Ministry of Environment of Denmark
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Diundecyl phthalate, branched and linear (D11P)

EC No 287-401-6

CAS RN 85507-79-5

(previously registered as diundecyl phthalate, EC No 222-884-9, CAS RN 3684-20-2)

Evaluating Member State(s): Denmark

Dated: 12 January 2022

Evaluating Member State Competent Authority

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

Member State concluded the evaluation without any request for more information from the registrants under an 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, diundecyl phthalate, branched and linear (DIUP; EC No. 287-401-6, CAS RN 85507-79-5) was originally included on CoRAP and selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (reproductive toxicity only)
- High (aggregated) tonnage
- Other exposure/risk based concern

During the evaluation an additional concern was identified:

- Endocrine disruption

Background for CoRAP listing and for the identified additional concern

The initial concern for reproductive toxicity of the 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, a number of other individual phthalates with alkylchain lengths within the same range as DHNUP (i.e. in the C7-C11 range) had been registered.
The Substance, diundecyl phthalate, branched and linear, 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 based on evidence of effects on the endocrine system observed for structurally similar substances.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The substance was investigated for PBT properties, with the conclusion that is was not a PBT or vPvB. A hazard assessment outcome document was filed by Denmark in December 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 on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

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

No reproductive toxicity or developmental toxicity studies on the Substance have been provided by the registrant. Instead read across from di-(C9-C11 alkyl) phthalate (D911P) and 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters was presented in the registration dossier.

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

The eMSCA has requested ECHA to conduct a compliance check of the Substance due to the data gaps, regarding the standard information requirements, identified during the substance evaluation: on the endpoints of repeated dose toxicity and reproductive toxicity.

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 reproductive toxicity and repeated dose toxicity in the registration of this Substance, and to an incompliant read-across justification. If provided, the missing standard information requirement data are expected to allow to evaluate and conclude on the two hazard endpoints raised under the substance evaluation. Therefore, the substance evaluation is concluded at this point.

If warranted by the information provided as a results of the Compliance Check decision, elaboration of a RMOA might be considered.

Should the testing provided as an outcome of the Compliance Check decision not allow for conclusion on the concerns raised by the Danish EPA in the substance evaluation process,

but indicate that further data are needed to clarify these concerns and to conclude 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 after completion of the compliance check 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, diundecyl phthalate, branched and linear (DIUP; EC No. 287-401-6, CAS RN 85507-79-5) was originally included on CoRAP and selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (reproductive toxicity only)
- High (aggregated) tonnage
- Other exposure/risk based concern

During the evaluation an additional concern was identified:

- Endocrine disruption

Table 3

EVALUATED ENDPOINTS Endpoint evaluated	Outcome/conclusion
Suspected CMR (reproductive toxicity only)	Concern unresolved. Continued concern based on classification of structurally similar substance. Read-across applied by REG to fill in data gaps not acceptable. No conclusion can be reached due to data gaps in standard information requirements. Compliance check requested.
High (aggregated) tonnage	Concern unresolved. Evaluation and conclusion pending compliance check and subsequent hazard assessment outcome.
Other exposure/risk based concern	Concern unresolved. Evaluation and conclusion await compliance check and subsequent hazard assessment outcome.
Endocrine disruption	Concern unresolved. Continued concern based on information from structurally similar substances. No conclusion can be reached due to data gaps in standard information requirements.

7.2. Procedure

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

During the evaluation, the eMSCA identified an additional concern endocrine disruption, i.e. disruption of sex- and thyroid hormones.

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

No reproductive toxicity or developmental toxicity studies on D11P have been provided by the registrant. Instead read-across from di-(C9-C11 alkyl) phthalate (D911P) and 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters was presented in the registration dossier.

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

The registrants comments were received June 2015.

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

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

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

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

The 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 initiated.

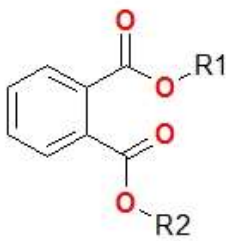
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Diundecyl phthalate, branched and linear
EC number:	287-401-6
CAS registry number:	85507-79-5
Index number in Annex VI of the CLP Regulation:	No annex VI entry
Molecular formula:	C30H50O4
Molecular weight range:	474.7156
Synonyms:	DIPLAST®L11

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

Structural formula



R1, R2: undecyl substitutes, branched and linear, branched in beta position of carboxylate groups.

Multiconstituent/UVCB substance/others

The registered substance is a UVCB.

Information about the exact composition of the registered substance is lacking. Some information has been provided by the Registrant in their comments to the draft decision in June 2015, supplemented with information provided upon direct request from the eMSCA. However, detailed specifications, especially on extent of branching of the molecules, is 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, pale yellow in colour and with faint odour. Value used for CSA; liquid Determined according to EPA test methods.
Vapour pressure	6.67 E-7 hPa Value used for CSA: 0.000000667 hPa at 25 °C
Water solubility	1.11 mg/L at 25 °C Value used for CSA: 1.11 mg/L at 25 °C Determined by a flask method. Solubility in aqueous media suitable for aquatic effects studies has also been evaluated. The highest practical stable concentration that could be maintained was 0.4 mg/L at 10 deg C. Water solubility has also been calculated using the computer program WSKOW (v1.41). It is predicted that the substance has a water solubility of 0.0007125 micrograms/L at 25 °C
Partition coefficient n-octanol/water (Log Kow)	8.70 Value used for CSA: Log Kow (Pow): 8.7 at 55 °C Determined according to OECD methods.
Flammability	Non-flammable Value used for CSA: non flammable Flash point has been determined and provides adequate information regarding the flammability of the substance.
Flash point	241.0 °C Value used for CSA: 241 °C at 1013 hPa Determined according to ASTM methods
Melting/freezing point	-40°C Value used for CSA: -40 °C at 1013 hPa Determined as pour point according to ASTM methods
Boiling point	336 °C Value used for CSA: 336 °C at 1013 hPa Determined by differential scanning calorimetry

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	**Formulation of the substance** **Process category** PROC 3: Use in closed batch process (synthesis or formulation) PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent **Chemical product category** PC 32: Polymer preparations and compounds Environmental release category ERC 2: Formulation of preparations ERC 3: Formulation in materials
Uses at industrial sites	**Manufacture of the substance** **Process category** PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent PROC 1: Use in closed process, no likelihood of exposure PROC 2: Use in closed, continuous process with occasional controlled exposure **Environmental release category**

	ERC 1: Manufacture of substances **Substance supplied to that use in form of** As such
	Manufacture of articles by tabletting, compression, extrusion, pellettisation, calendering, dipping and pouring **Process category** PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 6: Calendering operations PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 15: Use as laboratory reagent PROC 21: Low energy manipulation of substances bound in materials and/or articles **Chemical product category** PC 32: Polymer preparations and compounds **Environmental release category** ERC 5: Industrial use resulting in inclusion into or onto a matrix **Substance supplied to that use in form of** In a mixture As such **Sector of end use** SU 12: Manufacture of plastics products, including compounding and conversion **Subsequent service life relevant for that use?** yes
Uses by professional workers	**Professional use of articles obtained by tabletting, compression, extrusion, pellettisation, calendering, dipping and pouring** **Process category** PROC 21: Low energy manipulation of substances bound in materials and/or articles **Chemical product category** PC 32: Polymer preparations and compounds **Environmental release category** ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix **Substance supplied to that use in form of** As such In a mixture **Sector of end use** SU 12: Manufacture of plastics products, including compounding and conversion

Consumer Uses	**Exposure to building materials and car interiors** **Chemical product category** PC 32: Polymer preparations and compounds **Environmental release category** ERC 8c: Wide dispersive indoor use resulting in inclusion into or onto a matrix ERC 8f: Wide dispersive outdoor use resulting in inclusion into or onto a matrix **Substance supplied to that use in form of** In a mixture As such **Subsequent service life relevant for that use?** yes
Article service life	**Service life related to articles obtained by tabletting, compression, extrusion, pellettisation, calendering, dipping and pouring** **Process category** PROC 14: Production of preparations or articles by tabletting, compression, extrusion, pelletisation PROC 21: Low energy manipulation of substances bound in materials and/or articles **Environmental release category** ERC 10a: Wide dispersive outdoor use of long-life articles and materials with low release ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release **Article category related to subsequent service life** AC 1: Vehicles AC 2: Machinery, mechanical appliances, electrical/electronic articles AC 6: Leather articles AC 10: Rubber articles AC 13: Plastic articles Service lfe related to building materials and car interiors **Environmental release category** ERC 10a: Wide dispersive outdoor use of long-life articles and materials with low release ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release **Article category related to subsequent service life** AC 1: Vehicles AC 13: Plastic articles

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonised classification available.

7.6.2. Self-classification

No further notifications are included in the self-classification inventory.

7.7. Environmental fate properties

Not evaluated by eMSCA.

7.8. Environmental hazard assessment

Not evaluated by eMSCA.

7.9. Human Health hazard assessment

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 the registered substance to inform about these endpoints (long term repeated dose toxicity studies or reproductive toxicity studies).

The read-across provided by the Registrant to fill in the data gaps on repeated dose toxicity and on reproductive toxicity were reviewed and were challenged 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 section 7.10) cannot be resolved due to the lack of standard information requirements especially on repeated dose toxicity and reproduction toxicity studies with the registered substances.

7.9.1. Toxicokinetics

Not evaluated by eMSCA.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated by eMSCA.

7.9.3. Sensitisation

Not evaluated by eMSCA.

7.9.4. Repeated dose toxicity

Repeated dose toxicity was not identified as an area of concern during substance evaluation. However, repeated dose toxicity studies may include information on potential reproductive toxicity and/or on endocrine disruption, which have been identified as concerns for the registered substance. Therefore, the available information on repeated dose toxicity was thoroughly reviewed be the eMSCA.

No 90-day repeated dose toxicity study is available for the registered substance. Two shorter repeated dose toxicity studies were provided by the Registrant (Unpublished Study Report (1985); Lington *et al.,* 1993). Also, Kwack *et al.,* (2009) has described a shorter repeated dose toxicity study on diundecyl phthalate in the open literature, as described below. Moreover, a 90-day study on 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters (Unpublished Study Report, 1993), was provided by the registrant, as read-across from the latter compound was performed by the Registrant.

The read-across is challenged by the eMSCA as described 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.

7.9.4.1. Review of repeated dose toxicity data

Two repeated dose toxicity studies on the Substance, diundecyl phthalate, branched and linear (D11P) (Unpublished Study Report (1985) and Lington et al., 1993) were were included in the registration dossier. Also, Kwack et al., (2009) has described a repeated dose toxicity study on diundecyl phthalate in the open literature, as described below. No study reports from any of these studies were available.

Moreover, a 90-days study on 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters (Unpublished Study Report, 1993), were provided by the registrant, as read-across from the latter compound was performed by the Registrant.

Table 8 : Overview of endpoints relevant for reproductive toxicity and endocrine disruption in oral repeated dose toxicity studies on the registered substance and the proposed read-across substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters.

Species, strain and number of animals	Protocol	Results	Reference
Rat (SD), juvenile male, n=6	Test material: Called DUP in the article, CAS RN 3648-20-2. Oral: gavage Dose: 500 mg/kg bw/day Exposure: 28 days (PND 35 to 77) Vehicle: corn oil	NOAEL: Not determined LOAEL: 500 mg/kg bw/day. Decreased sperm count and sperm motility was found in exposed males. No effects on dietary consumption, body weight and relative weight of heart, lungs, liver, kidneys, adrenal glands, spleen, thymus, thyroid glands, testes and epididymides.	Kwack *et al.*, 2009
Rat, Fisher 344, n= 5 males and 5 females (41-44 days old)	Test material: D11P Oral: diet Doses: 0, 0.3, 1.2, 2.5% corresponding to 279-285, 1106-1183 and 2115-2495 mg/kg/day respectively (for females-males) Exposure: 21 days Vehicle: diet	NOAEL: 0.3% (279- 285 mg/kg/day) LOAEL: 1.2% (1106-1183 mg/kg/day) Increased absolute testis weight was found but the relative testis weight was not different from controls, although body weight gain was lower in the two highest dose groups. No histologic changes in testes were found.	Unpublished Study Report (1985)
Rat, Fisher 344, n=5 males	Test material: D11P Oral: diet Doses: 0, 0.3/0.6, 1.2, 2.5%. 2.5% corresponded to 2100-2600 mg/kg/day Exposure: 21 days	NOAEL: 2.5% No effects were found on testis weights and no changes were found in histology of testes.	Lington *et al.*, 1993
Rat, Fisher 344, n=10 per sex, males and females (42±2 days old)	Read Across: Test material: 1,2-Benzenedicarboxylic acid, di-C8-10 alkyl esters, CAS RN 71662-46-9 Oral: diet Doses: 0, 0.1, 0.3, 1%. 0.1 and 0.3% corresponded to 79.6 and 303.9 mg/kg/day, respectively Exposure: 90 days Vehicle: diet	NOAEL: 303.9 (females) and 79.6 (males) mg/kg/day LOAEL: 0.3% (303.9 mg/kg/day) for males. 1% for females. Relative testes weights were slightly higher in the mid and high dose groups (1%) (statistically significant lower mean body weight day 90 in low and high dose group). Histopathological changes, which were not related to treatment (according to the author), were seen in the epididymis and testes of male rats and ovaries and uterus of female rats (no details on dose or findings).	Unpublished Study Report, 1993

All of the studies are evaluated as reliable with restrictions (Klimisch score 2) due to the relatively low number of animals per group used.

In the open literature a study performed by Kwack *et al.,* (2009) showed a decreased sperm count in juvenile males after 28 days of gavage exposure to a dose of 500 mg/kg bw/day. This result may indicate reproductive effects of diundecyl phthalate (DUP). However, the study only included a low number of animals per group and only one dose of DUP, which limits the conclusions that can be drawn on the basis of this study. The repeated

dose studies on D11P provided by the registrant also all used a low number of animals per group. Conflicting data on testes weight were seen, as Unpublished Study Report (1985)) found indications of increased testes weights after D11P exposure. However, as the other study on D11P did not find this effect (Lington *et al.,* 1993), it is possible that the finding by Ford *et al.,* (1985) was a chance finding.

Further, read-across was performed by the registrant from 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl phthalate (CAS RN 71662-46-9) (Unpublished Study Report, 1993).The repeated dose toxicity study for this compound showed possible reproductive effects based on testes weights, but the increased relative testis weight could also be linked to the decreased body weight. If read-across between D11P and di-C8-10-alkyl phthalate (CAS RN 71662-46-9) had been properly justified, the information on di-C8-10-alkyl phthalate would additionally have led to concerns that D11P may cause adverse reproductive effects.

All in all, the findings from repeated dose studies on diundecyl phthalate, the registered substance and the proposed read across substance 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl phthalate add to the concern for reproductive effects of the registered substance (Kwack *et al.,* 2009; Unpublished Study Report (1985); Lington *et al.,* 1993 and Unpublished Study Report, 1993) It is not known whether these effects may be related to an endocrine mode of action. Relevant findings are further discussed in the sections on reproductive toxicity and endocrine disruption (7.9.7 and 7.10).

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 D11P 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 assessment of the read-across 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 registration 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 1,2 Benzenedicarboxylic acid, di-C8-C10-alkyl esters, DODP, CAS RN 71662-46-9. Study deemed equivalent or similar to OECD TG 408, conducted by Unpublished Study Report, 1993) and considered key study by the registrant.

- Two 21 day studies on D11P. Studies conducted by Unpublished Study Report (1985) and Lington AW, Gray TJB, Evans J, Lake BG, Moran B (1993), respectively and considered supporting studies by the registrant.

As explained in section 7.9.8, the adaptation of the information requirement is not accepted 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 not acceptable and thus, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement for sub-chronic toxicity study (90 day), Annex IX, Section 8.6.2.

In regards to substance evaluation, the 90-day study may provide information to help clarify the concerns for reproductive toxicity and endocrine disruption, e.g. through investigation of effects on the thyroid. Information from the 90-day study may further be used as supportive evidence to trigger the inclusion of the F2, DNT and/or DIT cohorts in the EOGRTS (OECD TG 443), for which a data gap is also identified (see section 7.9.7.4.1).

7.9.5. Mutagenicity

Not evaluated by eMSCA.

7.9.6. Carcinogenicity

Not evaluated by eMSCA.

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.

The Substance contains constituents in common with DHNUP, and there is a concern that some of these constituents may cause the adverse effects on reproduction (development and fertility) seen with DHNUP.

In addition, the concern for reproductive toxicity is based on structural similarities to other phthalates with evidence of reproductive toxicity. Firstly, the registered substance is a UVCB, and one constituent seems to have a C7 backbone (2-Bu-C7) according to the registrant (see section 7.9.8). This is coupled with indications that phthalate esters with straight-chain carbon backbone of C7 are associated with reproductive toxicity. Furthermore, a concern for reproductive toxicity of substances with longer carbon backbones also remains (see section 7.9.7.1 and 7.9.7.3).

No data on reproductive toxicity of diundecyl phthalate branched and linear (D11P) has been provided by the registrant, as di-(C9-C11 alkyl) phthalate (D911P, CAS RN 68515-43-5) and 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl ester (CAS RN 68515-51-5) have been used as read-across substances to provide toxicological information. Two two-generation studies with oral exposure of rats (Unpublished Study Report, 1998; Unpublished Study Report, 2001) and two prenatal developmental toxicity studies in rats (Unpublished Study Report, 2000; Unpublished Study Report, 1996) on the read-across substances were provided. Study reports were provided on the D911P studies.

This use of read-across is challenged by the eMSCA. Detailed information 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 in order to evaluate whether there is a continued concern for reproductive toxicity of the registered substance, D11P.

In addition to data from the registration dossier, a developmental toxicity study on diundecyl phthalate (Saillenfait *et al.,* 2013b) was available in the open literature and is also presented and discussed in the following.

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

There are no reproductive toxicity studies on the Substance in the registration dossier. For the source substances di-C6-10-alkyl phthalate (CAS RN 68515-51-5) and C911P (CAS RN 68515-43-5) results from two-generation studies are provided in the registration dossier.

Repeated dose studies as described above (section 7.9.4) are also included to evaluate toxicity to fertility.

Table 9. Summary of some studies used to evaluate the concern for effects on fertility

Species, strain and number of animals	Protocol	Results	Reference
Rat, Sprague-Dawley, 28 dams, 24 F1 offspring	Read Across: Test material: di-C6-10-alkyl phthalate (CAS RN 68515-51-5) Two-generation study, where pregnant rat dams (P) were exposed through the diet from 10 weeks prior to mating until weaning of the offspring. F1 offspring were exposed through the diet from weaning until weaning of F2 offspring. F2 offspring were exposed through the diet until termination. Doses: 0, 1000, 3000 and 10000 ppm in the diet, corresponding to 78-116, 235-346 and 809-1181 mg/kg bw/ day. Ranges are mean dosage for males and females respectively. Oral: diet	Reduced pup weights and marginal delay in sexual maturity was found at 10000 ppm (LOAEL) and increased liver and kidney weights were found in female F1 offspring at 1000 ppm. In parental animals from all generations, an apparently lower weight gain was found in the high dose group, but no effects were seen on body weights. Signs of hepatotoxicity were observed in all generations (liver weight and gross- and histopathology). An increased number of P and F1 animals lost more than 1 pup during lactation. This reduced litter size in the highest dose group over that period (observed in 5-6 litters in exposed animals versus 1-2 litters in controls). No significant effects on body weights, food consumption, mating performance or semen quality were observed in parental animals. Gestation length and number of implantations were not affected by exposure. In P animals absolute seminal vesicle weight was decreased. Weight of epididymides was also decreased but the authors rejected the reproductive importance of this finding due to the absence of similar findings in other generations. Relative kidney weights were increased in the two highest dose groups. In (F1 and F2) offspring pup weight appeared lower (14% lower compared to controls in F1 males on PND 22) in the high dose group compared to controls. Sexual maturation was marginally delayed in males and females (except for F2 females) and body weight at vaginal opening was marginally increased, but these effects were not statistically significant. Testes weights were decreased significantly in F1 males at 10000 ppm. In adult (F1) offspring prostate weight was decreased together with (absolute and relative) seminal vesicle weights and testis weight (with bw as covariate)	Unpublished Study Report, 1998

		was increased. Relative kidney weights were increased in the two highest dose groups and down to the lowest dose groups in female offspring. In F2 offspring seminal vesicle (absolute and relative) weight was decreased down to 3000 ppm.	
Rat, Sprague-Dawley, n=28	Read Across: Test material: D911P (CAS RN 68515-43-5) 2-generation reproduction study. 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 (0.1%) corresponded to 66-76 mg/kg/day, the middle dose group (0.5%) to 343-379 mg/kg/day and the highest dose group (1-2%) to 724-787 mg/kg/day. During lactation, the dose groups corresponded to 118-163, 593-867 and 1329-1760 mg/kg/day, respectively. Oral: diet	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 although testicular spermatid count was increased in all treatment groups. 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. In dams, a decrease in body weight gain during the first week of gestation was seen in all dose groups in F0 and in the two highest doses in F1. Decreased body weight during lactation was also found in dams in the highest dose group in F0 and the two highest dose groups for F1 generations. A decreased gestation length was seen in the two highest doses in F0 and in the highest dose in F1. Treatment effects were not seen for the oestrous cycle before mating, number of implantation sites, litter size or pup survival. In offspring, a decreased body weight was observed in males and females in F1 generation in the 2 last weeks of lactation. At sacrifice on PND 25, liver weight was increased at 5000 and 10000/20000 ppm, but no other organs or body weight was affected. In 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. Relative testis weight	Unpublished Study Report, 2001 The results were published in the open literature as Willoughby *et al.,* 2000

		was increased. 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 sexual maturation, ovary weights or histology of other organs than the liver were seen.	

All of the studies are evaluated as reliable (Klimisch score 1).

The initial concern for toxicity to fertility of the registered substance was based on the conclusion of the TC CL that branched C7-11P (DHNUP) may cause testicular damage, as the two substances include similar constituents.

A non-guideline repeated dose study (see also section 7.9.4) was found in the literature describing a study on diundecyl phthalate (Kwack *et al.,* 2009). Data from this study indicated reproduction effects (reduced sperm count) of diundecyl phthalate. The study performed by Kwack *et al.,* (2009) showed a decreased sperm count in juvenile males after 28 days of gavage exposure to a dose of 500 mg/kg bw/day. This result may indicate reproductive effects of the registered substance. However, this study only included a low number of animals per group and only one dose of the test compound, which limits the conclusions that can be drawn on the basis of this study. The repeated dose studies provided by the registrant also used a low number of animals per group. Conflicting data on testes weight in the repeated dose toxicity studies were seen, as Unpublished Study Report (1985) found indications of increased testes weights after D11P exposure. However, the other repeated dose toxicity study did not find this effect (Lington *et al.*, 1993),

In an Unpublished Study Report from 1998 it was concluded that di-C6-10-alkyl phthalate had reproductive effects based on reduced pup survival and weights and marginal delay in sexual maturity at the 10000 ppm level. Moreover, effects were seen on male reproductive organs, livers and kidneys. Effects on prostate, seminal vesicle and testis weights show a pattern known for other reproductive toxicants including other phthalates, and it is possible that this may be related to endocrine disruption.

In the offspring from two two-generation studies performed with C911P, subtle indications of reproductive toxicity were seen. Indications of adverse effects on male and female reproductive organs and possibly age of male sexual maturation were present in the two-generation studies (Unpublished Study Report, 1999b, Unpublished Study Report, 2001; Willoughby *et al.,* 2000).

Furthermore, the Registrant's main argumentation for lack of reproductive and developmental toxicity of the registered substance is that it belongs to the group of high molecular weight phthalates. 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). (see also section 7.9.7.3). It should also be noted that one of the listed esterification products of the registered substance contains a C7 backbone (2-Bu-C7) according to the registrant (see section 7.9.8).

In conclusion, the there is a continued concern for effects on fertility of the registered substance. In order to address this concern, the data gaps on repeated dose toxicity and reproductive toxicity needs to be filled (see section 7.9.4.2 and 7.9.7.4).

7.9.7.2. Review of information regarding the concern for developmental toxicity

There are no data available on the Substance, D11P, regarding developmental toxicity.

Two studies in rodents on source substances for read-across are presented, a prenatal developmental toxicity study on C911P (CAS RN 68515-43-5), and on di-C6-10-alkyl phthalate (CAS RN 68515-51-5). Additionally, a prenatal developmental toxicity study was found in the literature describing a study on source substance diundecyl phthalate (Saillenfait *et al.,* 2013b), but not identical to the registered substance.

Table 10. Overview of developmental studies on read-across compounds D911P and di-C6-10-alkyl phthalate

Species, strain and number of animals	Protocol	Results	Reference
Rat, Sprague-Dawley, n=22	Prenatal developmental toxicity study Read Across: Test material: D911P Doses: 0, 250, 500 or 1000 mg/kg bw/day Oral: gavage Exposure: 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.	Unpublished Study Report, 2000
Rat, Sprague-Dawley, n= 25	Prenatal developmental toxicity study Read Across: Test material: di-C6-10-alkyl phthalate, CAS RN 68515-51-5 Doses: 0, 100, 500, 1000 mg/kg bw/day Oral: gavage Vehicle: maize oil Exposure: GD 6-16	Increased incidences of foetuses with 14th ribs in mid and high dose groups; the incidence in low dose group was similar to control. Increased incidence of foetuses with retarded sternebrae in the high dose group compared with control.	Unpublished Study Report (1996)
Rat, Sprague-Dawley, n=20-22 pregnant dams	Prenatal developmental toxicity study Test material: CAS RN 3648-20-2 (called DUDP in the article) Doses: 0, 0.25, 0.5 and 1 g/kg bw/day Oral: gavage Exposure: GD 6-20	In dams, the number of implants was significantly decreased in groups exposed to 0.25 and 0.5 g/kg bw/d DUP, but not at 1 g/kg bw/d. In male fetuses, the anogenital index (AGDi, AGD adjusted to the body weight) was decreased in the group exposed to 0.5 g/kg bw/d DUP compared to controls, although AGD (not adjusted to the body weight) was not changed. At 1 g/kg bw/d 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). An increased number of lumbar ribs were found in foetuses from the two highest dose groups. No effects were observed in mean maternal body weight, bodyweight gain throughout the study or food consumption. Treatment effects were not seen on the number of corpora lutea in the ovaries or the incidence of pre-implantation loss,	Saillenfait A.M, Gallissot F., Sabaté J-P, Remy A. (2013b)

		post implantation loss, resorptions, live foetuses or fetal sex ratio. In the fetuses, no effects on body weight or positioning of the testis were observed. No other skeletal effects were observed in the foetuses besides the occurrence of lumbar ribs.	

Saillenfait *et al.,* (2013b) showed effects of diundecyl phthalate, DUP, on implantation in dams, anogenital index and skeletal development in foetuses.

Skeletal developmental effects were also found in foetuses exposed to di-C6-10-alkyl phthalate (Unpublished Study Report, 1996) but other developmental effects were not found for di-C6-10-alkyl phthalate or C911P (Unpublished Study Report, 1996; Unpublished Study Report, 2000).

Developmental effects (skeletal variations) observed for the phthalate of initial concern (C7-11P, DHNUP) have also been observed for other phthalates with similar constitutents as the registered substance, e.g. C911P (source substance), diundecyl phthalate, DIDP and DINP (ECHA 2013, Waterman 2000, Waterman 1999, Unpublished Study Report, 2000; Saillenfait *et al.,* 2013b). For DIDP, it was agreed 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 the proposed source substance C911P, the effects on supernumerary ribs was less marked and seen for lumbar and not cervical ribs, and therefore the effect was not considered a clear adverse developmental effect.

Overall, effects on skeletal development are frequently seen for the group of HMWPEs.

Furthermore, the Registrant's main argumentation for lack of reproductive and developmental toxicity of the registered substance is that it belongs to the group of high molecular weight phthalates. 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) (see also section 7.9.7.3). It should also be noted that one of the listed esterification products of the registered substance contains a C7 backbone (2-Bu-C7) according to the registrant (see section 7.9.8).

In conclusion, there is a continued concern for developmental toxicity of the registered substance. In order to address this concern, the data gaps on repeated dose toxicity and reproductive toxicity need to be filled (see section 7.9.4.2 and 7.9.7.4).

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 (HMWPEs) and are considered to have similar environmental and toxicological properties (OECD 2004).

The Registrant's main argumentation for lack of reproductive and developmental toxicity of the registered substance is that it belongs to this group of high molecular weight phthalates (HMPWEs). It is stated about the group of transitional phthalates (produced from alcohols with straight-chain carbon backbones of C4-6) that "*Members of this sub-group are distinguished by their greater mammalian toxicity compared to either the low or high molecular weight phthalate ester sub-groups, particularly with regard to reproductive and developmental effects."* in the "Justification for read-across" document.

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

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

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

As laid out in the previous sections, no reproductive toxicity data on D11P is provided by the registrant, as di-(C9-C11 alkyl) phthalate (D911P, CAS RN 68515-43-5) and 1,2-Benzenedicarboxylic acid, di-C6-10-alkyl ester (CAS RN 68515-51-5) have been used as read-across substances to provide toxicological information. Two two-generation studies with oral exposure of rats (Unpublished Study Report, 1998; Unpublished Study Report, 2001) and two prenatal developmental toxicity studies in rats (Unpublished Study Report, 2000; Unpublished Study Report, 1996) on the read-across substances were provided.

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

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

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

The standard information requirement under Annex X, 8.7.3 is an Extended One-Generation Reproductive Toxicity Study. 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 registration 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 considerd appropriate to address this standard information requirement is included in the registration dossier. Instead an adaptation of this information requirement according to Annex XI, Section 1.5. of the REACH Regulation was sought. The applicant has provided a justification for read across to waive the requirement.

The registrant provided following studies for read-across:

- A two-generation reproductive toxicity study on 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, D9-11P (CAS RN 68515-43-5) administered in feed. OECD TG 416 study (Unpublished Study Report, 1997) was conducted and considered key study by the registrant.
- A two-generation reproductive toxicity study on 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters (CAS RN 68515-51-5) administered in feed. An OECD TG 416 study

(Unpublished Study Report, 1998) was conducted and considered weight of evidence study by the registrant.

As explained in section 7.9.8, the proposed adaptation of the information requirement is rejected 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 information provided on this endpoint for the registered substance in the registration dossier does not meet the information requirement, Consequently there is an information gap and it is necessary to provide information 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, section 7.10 on endocrine disruption). 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 registration 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 registrant included the following studies for read-across:

- A prenatal developmental toxicity study on Diundecyl benzene-1,2-dicarboxylate (CAS RN 3648-20-2) administerd by gavage. Study deemd equivalent or similar to OECD TG 414 study conducted by Saillenfait A-M, Gallissot F, Sabate J-P, Remy A (2013b) and considered key study by the registrant.

- A prenatal developmental toxicity study on 1,2-Benzenedicarboxylic acid,di-C6-10-alkyl esters (CAS RN 68515-51-5) administered by oral gavage. OECD TG 414 study was conducted (Unpublished Study Report, 1996) and considered weight of evidence study by the registrant.

- A prenatal developmental toxicity study on 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, D9-11P (CAS RN 68515-43-5), administered by gavage. OECD TG 414 study was conducted (Unpublished Study Report, 1999a) and considered weight of evidence study by the registrant.

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

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

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

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

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

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

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

7.9.7.4.3. Prenatal Developmental Toxicity Studies in a second species

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

As explained above, the registration 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 registration dossier also does not contain information or an adaptation for the second species PND study in accordance with column 2 of Annex X, Section 8.7. or with the general rules of Annex XI on adaptation of the testing regime for this standard information requirement.

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

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

7.9.8. The eMSCA challenge of the read-across provided to fill the data gaps on repeated dose toxicity and reproductive toxicity

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 different chemicals as read-across source substances (analogue substances) for the endpoints required, in an attempt to fulfil the standard information requirements.

7.9.8.1. Hypothesis provided by the Registrant

In the registration dossier, the Registrant(s) has provided "Justification for read-across" documentation where the following hypothesis is proposed:

"*The substance is regarded as possessing a functional group common to a number of other substances and this principle has been used by the US EPA HPV challenge program when examining the phthalate esters and defined these into a category or group based on the principles outlined above. It describes the defined group as consisting of 1,2-benzenedicarboxylic acids, with side chain esters ranging in carbon chain length from C1 to C13. In addition to carbon chain length, structure will vary depending on the isomeric composition of the alcohol used in their manufacture.*

Ester side chains may be linear isomers (for example: di-methyl and di-n-heptyl phthalates), branched isomers (for example: diisohexyl phthalate), and/or a combination of benzyl and linear or branched isomers (for example: benzyl butyl phthalate and benzyl C7-C9 branched and linear phthalate).

The US EPA HPV program further divides the group into three subcategories based on their physicochemical and toxicological properties, these being described as low molecular Weight, transitional or high molecular weight phthalates.

Low molecular weight phthalates are regarded as being those produced from alcohols with straight-chain carbon backbones of <C3. They are distinguished from phthalates in other subcategories by their higher volatility and water solubility which gives them different physicochemical properties compared with other phthalate esters. Their greater water solubility results in a greater aquatic toxicity potential than the transitional and higher molecular weight phthalates and they are regarded as exhibiting lower mammalian toxicity potential than do the transitional phthalates.

Transitional phthalates are regarded as being those produced from alcohols with straight-chain carbon backbones of C4-6. Their physicochemical properties may vary in that the lower transitional phthalates (shorter ester carbon chain length) are somewhat more water-soluble than the higher transitional phthalates (longer ester carbon chain length). Members of this sub-group are distinguished by their greater mammalian toxicity compared to either the low or high molecular weight phthalate ester sub-groups, particularly with regard to reproductive and developmental effects.

High molecular weight phthalates regarded as being those produced from alcohols with straight-chain carbon backbones of >C7 or a ring structure. They exhibit low water solubility and have a very low vapour pressure. Members of this sub-group are regarded as typically exhibiting low mammalian toxicity although it should be noted that liver toxicity and hepatocarcinogenicity has been observed for di-isononyl phthalate. This is by a mechanism of peroxisomal proliferation to which rodents are particularly sensitive and to which humans are currently being regarded as insensitive."

It may be noted that the justification does not reveal whether phthalate esters with straight-chain carbon backbone of exactly C7 are regarded as members of the high molecular weight phthalates with low mammalian toxicity or not.

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 registration dossier and in the Chemical Safety Report (CSR). The following substances are used as source substances in the read-across for the individual end-points:

Repeated dose toxicity, oral exposure

- Source 1:1,2 Benzenedicarboxylic acid, di-C8-C10-alkyl esters/ EC number 275-809-7/ CAS RN 71662-46-9, DODP (OECD TG 408 similar study, key study).
- Source 2: DUP (but different compound than the registered substance), diundecyl benzene-1,2-dicarboxylate/ EC number 222-884-9/ CAS RN 3648-20-2, 21 days, 2 supporting studies

Toxicity to reproduction, fertility

- Source 3: 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, D9-11P, dioctyl phthalate/ EC number 271-085-1/ CAS RN 68515-43-5 (OECD TG 416, key study)
- Source 4: 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters/ EC number 271-094-0/ CAS RN 68515-51-5 (OECD TG 416, weight of evidence)

Toxicity to reproduction, development

- Source 2: Diundecyl benzene-1,2-dicarboxylate/EC number 222-884-9/ CAS RN 3648-20-2 (equivalent or similar to OECD TG 414, key study)
- Source 3: 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters, D9-11P, dioctyl phthalate / EC number 271-085-1/ CAS RN 68515-43-5 (equivalent or similar to OECD TG 414, weight of evidence)
- Source 4: 1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters, D6-10P/ EC number

271-094-0/ CAS RN 68515-51-5 (OECD TG 414, weight of evidence)

The registrant does not provide data on prenatal developmental toxicity (PNDT) in a second species, and a data gap is thus recognized regarding developmental toxicity.

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 287-401-6'), 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
iii) No bridging studies are presented to allow side-by-side comparison of substances.

In the text below the MSC goes into detail with the three issues.

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

Target substance

- The Registrant(s) has not provided detailed information on backbone length of all present constituents, their composition concentrations and ranges in the REACH IUCLID dossier, including the "justification for read-across" document.

For the registered substance, typical concentrations and concentration ranges were given for 5 specific constituents and 3 "non-specific" constituents (Confidential Appendix A).

However, the information is inadequate since it does not allow for estimation of the total content of C7-backbone due to lack of details on the main 'non-specific' constituent.

Source substance

Four substances are applied for read-across: Source 2 (DUP;CAS RN 3648-20-2, which the registered substance has commonly and historically been regarded as); Source 3 (1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters , D9-11P ,CAS RN 68515-43-5); Source 1 (1,2-benzenedicarboxylic acid, di-C8-10-alkyl esters, L8-10P,CAS RN 71662-46-9); Source 4 (1,2-benzenedicarboxylic acid, di-C6-10-alkyl esters, D6-10P,CAS RN 68515-51-5)."

- The Registrant(s) has not provided detailed information on backbone length of all present constituents and the composition concentrations of these in the source substances as tested in the experimental tests used for the proposed read across.
- The information on the C-11 alcohol (CAS RN: 128973-77-3, EC no: 603-309-4) used for synthesis of the target compound as well as information on the C9-11 alcohol (CAS RN: 66455-17-2, EC no: 266-376-6) used for synthesis of Source 3 is not sufficient as the backbone length of the branched constituents are not given and neither are specific concentrations of these branched constituents.
- The information provided on Source 3 (D9-11P) it is not sufficient to assess the typical concentrations and concentration ranges of the individual phthalate constituents with different backbone lengths.
- The Registrant(s) has not provided information on constituents for Source 4 (D6-10P)
- When comparing the registered substance with one of the source substances, Source 3 (D9-11P), the percentage of phthalate constituents with at least one branched sidechain is maximum 26% for Source 3. For the registered substance it is typically 75% (sum of max. ranges 91%) for which reason the eMSCA questions the use of Source 3 as source compound.

According to ECHA 2017b (page 29) detailed information on constituents and their concentrations in source material is necessary to evaluate the similarity and difference between the source and target UVCB to enable a prediction by read-across. Some information on the C-11 alcohol (CAS RN: 128973-77-3, EC no: 603-309-4) used for synthesis of the target compound as well as for the C9-11 alcohol (CAS RN: 66455-17-2, EC no: 266-376-6) used for synthesis of Source 3 has been provided in a communication letter (a PDF received August 2014) from the registrant. Also, more information on the C9-11 alcohol, Source 3, and Source 2 has been provided in a communication letter (an excel file received August 2014). However, the information is not sufficient, as the backbone lengths of the branched constituents are not stated. For Source 1 and Source 4 no details were provided in the communication letter.

According to the supplied information, the branched sidechains in the alcohol (C9-11) used for esterification of Source 3, of the substance is maximum 26% (4% C9, 10% C10 and 12% C11 branched). For these branched alcohols, the branching is typically in position 2 on the alkyl chain, and the typical branching is Methyl (5-10%), Ethyl (1-5%) and Propyl

(1-5%). Furthermore, the C9-11 alcohol can contain C8 and C12 alcohols having approximately the same linear and branched composition (position 2 on the alkyl chain with typical branching Methyl (5-10%), Ethyl (1-5%) and Propyl (1-5%), in the comprehensive quantity less than 5% w/w. Based on this information the MSCA cannot conclude the typical concentrations and concentration ranges of the individual phthalate constituents with different backbone lengths.

In ECHA 2017b (page 31) it is outlined that read-across of UVCB substances require an explanation of whether and how the constituents influence or do not influence each other's toxicity, to address variations in concentrations of structurally similar constituents, as well as discuss the potential impact these concentration differences may have on the prediction. Regarding variation in branching, the only information given by the registrant is that the registered substance has a much higher percentage of branched constituents than the source substance Source 3 (as listed above). It is not clarified how this might affect toxicity. For the other source substance no information is given by the Registrant(s) in relation to the percentage of branched constituents.

Differences such as this one needs to be carefully considered and potential impact on the prediction needs to be taken thoroughly into consideration in the read-across. Thus, documentation of the target and source compounds is not complete and their similarities/differences not comprehensively discussed as required for appropriate read-across of UVCB substances according ECHA 2017b.

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 take into account: *"Variations in the concentrations of the structurally similar constituents (or pool of constituents) and the impact of these variations on the predicted type and the strength of effects. The variations in proportion of constituents may influence the assumed dose response of the substance. Consequently, the quantitative nature (i.e. magnitude of the effects) of the predicted effect is a further issue that has to be assessed, taking account of the precise proportion of constituents in the source substance, in relation to the precise proportion of constituents in the target substance."* (ECHA 2017b, page 31).

To this end, the Registrant(s) has provided very limited information. In the document "Justification for read-across", the registrant refers to principles of grouping used by the US EPA HPV program stating that "*High molecular weight phthalates regarded as being those produced from alcohols with straight-chain carbon backbones of >C7 or a ring structure*". In 2004, the OECD assessed the HMWPE (High Molecular Weight Phthalate Esters) category in their work on Chemical Safety under the Environment, Health and Safety (EHS) program. The OECD concluded that for members of the HMWPE Category "*no or minimal developmental toxicity and no adverse effects on reproductive capability have been observed in rodent studies*" (OECD 2004). Since 2004, newer data have shown that this approach may to be too simplistic.

The HMWPE category is described as esters with an alkyl carbon backbone with 7 carbon (C) atoms or more. This is in contrast to the description by the registrant "backbones of >C7 or a ring structure". It is not fully clarified whether phthalates with straight-chain carbon backbone of exactly C7 is to be considered a concern or not. This is important, as a relevant fraction (11.3%) of the registered substance has a straight-chain carbon backbone of C7 (2-Bu-C7, see above). Hence, it is key to consider, in detail, the backbone

length of all present constituents, the composition concentration of these in the tested substances as well as backbone lengths of all possible constituents and the composition concentration of these in the registered substance (target) when attempting to apply justifiable read across approaches.

In addition, for the experimental information provided for the source substances overall the MSCA notes that different source substances are used for read-across for different endpoints and no endpoint-specific comparisons are performed to determine whether effects of one source substance may or may not be predicted for the target substance.

As an example, Source 2 (DUP, diundecyl phthalate) and Source 1 (1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters) are used as source substances for read-across regarding repeated dose toxicity (oral), whereas Source 3 (C9-11P) and Source 4 (DODP,1,2-Benzenedicarboxylic acid, di-C6-10-alkyl esters) are used for read-across for reproductive toxicity. As the provided justification for read-across is based on structural similarities for the whole group of HMWPEs (alkyl carbon backbone $\geq$7), it is not evident to the MSCA why certain longer chain phthalates are relevant source substances for the read-across for some of the endpoints relevant for reproductive toxicity, and not for others.

Re: **iii) no bridging studies are presented to allow side-by-side comparison of substances**

> With regards to bridging studies, the RAAF document notes*: "The test results obtained with a test material containing several constituents do not provide information on the individual contribution of the constituents to the observed toxicity or their possible interactions. The assessment of the read-across approach needs to evaluate what further information is presented by bridging studies and/or mechanistic explanations to explain why and how the results from the source substance are used to predict the properties of the target substance taking into account also possible interaction between constituents in the target substance. Bridging studies are comparable studies on the source and target substance, and these bridging studies allow side-by-side comparison of the substances for a particular property (e.g. properties as determined in a 90-day study). Bridging studies may enable the demonstration that two multi-constituent substances or UVCBs have similar properties for a particular endpoint, and thus play a key role in a read-across justification. In the absence of such an empirical demonstration, read across may be difficult to justify for complex compositions."* (ECHA 2017b, page 31)

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

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 and therefore the eMSCA challenges the proposed read-across.

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated by eMSCA

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

The eMSCA cannot evaluate due to data gaps as 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 as 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 by eMSCA.

7.10.2. Endocrine disruption - Human health

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

No data on anti-androgenecity of the registered substance is provided by the registrant, and assessment of endpoints sensitive to endocrine disruption has not been performed in available studies on the registered substance. Testosterone levels and other estrogen- or androgen sensitive endpoints such as nipple retention, sexual maturation and histology and weights of reproductive organs were not measured in exposed offspring in studies on diundecyl phthalate and no *in vitro* studies have investigated possible anti-androgenic or estrogenic activity of this phthalate.

It is well known that phthalates with a backbone of 4 to 6 carbon atoms (C4-C6) generally have anti-androgenic effects in fetal rats, but also phthalates with backbones C3 to C7 are able to reduce fetal testosterone production (Furr *et al.,*2014; Saillenfait *et al.,* 2009; Saillenfait, 2013b; Boberg *et al.,* 2011). As noted in section 7.9.8, one of the listed constituents contains a C7 backbone, according to the registrant. This further increases the concern for anti-androgenic effects.

In the developmental toxicity study on the proposed source substance diundecyl phthalate, DUP (Saillenfait *et al.,*, 2013) increases in anogenital distance index (AGDi) of similar extent were seen at at 0.5 and at 1 g/kg bw/d (although not reaching statistical significance at the latter group), (1.65±0.08, 1.59±0.05, 1.60±0.09 in 0, 0.5 and 1 mg/kg bw/d, respectively). It is unclear whether the observation of decreased AGDi indicates an anti-androgenic mode of action. Further studies are warranted to determine possible anti-androgenic effects of the registered substance. The findings from the repeated dose study described by Kwack *et al.,* (2009) point to reproductive toxicity of source substance diundecyl phthalate, DUP, as sperm counts were decreased. It is not clear whether this is related to an endocrine disrupting mode of action. In other repeated dose studies, weights of testes and epididymides and testes histology did not appear to be affected, although increased relative testes weights were found in one study (Unpublished Study Report, 1985).

In the registration dossier of the registered substance, read-across was made from D911P and di-C6-10-alkyl phthalate for reproductive effects. As mentioned in section 7.9.8, read across from D911P and di-C6-10-alkyl phthalate to the registered substance is not sufficiently substantiated and rejected by the eMSCA. The reproductive toxicity study on di-C6-10-alkyl phthalate showed adverse reproductive effects including effects on sexual maturation and male reproductive organ weights in adults (seminal vesicle, prostate and epididymides) as well as in young offspring (testes). These effects are indicative of endocrine disruption.

If sufficient documentation for read-across had been submitted, these results would support indications of endocrine disrupting effects of the registered susbtance.

<u>Considerations on anti-androgenic effects of phthalates in relation to the phthalate ester backbone length</u>

In addition to the phthalates DEHP, DBP, BBP and DIBP, a number of other phthalates have also been identified as being able to reduce fetal testosterone production in rats and

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

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

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

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

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

Further, as noted in section 7.9.8, one of the listed esterification products of the registered substance contains a C7 backbone (2-Bu-C7) according to the registrant.

Conclusion on review of information regarding the concern for anti-androgenecity

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

Further, as noted in section 7.9.8, one of the listed constituents of the registered substance contains a C7 backbone (2-Bu-C7), according to the registrant.

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

The eMSCA concludes that there is a concern for anti-androgenecity of the registered substance. Standard information requirement data on the registered substance on repeated dose toxicity and reprotox are expected to enable conclusion on this end-point (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 was raised during the substance evaluation process 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 the registered substance 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), but as e.g. thyroid hormone levels are rarely registered, it is unclear 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.

It should also be noted that one of the listed esterification products of the registered substance contains a C7 backbone (2-Bu-C7) according to the registrant (see section 7.9.8).

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

- Di-n-octyl phthalate: According to US Consumer Product Safety Commission (CPSC 2014), substantial evidence of DnOP-induced thyroid toxicity in experimental animals and in vitro has been presented in studies reviewed. Structural alterations such as reduced thyroid follicle size and decreased colloid density were reported in rat studies, as were alterations in thyroid hormones T3 and T4. In addition, ToxCast data show that DnOP is active in TPO assay, whereas other HMWPE are not currently tested (ToxCast accessed August 2018).
- Di(2-propylheptyl) phthalate: In a 90-day study changes in thyroid histology (hypertrophy of the follicular epithelium of the thyroid glands) were seen in both sexes. In a two-generation study, follicular hypertrophy/ hyperplasia was seen in the thyroid glands of 16 males and 18 females of the 600 mg/kg dose group as well as in 13 male and 6 female animals of 200 mg/kg dose group (F1 generation). Increases in thyroid weights were observed (CPSC 2010).
- Diisododecyl phthalate (DIDP) and Diisononyl phthalate (DINP): In an evaluation by ECHA recent toxicological data on DIDP and DINP were evaluated (ECHA 2013). No clear conclusions regarding possible effects on the thyroid system were made, 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 endocrine disrupting properties of the registered substance was provided by the registrant.

eMSCA cannot draw a conclusion due to the identified data gaps on repeated dose toxicity and reproductive toxicity (see section 7.9.7.2 and 7.9.7.4).

The standard information requirement on reproductive toxicity in Annex X is the extended one-generation reproductive toxicity study (OECD TG 443). In order to address the concern for thyroid disruption, inclusion of examination of thyroid hormones and thyroid histology as well as triggering of the Developmental Neurotoxicity cohort should be considered when this 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 by eMSCA.

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

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

7.11. PBT and VPVB assessment

A PBT Hazard assessment outcome document was published on the ECHA website in February 2020, concluding that the substance does not overall fullfill the criteria to be a PBT substance, with a residual uncertainty on persistence in sediments (ECHA, 2020)

7.12. Exposure assessment

The registered substance is not classified and no exposure information is included in the registration dossier. The end-point was not evaluated by the eMSCA.

7.13. Risk characterisation

Not evaluated by eMSCA.

7.14. References

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