-androgenic properties. In addition to these phthalates, several other phthalates have also been identified as being able to reduce foetal 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.

In addition, there are indications of anti-androgenic properties of DIDP in a Hershberger assay.

All in all, there is a continued concern for anti-androgenicity of the registered substance. 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 D1012P 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, CPSC 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, D1012P.

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 elevated 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 ECHA 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 from 2018 show that DnOP is active in TPO assay, whereas other HMWPE had not been 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 (CPSC 2010b).

- Diisododecyl phthalate (DIDP): A 3-month study indicated thyroid disrupting effects of DIDP *in vivo* (see also section 7.9.4.1) (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

A concern for interference of the registered substance with the thyroid hormone system was raised 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 due to the identified data gap on repeated dose toxicity and reproductive toxicity (see section 7.9.7.4). Further studies on D1012P 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).

The data gap in the standard information requirements on reproductive toxicity includes the extended one-generation reproductive toxicity study (OECD TG 443) (section 7.9.7.4.1). 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.

7.10.3. Conclusion on endocrine disrupting properties

A concern for endocrine disruption of sex- and thyroid hormones was raised during the substance evaluation.

eMSCA could not conclude regarding this concern for endocrine disruption (i.e., anti-androgenicity and thyroid disruption) due to the identified data gap on repeated dose toxicity and reproductive toxicity (see section 7.9.4.2 and 7.9.7.4). To address the concern, these data gaps need to be filled. Furthermore, an extended one-generation reproductive toxicity study (OECD TG 443) is missing (section 7.9.7.4.1). 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 an extended one-generation reproductive toxicity study (OECD TG 443) is requested once a compliance check is initiated.

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 eMSCA concludes that D1012P is not persistent (P) or very persistent (vP) in surface water and sediment. This is based on:

- Two biodegradation screening tests showing readily biodegradability and just below the 60 % cut-of value, respectively.
- Biowin QSAR estimates showing that D1012P does not meet the screening criteria for P.
- Information on the degradation product (mono phthalate ester), showing a rapid primary degradation in sediment under environmentally relevant conditions.
- Information from other phthalate esters indicating a general tendency for readily biodegradability.
- Considerations on the structural features (ester bonds close to the aromatic ring) and information on the general biodegradation pathway of phthalates that does not indicate the formation of persistent metabolites/degradation products.

Inadequate information is presently available to conclude on persistency of D1012P in soil. D1012P is not expected to undergo significant abiotic degradation.

7.11.1.2. Bioaccumulation assessment

The eMSCA concludes that D1012P is not bioaccumulative (B) or very bioaccumulative (vB). This is based on a combination of the following information:

- A dietary bioaccumulation study in fish showing a fast tissue elimination half-life (the study has some uncertainties about validity).
- QSAR predictions indicating a low potential for bioaccumulation.
- Consideration on structural features of D1012P (ester bonds close to the aromatic ring that are predicted to be metabolised).
- Information from other phthalate esters of which none of the tested substances are displaying high bioaccumulation potential in fish.

Toxicity assessment

Not assessed.

7.11.1.3. Summary and overall conclusion on PBT and vPvB properties

The eMSCA concludes that the parent substance (D1012P) does 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.

7.12. Exposure assessment

No information available in registration therefore not evaluated.

7.13. Risk characterisation

Not evaluated by the eMSCA.

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