Ministry of Environment of Denmark
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (D911P)

EC No 271-085-1

CAS RN 68515-43-5

Evaluating Member State(s): Denmark

Dated: 08 April 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 Article 46(1) decision.

Further information on registered substances here:

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

DISCLAIMER

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

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (D911P; EC No 271-085-1, CAS RN 68515-43-5) was originally included on CoRAP and selected for substance evaluation in order to clarify concerns about:

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

During the evaluation also another concerns was identified:

- Endocrine disruption

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

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. Initiation of a Compliance Check is requested by the eMSCA.	X

4. FOLLOW-UP AT EU LEVEL

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

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

There is a continued concern for reproductive toxicity and endocrine disruption of sex- and thyroid hormones. No conclusion can be reached on these endpoints due to data gaps in

the standard information on repeated dose toxicity and reproductive toxicity in the registration of this substance and incompliant read across justification. A Compliance Check is thus needed to request the missing standard information.

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

However, should the testing provided as an outcome of the Compliance Check decision not allow for conclusion on end-points of reproductive toxicity and endocrine disruption raised by the Danish EPA in the substance evaluation process, and further data are needed to clarify the concerns raised under SEv, 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 and a possible voluntary update of the registration with exposure information on this high tonnage chemical.

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

5.2. Other actions

Not applicable.

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
Possiblesubsequent substance evaluation	tbd	DK

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters (D911P; EC No 271-085-1, CAS RN 68515-43-5) was originally included on CoRAP and selected for substance evaluation in order to clarify concerns about:

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

During the evaluation also another concerns was identified:

- Endocrine disruption

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Suspected reproductive toxicity	Concern unresolved: Continued concern based on information from structurally similar substances. Read-across applied by REG to fill in data gaps not acceptable. No conclusion can be reached due to data gaps in standard information.
Exposure/lack of exposure assessment	Concern refuted. No further action.
Lack of RCR	Concern refuted. No further action.
High (aggregated) tonnage	Concern refuted. No further action.
Endocrine disrupting effects on the thyroid hormone system	Concern unresolved: continued concern based on information from structurally similar substances. No conclusion can be reached due to data gaps in standard information. .

7.2. Procedure

The Substance D911P was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014 due to initial grounds for concern relating to Human health/supected CMR (reproductive toxicity); Exposure/Lack of exposure assessment, Lack of risk characterisation ratio, High (aggregated) tonnage. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of Denmark was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified an additional concern endocrine disrupting properties i.e. disruption of sex- and thyroid hormones.

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

Based on the available information, no conclusion could be reached on the end-points of concern.

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

- Based on the evaluation of the available information a draft decision was prepared by the eMSCA and sent through ECHA to the registration on 25 March 2015, asking for further information. The comments from the registrant was received 18 June 2015.
- The eMSCA analysed the read across justification proposed by the applicant and qualified by information provided by the registrant(s) in their comments to the draft decision, applying the ECHA Read-Across Assessement Framework (RAAF) guidance. For use in this analysis, the eMSCA requested and received additional information from the Registrant about the composition of the registered substance and proposed read across substances.
- This evaluation concluded that the read across does not fulfil the criteria of the RAAF. Thus, there are standard information gaps on the end-points of repeated dose toxicity and on reproductive toxicity (i.e. developmental toxicity study in a second species) in the registration.
- The eMSCA decided that the evaluation of exposure would await the results of the hazard assessment, which in turn depend on the provision and the results of standard information data once a compliance check is initiated.

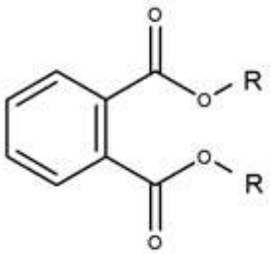
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	**Di-(C9-C11 alkyl) phthalate (D911P)**
EC number:	271-085-1
CAS number:	68515-43-5
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C28 H46 O4
Molecular weight range:	446.68
Synonyms:	DIPLAST L 9-11 Di-(C9-C11 alkyl) phthalate (D911P)

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

Structural formula:



R = C_9H_{19} to $C_{11}H_{23}$ (branched and linear) [>80% linear]

UVCB substance

The information on constituents, branching and purity available in the registration dossier is confidential.

7.4. Physico-chemical properties

Not evaluated by eMSCA.

7.5. Manufacture and uses

7.5.1. Quantities

Table 5

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 6

USES	Use(s)
Uses as intermediate	This substance is used in the following products: polymers. Other release to the environment of this substance is likely to occur from: indoor use and outdoor use resulting in inclusion into or onto a materials (e.g. binding agent in paints and coatings or adhesives).
Formulation	This substance is used in the following activities or processes at workplace: transfer of chemicals, closed batch processing in synthesis or formulation, mixing in open batch processes, transfer of substance into small containers and laboratory work.
Uses at industrial sites	This substance is used for the manufacture of: plastic products. This substance is used in the following activities or processes at workplace: transfer of chemicals, closed batch processing in synthesis or formulation, batch processing in synthesis or formulation with opportunity for exposure, mixing in open batch processes, calendering operations, transfer of substance into small containers, treatment of articles by dipping and pouring and the low energy manipulation of substances bound in materials or articles.
Uses by professional workers	This substance is used in the following products: polymers. This substance is used for the manufacture of: plastic products. This substance is used in the following activities or processes at workplace: the low energy manipulation of substances bound in materials or articles.
Consumer Uses	This substance is used in the following products: polymers. Other release to the environment of this substance is likely to occur from: indoor use and outdoor use resulting in inclusion into or onto a materials (e.g. binding agent in paints and coatings or adhesives).

Article service life	This substance is used in the following activities or processes at workplace: the low energy manipulation of substances bound in materials or articles and production of mixtures or articles by tabletting, compression, extrusion or pelletisation. Other release to the environment of this substance is likely to occur from: outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials) and indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, curtains, foot-wear, leather products, paper and cardboard products, electronic equipment). This substance can be found in complex articles, with no release intended: vehicles and machinery, mechanical appliances and electrical/electronic products (e.g. computers, cameras, lamps, refrigerators, washing machines). This substance can be found in products with material based on: plastic (e.g. food packaging and storage, toys, mobile phones) and rubber (e.g. tyres, shoes, toys).

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonised classification for the Substance.

7.6.2. Self-classification

- In the registration(s)*:* Not classified.

91 notifiers have also not classified D911P according to the ECHA C&L inventory. One notifier has self-classified D911P as Acute tox. 2, H300

7.7. Environmental fate properties

Not evaluated by eMSCA.

7.7.1. Degradation

Not evaluated by eMSCA.

7.7.2. Environmental distribution

Not evaluated by eMSCA.

7.7.3. Bioaccumulation

Not evaluated by eMSCA.

7.8. Environmental hazard assessment

Not evaluated by eMSCA.

7.8.1. Aquatic compartment (including sediment)

Not evaluated by eMSCA.

7.8.2. Terrestrial compartment

Not evaluated by eMSCA.

7.8.3. Microbiological activity in sewage treatment systems

Not evaluated.

7.8.4. PNEC derivation and other hazard conclusions

Not evaluated by eMSCA.

7.8.5. Conclusions for classification and labelling

For information, one out of 92 notifications self-classified as Acute Tox. 2 (H300).

7.9. Human Health hazard assessment

After assessment of the available information, initial grounds for concerns related to suspected reproductive toxicity were not considered sufficient to justify regulation or further testing.

The concern on prenatal developmental effects in rats were rejected, as the Substance has no or limited effects on these endpoints. Further, a concern for toxicity to fertility and developmental toxicity to the male reproductive system and endocrine disrupting mode of action was identified, but was not considered sufficient to justify regulation or further testing.

No 90-day repeated-dose toxicity study has been performed on the Substance. Instead the Registrant provided a read-across analysis to the structurally related 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters (CAS RN 71662-46-9). The eMSCA reviewed and did not accept the read-across. The dossier has data-gaps on the standard information requirements including pre-natal developmental toxicity study in a second species.

Concern for fertility effects: In the full 2-generation reproductive toxicity study (Unpublished Study Report 1999; 2001) no statistically significant treatment related effects on reproductive organ weight and sperm counts were seen in parental animals, however a statistically non-significant incidence of small testes and epididymis was seen in all exposed groups, but not in controls.

In the parental females (F0) from the high dose group (10000 ppm significantly reduced weights of uterus and cervix were seen. These effects could not be explained by the concomitantly reduced body weights, and an evaluation by United States Consumer Product Safety Commission (CSPC, 2010) concluded that in contrast to the organ weight changes in males, the observed decreases in absolute and relative uterus + cervix weights in parental females did not appear to be a simple reflection of altered body weights.

Based on these effects on reproductive organs in females a residual concern for an effect on fertility subsists, although not considered sufficient to justify regulation or further testing.

Concern for developmental effects: A prenatal developmental study (OECD TG 414) in rats was provided by the registrant. Based on this study the concern on prenatal developmental effects (postimplantation loss and visceral and skeletal malformations and variations) in rats could be rejected, as the registered substance did not seem to have clear effects on these endpoints. However, a data gap regarding prenatal developmental toxicity in a 2nd species was identified (see below).

Additional concerns for male reproductive development: Potential adverse effects on development were indicated in the full reproductive toxicity study, as a reduction in

absolute epididymis weight was seen in adult offspring of the high dose group, but this was not considered sufficient to justify regulation or further testing.

*Additional concerns for anti-androgenic effects***:** Indications of possible toxicity to development of the male reproductive system were seen as effects on epididymis weights of offspring and a low incidence of macroscopic changes in testes and epididymides were observed in the available reproductive toxicity studies. These effects could be mediated by an anti-androgenic mode of action, however, no information is available on possible modes of action for the registered substances.

Several important endpoints in relation to endocrine disrupting mode of action were not investigated in the available studies, as no measurements of sex hormone levels and androgen sensitive endpoints of anogenital distance and nipple retention of male offspring were performed.

*Additional concerns for thyroid hormone disrupting effects***:** No data is available on thyroid gland weight or histology or thyroid hormones in the reported reproductive toxicity studies on the registered substance and no repeated dose studies including thyroid examination are available. The Registrant presents data for the structurally related 1,2-Benzenedicarboxylic acid, di-C8-10-alkyl esters (DODP) showing no effects on thyroid histology in a 90-day study. However, the Registrant does not present all available data on substances with shared constituents with the registered substance. As the registered substance share constituents with some of the thyroid toxic phthalate esters, a possible concern for a thyroid toxicity possibly related to a thyroid hormone disrupting mode of action is identified but not considered sufficient for regulation or further testing.

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

7.9.4.1. Non-human information

7.9.4.1.1. Repeated dose toxicity: oral

In the registration dossier, a oral study in rats for the duration of one week on ”9 to 11 alcohols and the dialkyl phthalates derived from them” was included (Unpublished study report, 1970). It was however considered “not reliable” by the registrant, because it did not have the required duration to comply with current test guidelines for a sub-acute / sub-chronic study and few details on methods and results were available. The eMSCA agrees with this conclusion, therefore this study is not included in the current evaluation.

Additionally a repeated dose toxicity study on the read across substance 1,2 Benzenedicarboxylic acid, di-C8-10-alkyl esters is presented in the registration dossier. However, the read across justification from 1,2 Benzenendicarboxylic acid, di-C8-10-alkyl esters has not been sufficiently substantiated and is rejected. Therefore, the results from this study have not been included in the present evaluation and a data-gap identified for repeated dose toxicity of the Substance D911P.

7.9.4.1.2. Repeated dose toxicity: inhalation

No information available in the registration dossier.

7.9.4.1.3. Repeated dose toxicity: dermal

A study (Brown, 1970) is included in the registration dossier, but considered not reliable by the registrant due to methodology and reporting deficiencies.

7.9.4.1.4. Repeated dose toxicity: other routes

No information available in the registration dossier

7.9.4.2. Human information

7.9.4.3. Summary and discussion of repeated dose toxicity

For repeated dose toxicity the Registrant(s) included a study they considered 'not reliable' because it did not have the required duration to comply with current test guidelines for sub-acute/sub-chronic study and because few details on methodology and results were available. The eMSCA agrees with this conclusion.

Instead, the Registrant(s) used the read across from a 90-day repeated dose toxicity study on the a structurally related substance 1,2 Benzenendicarboxylic acid, di-C8-10-alkyl esters (DODP). However, the read across justification was evaluated by eMSCA and considered not acceptable. Therefore, the results from this study have not been included in the present evaluation.

Consequently, there is a data gap on the registered substance with regards to the end-point of repeated dose toxicity compared to the standard information requirements of REACH, Annex IX, point 8.6.2.

7.9.5. Mutagenicity

Not evaluated by the eMSCA.

7.9.6. Carcinogenicity

Not evaluated by the eMSCA.

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

7.9.7.1. Effects on fertility

A preliminary and a full reproduction study are provided by the registrant. The studies are presented in table 7 and described below. Willoughby et al. (2000), also describes the full 2-generation reproduction toxicity study and provides discussion on the relevance of effects. No additional reproduction studies on D911P were found in the open literature.

Table 7. Overview of reproduction studies provided by the registrant

Species, strain, number of animals	Protocol	Results	References
Rat, Sprague-Dawley, n=6 Klimisch 2 (reliable with restrictions)	Preliminary reproduction study, where pregnant rat dams (F0) and offspring (F1) were exposed through the diet continuously from 15 days prior to mating until termination. F0 males were killed after birth of F1 and F0 females were killed after weaning of the pups. Selcted offspring were terminated at PND43. Doses were 0, 1000, 5000 and 10000 ppm in the diet, corresponding to 750-1100 mg/kg bw/ day and in lactation periods to 1400-1800 mg/kg/day.	No statistical analysis was presented in the study report. In the F0 generation absolute and relative prostate weights appeared decreased (78% and 82% of controls, for absolute and relative weights in the high dose group, respectively), whereas body weight was not altered. Body weight gain in dams and offspring, oestrous cycle, mating performance, fertility, gestation length, litter size, survival or sex ratio were unaffected in all dose groups. No effects were found in testes, seminal vesicle or epididymides weights or sperm motility, count or morphology in F0 generation. In the offspring (F1), balano-preputial separation (PPS) was delayed (3 days, no statistics). At terminal sacrifice at PND 43, absolute and relative seminal vesicle weight appeared reduced (87% and 88% of controls, for absolute and relative weight in the highest dose group, respectively). Male livers had accentuated liver lobular pattern in the two highest dose groups (3/6 and 5/6 in 5000 and 10000ppm dose groups respectively). In the offspring (F1), no effects were observed in male reproductive organ weights (prostates, testes, and epididymides) or female sexual maturation.	Unpublished study report (1999)
Rat, Sprague-Dawley, n=28 Key study Klimish 1, reliable without restriction.	2-generation reproduction study (OECD TG 416). Doses were 0, 1000, 5000 and 20000 ppm in the diet. After six weeks of treatment, the highest dose was reduced to 10000 ppm. During gestation, the lowest dose group (1000 ppm) corresponded to 66-76 mg/kg/day, the middle dose group (5000 ppm) to 343-379 mg/kg/day and the highest dose group (10000 ppm) to 724-787 mg/kg/day (after reduction of dose in high dose group). During lactation, the dose groups corresponded to 118-163, 593-867 and 1329-1760 mg/kg/day, respectively.	In the F0 generation, a markedly lower body weight in males of the high dose group complicated the assessment of possible effects of treatment on organ weights. Absolute weights were decreased for adrenals, brain, epididymides, kidneys, prostate (86% of controls), seminal vesicles and spleen, whereas relative weights were increased for epididymides, kidneys, seminal vesicles and testes. Epididymal sperm count and sperm motility were unaffected. Testicular spermatid count was increased in all treatment groups, likely due to an unusually low control level. A few males in all groups exposed to D911P had small testis and/or small epididymis, whereas this was not seen among controls. Histological changes in liver were indicative of hepatotoxicity in both F0 and F1 males and females from the high dose group. In females of the F0 generation, the absolute and relative weight of uterus and cervix was decreased in the highest exposure group and relative weight of female livers was increased down to 5000 ppm of D911P. Slight reductions in absolute ovary weight (11%) and relative ovary weight (8%) in the high dose group were not statistically significant. In dams, a decrease in body weight gain during the first week of gestation was seen in all dose	Unpublished Study Report (2001) Willoughby et al., 2000

Species, strain, number of animals	Protocol	Results	References
		groups in F0 and in the two highest doses in F1. Decreased body weight during lactation was also found in dams in the highest dose group in F0 and the two highest dose groups for F1 generations. A decreased gestation length was seen in the two highest doses in F0 and in the highest dose in F1. Treatment effects were not seen for the oestrous cycle before mating, number of implantation sites, litter size or pup survival. In offspring, a decreased body weight was observed in males and females in F1 generation in the 2 last weeks of lactation. At sacrifice on PND 25, liver weight was increased at 5000 and 10000/20000 ppm, but no other organs or body weight was affected. In males, a slight and not statistically significant delay of sexual maturation was observed in the high dose group (1.3 day delay of preputial separation; this was within historical control range and not associated with altered body weight at preputial separation). In adult offspring (F1), male body weight was reduced in both generations and female body weight was decreased at the highest dose level. Absolute organ weights were also decreased in the high dose group males for adrenals, epididymides, kidneys, seminal vesicles and spleen. These effects are most likely related to the low body weight, as these effects were not retrieved in the relative organ weights (see below for discussion on epididymis weight). Relative testis weight was increased. No significant effects on sperm parameters were seen, and a slight reduction (by 7%) in epididymal sperm count was not statistically significant. In high dose females, reduced absolute weights of adrenals, spleen and thymus were observed, but no reductions of relative organ weights were seen. In offspring, no significant effects on female sexual maturation, ovary weights or histology of other organs than the liver were seen. Slight reductions in absolute ovary weight (11%) and relative ovary weight (5%) in the high dose group were not statistically significant.	

A thorough evaluation of data from the two reproductive toxicity studies (Unpublished Study Report 1999; 2001) showed no clear reproductive effects, but due to subtle effects on male and female reproductive organs, the concern for toxicity to fertility and development cannot entirely be dismissed.

7.9.7.1.1. Fertility effects in 2-generation studies (parental animals)

In the preliminary study (Unpublished Study Report, 1999) absolute and relative prostate weights of adult males (F0) were lower than controls, but no statistical information was presented. In the full reproductive toxicity study, absolute but not relative prostate weight was decreased (to 85% of controls) in parental (F0) males in the highest dose group

(10000 ppm) (Unpublished Study Report, (2001). However, this could be related to the markedly lower body weight in that group (81% of controls), and this finding is therefore not considered to be related to reproductive toxicity of D911P. In the full reproductive toxicity study, absolute weights of several male reproductive organs were reduced, but this is not considered reproductive toxic effects, as relative weights were unaffected or even increased, indicating that the changes are secondary to the markedly lower body weights.

In both generations of the full reproductive toxicity study, a few animals with macroscopic changes of the testis and epididymis were seen in all dose groups, but not in the control groups. The incidence of small testes and small epididymides was very low, not statistically significant and did not show clear dose-response relationship. However, in the peer-reviewed paper discussing the full reproductive toxicity study, a similar study on the phthalate D79P is reported in parallel with D911P. When comparing data from the two studies, it is clear that none of the 112 control animals had small epididymides or testes, whereas 3 of 84 parental males and 4 of 84 offspring males exposed to D911P had small epididymides and/or testes (Willoughby et al., 2000). It cannot currently be determined whether this finding reflects an actual reproductive effect of D911P. These findings are however relevant, as small testes and epididymides have been seen in adults as well as offspring exposed to other phthalates with well-described reproductive toxic effects including diethylhexyl phthalate (ECB, 2008). In the current study, slight effects were seen in both generations pointing to a direct effect on reproductive organs (toxicity to fertility), rather than a developmental effect.

In the full reproductive toxicity study, gestation length was decreased, and dam body weight was decreased at 5000 and 10000 ppm (Table 7). Significantly decreased weight of uterus and cervix was found in F0 dams (absolute weight reduced by 23%; relative weight reduced by 20%), and ovary weights were slightly reduced (absolute weights reduced by 11%, relative weights reduced by 8%, not statistically significant). In the peer-reviewed paper discussing the full reproductive toxicity study, the reduction of ovary weight is discussed as a possible specific effect of exposure (Willoughby et al., 2000). The authors find a more marked effect on ovary weights of another phthalate, D79P, and suggest that the slight reductions in ovary weights of D911P support the findings for D79P, i.e. these findings indicate a specific effect of exposure on ovaries. In the F1 generation, reductions of uterus, cervix and ovary weight were still present, but less marked and not statistically significant. It is unclear whether these findings reflect adverse reproductive effects of D911P, and the mode of action has not been determined. No other adverse effects were observed in reproductive or fertility parameters in dams.

7.9.7.1.2. Developmental effects in 2-generation studies (offspring)

Male sexual maturation was delayed (by 3 days) in the offspring of the preliminary study, but this was not confirmed in the full reproductive toxicity study, in which only a slight and not statistically significant delay of male sexual maturation was observed (1.3 days delay). Signs of hepatotoxicity in offspring were observed in both studies, as liver weights were reduced and histological changes were observed in the high dose group. In the full reproductive toxicity study, male and female body weights were reduced in offspring in lactation and adulthood (Table 6). Absolute weights of male and female reproductive organs were reduced in the high dose group, but this was possibly related to body weight, as no changes were seen for relative weights of the same organs. However, in the peer-reviewed paper discussing the full reproductive toxicity study, the reduction of epididymis weight is discussed as a possible specific effect of exposure (Willoughby et al., 2000). It is noted that absolute epididymis weight was significantly reduced by 7% in the high dose D911P group, and that this may be a direct effect of the test substance, as the epididymis is generally resistant to starvation. The epididymal sperm count in the high dose group offspring is reduced by 7%, but this is not statistically significant. However, the authors (Willoughby et al., 2000) note that the variability in epididymis weight is less than the variability for sperm count, and that organ weight is more sensitive than sperm count to treatment-related toxicity. Epididymis weight was also reduced in the parental males, but that effect was not considered a sign of reproductive toxicity as it was associated with an

increase in relative epididymis weight and likely secondary to the reduced body weight. This apparent reduction in epididymis weight of offspring may thus be a relevant developmental effect of D911P. Effects on epididymal development have been described for other phthalates and may be related to an anti-androgenic mode of action (Barlow and Foster, 2003) (see section 7.10.3).

Anogenital distance and nipple retention, which could be relevant markers of developmental toxicity to the male reproductive system, were not measured.

However, this residual concern for toxicity to reproduction was not considered sufficient to justify regulation or further testing.

7.9.7.2. Developmental toxicity

7.9.7.2.1. Non-human information

A preliminary and a full prenatal developmental study are provided by the registrant. The studies are presented in table 8 and described below.

Table 8. Overview of developmental studies provided by the registrant.

Species, strain, number of animals	Protocol	Results	References
Rat, Sprague-Dawley, n=6 Klimisch 2 (reliable with restrictions)	Prenatal developmental toxicity study with termination on GD 20. Pregnant rat dams were exposed by oral gavage with 0, 250, 500 or 1000 mg/kg bw/day of D911P from GD1-19.	A slight increase in the (absolute and relative) liver weight of dams was observed in the highest exposure group. No effects were seen on body weight gain, implantation rate, foetal growth or survival.	Unpublished Study Report (2000a)
Rat, Sprague-Dawley, n=22 Key study Klimish 1, reliable without restriction	Prenatal developmental toxicity study with termination on GD 20 (OECD TG 414). Pregnant rat dams were exposed by oral gavage with 0, 250, 500 or 1000 mg/kg bw/day of D911P from GD1-19.	No effects on maternal weight gain, food consumption, number of implantations, gravid uterus weight or macroscopic foetal malformations (skeletal or visceral) was observed. An increased body weight in foetuses in the highest dose group (1000 mg/kg) was observed but this effect was only statistically significant in females and was not considered of toxicological relevance. Organ weights were not assessed, except for the weight of the gravid uterus with cervix.	Unpublished Study Report (2000b)

The developmental studies with mated females exposed by gavage to 0, 250, 500 or 1000 mg/kg bw/day from GD1-19 showed no effects on reproductive or developmental parameters investigated, except for increased body weight in female foetuses in the highest dose group (1000 mg/kg) (Unpublished Study Report (2000b). This is not considered to be a sign of developmental toxicity. A slight increase in absolute and relative liver weight in pregnant dams exposed to 1000 mg/kg was observed in the preliminary study (Unpublished Study Report, 2000a), but organ weights were not assessed in the full study (Unpublished Study Report, 2000b). No other developmental endpoints were affected. Anogenital distance and hormone levels were not assessed in any of the studies.

Overall, the concern on prenatal developmental effects (postimplantation loss and visceral and skeletal malformations and variations) can be rejected, as the registered substance does not seem to have clear effects on these endpoints.

7.9.7.2.2. Human information

Not evaluated by eMSCA.

7.9.7.3. Summary and discussion of reproductive toxicity

The reproduction toxicity studies (described in section 7.9.7) and the developmental studies (described in section 7.9.8) showed no clear signs of reproductive or developmental effects of D911P in pregnant rat dams or foetuses. However, subtle changes in reproductive organ weights and a low incidence of macroscopic changes in testes and epididymides indicated possible toxicity to fertility and development. Therefore, the concern for effects of D911P on reproduction cannot entirely be ruled out based on the provided studies.

In summary, indications of effects on fertility were seen in the full reproductive toxicity study, as parental females (F0) from the high dose group had significantly reduced weights of uterus and cervix, and slightly (not statistically significant) reduced ovary weight that could not be explained by the concomitantly reduced body weight. Parental males (F0) had a low incidence of small testes and epididymides in all exposed groups, and not in controls.

Effects on development were seen in the full reproductive toxicity study, as a reduction in absolute epididymis weight in adult offspring of the high dose group, and this could not be explained by reduced body weights. A delayed age of sexual maturation in the preliminary reproductive toxicity study was less marked and not statistically significant in the main study.

Collectively, these indications of fertility effects on parental males and females and indications of developmental effects on the male offspring lead to the conclusion that the concern for reproductive toxicity of D911P cannot be entirely dismissed.

7.9.8. Hazard assessment of physico-chemical properties

Not evaluated by eMSCA.

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

Not evaluated by eMSCA.

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

Not evaluated by eMSCA.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated by eMSCA

7.10.2. Endocrine disruption - Human health

7.10.3. Conclusion on endocrine disrupting properties (combined/ separate)

Results from the reproductive and developmental toxicity studies on D911P included in the registration dossier and described in sections 7.9.7 and 7.9.8 do not provide clear indications of reproductive toxicity of D911P. However, subtle effects on male and female reproductive organs point to possible reproductive toxicity induced via an endocrine

disrupting mode of action as known for other phthalates. Thyroid toxicity has been observed for other phthalates and effects of D911P on thyroid are possible. A concern for endocrine disrupting properties of D911P was thus identified.

7.10.3.1. Anti-androgenic effects

Several important endpoints in relation to endocrine disruption were not investigated in the available studies, as no measurements of androgen sensitive endpoints of anogenital distance and nipple retention of male offspring were performed. A delay in sexual maturation of males can be an indication of anti-androgenic effects of a chemical (Mylchreest et al., 1999; Wolf et al., 1999). In the preliminary reproductive study delayed sexual maturation was seen in male offspring, but this was not confirmed in the large reproductive study, although a slight delay (not statistically significant) was also seen in that study.

For some phthalates, an anti-androgenic mode of action has been shown in developmental studies in which foetal testosterone levels were reduced by the test compounds, but no studies on fetal testosterone levels have been performed with D911P. Also, no *in vitro* studies have investigated the anti-androgenic activity of this phthalate. It is therefore, based on the presently available data, not possible to conclude whether this phthalate has anti-androgenic properties.

The concern for an anti-androgenic activity of D911P is also related to the known anti-androgenic properties and reproductive toxicity of certain other phthalates. The reproductive toxicity of phthalates appears to be associated with certain backbone lengths, and a division into low, intermediate and high molecular weight phthalates has previously been proposed with the highest degree of reproductive toxicity seen for "intermediate" backbone lengths (C4-C6).

From the open, peer reviewed literature 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, as they are able to reduce fetal testosterone synthesis leading to adverse reproductive effects including decreased anogenital distance, increased incidence of nipple retention and genital malformations, reduced number of spermatocytes and increased incidence of histological changes in testes and epididymides. Recent studies have shown that 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). No effects on fetal anogenital distance were found in studies on phthalates with a backbone 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.

D911P is a UVCB substance consisting mainly of linear C9 to C11 alcohols, but some components are C9 to C11 alcohols with methyl, ethyl or propyl branching, i.e. backbones below C9 to C11 (see section 11 and Annex A). It is noted by the registrant that a small fraction of D911P is C8 branched and linear, i.e. with a minor fraction having backbone length below C8.

Additionally, a recent 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 or UVCBs and include compounds with backbone lengths around 7 carbon atoms, it appears important to

perform individual toxicity evaluations for each UVCB and its components individually rather than a group of high molecular weight, unspecified UVCBs.

A concern for anti-androgenic effects of D911P is based on a) the subtle indications of reproductive effects in studies on D911P, b) the presence of minor constituents with backbones below C8, and c) a general concern for reproductive toxicity of phthalates also with longer backbones.

However, the concern is currently not considered strong enough to justify regulation or request for further testing.

7.10.3.2. Estrogenic effects

No indications of estrogenic properties were found for D911P in the reproductive studies reported by the registrant, as no effects on ovary weights and age of female sexual maturation was seen in offspring, and oestrous cyclicity in dams was unaffected by exposure (Unpublished Study Report 1999; 2001). Decreased weight of uterus and cervix was found in F0 dams in the full reproductive toxicity study (Unpublished Study Report (2001) study, but it is not clear whether this is related to endocrine disruption. No additional *in vivo* or *in vitro* studies on D911P investigating estrogenic effects are available in the open literature. A review by David (2006) shows that intermediate length phthalate diesters may in some *in vitro* assays interact with the androgen receptor, as well as the estrogen receptors. However, no interactions with monoesters have been found. In conclusion, as no *in vivo* indications of estrogenic properties of D9-11P were seen in offspring at any dose groups and no interactions with monoesters of intermediate length phthalates have been found, no concern for potential estrogenic effects of D9-11P has been identified.

7.10.3.3. Thyroid hormone disrupting effects

Thyroid toxicity has been registered for phthalates with backbone lengths of C6-C8 (Pereira et al 2007, Howarth et al 2001, Poon et al 2007, Hinton et al 1986), but as e.g. thyroid hormone levels are rarely registered, it is unclear whether thyroid toxicity is related to phthalates with specific backbone length only. No data were available on thyroid gland weight or histology, and therefor a thyroid disrupting mode of action of D911P cannot be excluded.

As the registered substance shares constituents with some of the thyroid toxic phthalate esters, a possible concern for thyroid toxicity can not be excluded from the available data although the concern is not currently considered strong enough to justify regulation or requirements for further testing.

7.11. PBT and VPVB assessment

Not evaluated by the eMSCA.

7.12. Exposure assessment

The end-point was included in CoRAP as a concern, as no information provided in the registration for this high volume substance of potential concern. However, as the substance is currently not classified, and no hazards were identified by the registrant. The endpoint was not evaluated by the eMSCA. Revisitation of the end-point may become relevant depending on the outcome of the requested Compliance Check.

7.13. Risk characterisation

Not evaluated by the eMSCA.

7.14. References

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