Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

1,2-Benzenedicarboxylic acid, di-C8-10-branched alkylesters, C9- rich; [1] di-"isononyl" phthalate; [2] [DINP]

EC Number: 271-090-9 [1] 249-079-5 [2]
CAS Number: 68515-48-0 [1] 28553-12-0 [2]

CLH-O-0000001412-86-201/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1,2-BENZENEDICARBOXYLIC ACID, DI-C8-10-BRANCHED ALKYLESTERS, C9-RICH; [1] DI-"ISONONYL" PHTHALATE; [2] [DINP]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkylesters, C9-rich; [1] di-"isononyl" phthalate; [2]
EC number: 271-090-9 and 249-079-5
CAS number: 68515-48-0 and 28553-12-0
Dossier submitter: Denmark

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	United Kingdom	British Coatings Federation	Industry or trade association	1
Comment received				
The BCF does not agree that evidence in the dossier submitted justifies the classification of DINP as a reproductive toxicant according to the criteria of the CLP. The evidence does not demonstrate conclusively there are adverse reproductive effects following the exposure to DINP and therefore the British Coatings Federation proposes that classification (Cat 1B H360D) for reproductive toxicant is not required. Further details are given in the attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BCF comments on DINP reclassification May 17.docx				
Dossier Submitter's Response				
Thank you for the comments. The issues raised in comment no 1 (by British Coatings Federation) have also been addressed in some of the comments from other stakeholders. The answers given below have thus been elaborated so that they also cover additional comments/details provided in the public consultation on the same issues. We have grouped your comments and our response under the 5 main headlines below: 1. *Comparability of DINP with classified lower molecular weight phthalates in relation to fertility effects* The comparison of the effects observed for DINP with those of the already classified C4-C6 phthalates DBP, BBP, DEHP and DIBP are primarily related to the observed developmental effects, e.g. effects on nipple retention, AGD, and sperm motility.				

It is acknowledged in the dossier that there are only few studies on DINP showing effects on the male reproductive system indicating effects on fertility (impact on sperm count and velocity in juvenile rats, 28 d; impact on sperm motility in rats exposed perinatally, adverse effects on reproductive organs in a 2 year study). The older 1- and 2-generation studies have not assessed sperm parameters. Based on the findings mentioned and the proposed mode of action for DINP, which is similar to that of other phthalates with demonstrated effects on reproduction and fertility, a classification for fertility effects in category 2 is thus proposed as there is some evidence from experimental animals of an adverse effect on fertility, but this evidence is not sufficiently convincing to place the substance in Category 1.

2. *Lack of reference to the review by Dekant and Bridges from 2016 and selectivity of data used*
The publication "Assessment of reproductive and developmental effects of DINP, DnHP and DCHP using quantitative weight of evidence" from November 2016 by Dekant and Bridges does not provide new scientific evidence on the effects of DINP, which is the basis of a classification proposal. Rather, the review lists the publications of key findings on DINP and compares the findings to those of the phthalates DCHP (classified Repr. 1B for developmental effects) and DnHP (classified Repr. 1B for developmental and fertility effects).
In other comments provided to the CLH dossier for DINP it is questioned why the publications by Dekant and Bridges (2016a and 2016b) have not been included in the CLH dossier. These publications were published online in November 2016 coinciding with the finalisation of the CLH dossier. While they did not bring new scientific information about the properties of DINP they summarise and assess the available data for DINP and two other phthalates according to a WoE methodology proposed by the authors which e.g. introduces arbitrary limit values for deciding on a classification. In the opinion of the DS this approach introduces an additional set of classification criteria which are not set out in the CLP Regulation.

The WoE assessment is based on the assignment of overall quality score for each observation identified in animal studies that have been identified as relevant with respect to the quality of the studies and the strength of the effects. This scoring has been conducted based on the available data for each of the three substances DINP, DCHP and DnHP. The scores assigned to each observation have been elaborated for the purpose of this publication and is based on the judgement of the two authors and not according to any officially established or recognised methodology. The overall assessment of the reproductive effects in relation to whether a classification is considered justified is based on (arbitrary) limits for the cumulative quality scores for the substances (e.g."Limited evidence to support the hypothesis of induction of adverse effects requires a minimum score of 246 and strong evidence a minimum score of 350"). These limits are chosen by the authors as a kind of cut-off value for classification and are not based on the CLP classification criteria. In the opinion of the Dossier Submitter, the WoE assessment and the established cut-off limits described in the publication cannot be used to demonstrate whether DINP fulfils the classification criteria or not. It is also noted that according to the authors DCHP, which is classified as Repr. 1B, the overall WoE assessment would point to a classification as Repr. 2.

Based on the above considerations the DS does not intend to provide a detailed response or assessment of the quantitave WoE assessment conducted by Dekant and Bridges. The DS would, however, like to note that there seem to be some pitfalls associated with the scoring system for the single observations and that

achievement of a high quality score e.g. depends on the availability of the full raw data set – which is rarely the case for data published in scientific journals and a high number of findings reported in each study. The scores to a high extent depends on the design of the study, methodology used, which parameters and the number of parameters that have been assessed etc. which are all part of the normal quality assessment of the identified information. However, a study containing only a single or a few relevant findings (e.g. due to the design/nature of the study) may get a low score even though the finding is relevant for a decision of classification. Furthermore the cumulative scoring of the available findings does not necessarily take into account the significance of the findings observed when looking across the relevant studies identified.

3. *The reliance of the CLH dossier on the Boberg study from 2011*
A group of representatives and members from the trade association European Plasticisers (previously: ECPI) (Morfelt et al., 2017) have questioned the relevance and reliance on the study by Boberg et al, 2011. Upon dialogue between the parties and the journal Reproductive Toxicology Dr. Boberg has submitted a corrigendum to the article (published 2016) to clarify the methodology and statistics used. Although Morfeld et al, 2017, have stated that Boberg et al have modified the methodology in order to fit the results obtained, this is not true. Results were obtained using a statistical method, which is described in detail in the Corrigendum (Boberg et al., 2016), but was insufficiently described in the original paper (Boberg et al., 2011). It is not clear why Morfeld et al., 2017, request publication of data corrected for multiple comparisons (p-values for Dunnett´s test), as these results are presented in the Corrigendum showing statistically significant reduction in sperm motility.
Morfeld et al., 2017, acknowledge that using the statistical methods described in the corrigendum they were able to reproduce the results presented in Boberg et al., 2011, i.e statistically significant reduction in AGD and reduction in sperm motility.
Thus, the only controversy remaining between the Morfeld et al., 2017, edior letter and the Boberg et al., 2016, corrigendum appears to be the question whether applied statistical methods were changed in the corrigendum to fit the published statistical results, or whether the published statistical results were originally achieved using the methods described in the corrigendum. It is, however, unclear how the published statistical results should have appeared in the 2011 publication, if the applied statistical methods were any different from what is published in the corrigendum. Thus, as stated by Boberg et al., 2016 and 2017, indeed the published statistical results were originally achieved using the methods described in the corrigendum.

Morfeld et al also question the use of data on sperm motility in the Boberg et al., 2011, study, as control values are below 70% motile sperm, which is considered a standard requirement in OECD guidance document. We can confirm that control values in the DINP study were below 70%, but within the range of control values in other studies on Wistar Han rats performed using the same methods in the same laboratory. Morfelt et al., 2017, conclude that changes in sperm motility for DINP exposed animals do not differ substantially from historical controls, but in fact the mean value in the high dose DINP group are 47.4%, whereas the lowest mean value in a historical control group is 12% higher, i.e. 53.1% (Boberg et al., 2017).

In relation to the letter by Morfeld et al. 2017 and the rebuttal letter from Boberg et al. 2017 other stakeholders have commented on the fact that the CLH dossier

does not contain a reference to the letter from Morfeld et al. The letter by Morfeld et al. (2017) and the rebuttal to this letter by Boberg et al. (2017) were published online in April 2017, i.e. after the finalization and submission of the CLH dossier for DINP. At the time of submission of the CLH dossier it was not known to the DS when the letters were expected to be published or what the final content of these letters would be as the letters were subject to review by Reproductive Toxicology at the time. The DS has not intended to withhold any information about this process but in order to ensure full transparency and to avoid bias the DS did not consider it pertinent to refer to a non-published debate on the specific study in the CLH dossier before the letters to the editor from both parties (Morfeld et al and Boberg et al) were finally reviewed and published. However, the CLH report does refer to the fact that a corrigendum to the Boberg et al. study from 2011 was published in 2016 and further that minor errors have subsequently been corrected in a letter submitted to Reproductive Toxicology in November 2016 (i.e. the Rebuttal letter from Boberg et al.).

4. *Adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains*
   Reproductive effects of phthalates are not considered as exclusively related to phthalates with alkyl side chain lengths between C3-C6.
   Recent studies have shown that also phthalates with backbones C7 are able to reduce fetal testosterone production (Furr et al., 2014; Saillenfait, 2011), whereas no effects on fetal anogenital distance were found in studies on phthalates with a backbone of 8 carbon atoms or more (Saillenfait et al, 2013a; Saillenfait, 2013b). Rat studies have shown that di-n-heptyl phthalate (with C7 backbone) reduces fetal testosterone (Furr et al., 2014), and reduce male AGD and AGDi (Saillenfait et al., 2011). The observed changes showing impaired masculinization of rat offspring indicate endocrine changes that would likely also influence human male reproductive development. Therefore, the described findings are predictors of adverse male reproductive health effects also in humans
   In a recent publication Health Canada (Health Canada 2015a) has proposed a different subgrouping/category definition of phthalates for human health assessment. This approach is related to effects on the developing male reproductive system in rats. DINP has thus been included in the subgroup of intermediate chain length phthalates (between C3-C7) based on specific lines of evidence (gene expression changes related to steroidogenesis in the fetal testes, foetal testicular testosterone production in rats and decreased AGD as an indicator of androgen deficiency during early development in male rat offspring) that are considered to be related to the proposed mode of action (MOA) behind the rat phthalate syndrome. The rat phthalate syndrome is characterised by malformations of male reproductive organs and incomplete masculinisation which in turn can lead to adverse effects on development and fertility.
   This supports that not only C3-C6 phthalates are associated with reproductive effects. However, a lower potency may be associated with phthalates with alkyl side chain lengths ≥C7.

5. *Socioeconomic aspects of a (re-)classification of DINP*
   The CLH process under the scope of the CLP Regulation only addresses identification of the intrinsic properties of substances based on the available data and comparison with the criteria. Socioeconomic considerations adressing the impact of a potential harmonised classification is not part of this process and thus not for the DS to comment on. It is noted that a classification of DINP as toxic to reproduction does not in itself lead to a restriction of its use.

References cited above that are not included in the CLH dossier:
Boberg, et al. (2017). Rebuttal to letter by Morfeld et al., Boberg et al. (2011) – Corrigendum (2016): Further significant modifications needed. Reproductive Toxicology 2017. http://www.sciencedirect.com/science/article/pii/S0890623816304099

Dekant W and Bridges J., 2016a: Assessment of reproductive and developmental effects of DINP, DnHP and DCHP using quantitative weight of evidence. Regulatory Toxicology and Pharmacology 81: 397-406.

Dekant W. and Bridges J., 2016b. A quantitative weight of evidence methodology for the assessment of reproductive and developmental toxicity and its application for classification and labeling of chemicals. Regulatory Toxicology and Pharmacology 82, 173-185.

Health Canada 2015a: Proposed Approach for Cumulative Risk Assessment of Certain Phthalates under the Chemicals Management Plan. Health Canada Environment Canada. August 2015.

Morfeld et al. (2017). Boberg et al. (2011) – Corrigendum (2016): Further significant modifications needed. Reproductive Toxicology 2017. http://www.sciencedirect.com/science/article/pii/S0890623816303719

Saillenfait AM, Roudot AC, Gallissot F, Sabate JP (2011). *Prenatal developmental toxicity studies on di-n-heptyl and di-n-octyl phthalates in Sprague-Dawley rats.* Reprod Toxicol. 32:268-76.

Saillenfait AM, Gallissot F, Sabaté JP, Remy A (2013a). *Prenatal developmental toxicity studies on diundecyl and ditridecyl phthalates in Sprague-Dawley rats.* Reprod Toxicol. 37:49-55.

Saillenfait AM, Sabaté JP, Robert A, Cossec B, Roudot AC, Denis F, Burgart M (2013b). *Adverse effects of diisooctyl phthalate on the male rat reproductive development following prenatal exposure.* Reprod Toxicol. Dec;42:192-202.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	Germany		Individual	2

Comment received

Based on my professional experience in toxicology and risk assessment, recognized by being elected member of several EU-Commission Scientific Advisory bodies (CSTEE, SCHER, SHENHIR) EFSA-Panels, and WHO/FAO groups, I would like to comment on the CLH-proposal.
The proposal to classify 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkylesters, C9-rich, di-"isononyl" phthalate (DINP, CAS 68515-48-0 and 28553-12-0) as a category 1B reproductive toxicant regarding effects on development and as a Category 2 reproductive toxicant regarding effects on fertility (CLH proposal) has been submitted to ECHA. However, the CLH proposal does not follow the guidance and criteria outlined in the CLP regulation regarding requirements for classification as a reproductive toxicant. The

proposal to classify DINP is not based on adverse effects as defined by WHO/IPCS but on small and inconsistent changes in some parameters observed only in some selected studies with DINP. The large database available on DINP including a two-generation reproductive and developmental toxicity study without effects on development and fertility is not further considered in the CLH-proposal and is not adequately integrated into the conclusions. Since the CLH-proposal does not rely on adverse effects as defined by WHO/IPCS and only lists a variety of unrelated changes seen in isolated studies in support of its conclusions, the CLH proposal does not have a scientific basis for its conclusions. Based on a weight of evidence approach integrating the available database, it can be concluded that DINP does not induce adverse or permanent effects on sexual function and fertility. Thus, classification is not supported since an "adverse effect on sexual function and fertility" is required as a basis for any classification. A detailed justification of my conclusions is provided in the attached comments and further supported by copies of two recent publications that have developed a quantitative weight of evidence approach to classification and labelling regarding reproductive toxicity and applied this approach to compare requirements for classification for DINP and two other phthalates.

A proposal to classify 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkylesters, C9-rich, di-"isononyl" phthalate (DINP, CAS 68515-48-0 and 28553-12-0) as a category 1B reproductive toxicant regarding effects on development and as a Category 2 reproductive toxicant regarding effects on fertility (CLH proposal) has been submitted to ECHA.
The CLP regulation (Regulation (EC) No 1272/2008) gives detailed guidance and criteria regarding points to consider when proposing classification for reproductive toxicity. As clearly stated in the CLP regulation, adverse effects (3.7.1.2) in appropriately conducted animal toxicity studies serve as the basis for classification as a reproductive toxicant both for developmental effects and for fertility. The guidance also states that weight of evidence (3.7.2.2.1, 3.7.2.3) should be applied considering consistency of the identified adverse effects over studies, including taking into account study quality, interference of maternal toxicity (3.7.2.2.2), secondary effects on reproductive endpoints due to other toxicities, and doses needed to induce toxicities. Moreover, the regulation explicitly states that small effects on a number of parameters such as small changes in the incidence of skeletal variations or small changes in sperm parameters should not trigger classification (3.7.2.3.3).
DINP is a data rich chemical with a large number of studies available for evaluation including guideline compliant reproductive and developmental toxicity studies. The large database on reproductive and developmental toxicity of DINP has been reviewed by the former ECB in 2003. The conclusion of this review, which was peer-reviewed by the responsible scientific advisory committee of the EU-commission was that classification of DINP for reproductive endpoints is not warranted based on the available database. The RAR provided the following summary of the available studies:
"Fertility assessment may be inferred from effects on reproductive organs and the two-generation study. …….
In the two-generation study no changes in reproductive indices are observed.
From those assays, no adverse effects on fertility may be anticipated."
Only investigative studies have been published since the ECB review in 2003 (Masutomi et al., 2003; Lee et al., 2006; Kwack et al., 2009; Boberg et al., 2011; Clewell et al., 2013a; Clewell et al., 2013b; Li et al., 2015).
The CLH proposal selectively picks effects from both the guideline studies reviewed in 2003 and the studies published after the ECB-review to justify classification. In the compilation of effects and the summary conclusions, the CLH proposal does not follow the guidance and criteria outlined in the CLP regulation.
• The proposed classification is not based on adverse effects as defined by WHO/IPCS.

Conclusions on a need for classification in the CLH proposal are based on small and inconsistent changes in some parameters in selected studies with DINP.
• The CLH proposal does not adequately consider the large available database on reproductive and developmental toxicity of DINP. Consistency of observations over studies is not assessed and results from high quality studies not showing adverse effects are neglected.
• Toxicological significance of the reported effects is not considered in the conclusions.
• The CLH proposal does not perform a quality assessment on the studies used to support its conclusions.
• The CLH proposal does not consider the well-described toxicities of DINP on other targets and/or maternal toxicity as confounders regarding reproductive and developmental effects.
• Consequently, the required weight of evidence analysis is not performed. Instead, insufficient evidence of adverse of effects is compiled in the CLH-proposal with the aim of concluding "sufficient evidence" in support of an adverse effect. This is not an appropriate approach since weight of evidence in the context of CLP classification refers to sufficient evidence in support of a treatment-related adverse effect from independent reports, or several consistent observations within one report. These have to be combined to support the occurrence of an adverse effect.
A quantitative weight of evidence (QWoE) analysis based on well-defined assessment criteria for both study quality and study outcome and adversity of effects reported (Dekant and Bridges, 2016 a,b) concluded "The application of the QWoE and a narrative assessment of DINP for both developmental and fertility effect assessments are in good agreement and do not support the presence of adverse effects induced by DINP in appropriately conducted animal studies. Therefore, there is no evidence to support a classification of DINP for reproductive toxicity". A more detailed justification for these conclusions is presented below and in copies of the publications that are submitted with these comments.
Small and reversible effects on reproductive and developmental parameters without functional or pathological consequence cannot be considered as adverse as it is done in the CLH proposal.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment DINP-WolfgangDekant.zip

Dossier Submitter's Response

Thank you for your detailed comments. We have grouped your comments and our response under the 5 main headlines below. The issues raised in comment no. 2 (From Individual, Germany) have also been addressed in some of the comments from other stakeholders. The answers given below are thus also referred to elsewhere in this document.

1) *The CLH proposal does not follow criteria nor guidance as it is not based on adverse effects but on small and inconsistent changes seen in selected studies:* Many of the comments provided in the public consultation address this point which has also been discussed during the process of preparing the CLH dossier with .e.g. European Plasticisers (previously: ECPI) and other stakeholders. As argued in the CLH proposal the DS considers that collectively the available information of DINP from animal studies provides clear evidence of an adverse effect on development and some evidence of an adverse effect on fertility. These effects are not considered to be a secondary, non-specific consequence of other toxic effects incl. maternal toxicity. Further, there is no mechanistic information excluding that that the effects are irrelevant for humans.

While some of the key findings (e.g. effects on sperm quality, increased nipple retention and reduced AGD) are not observed consistently when looking across the available data for DINP and while the some of the effects may be transient, this does not neglect the importance of the findings. With respect to the older one- and two-generation studies, parameters like sperm quality, AGD and presence of nipple/aereola were not examined as these parameters were simply not included in the former guidelines. This explains why impact on sperm quality, reduced AGD and nipple retention is only seen in some of the newer studies published after the EU Risk assessment as these parameters were not examined in previous guideline studies. The lack of confirmatory findings can thus partly be explained the different study designs used. The findings on e.g. AGD and nipple retention are not found consistently in comparable studies where these parameters have been assessed at comparable dose levels (e.g. increased nipple retention at two weeks of age and decreased neonatal male AGD was demonstrated by Boberg et al., 2011 but in the study by Clewell et al., 2013b, AGD reduction was only seen at two weeks of age). This could be due to minor differences in assessment methods, the test design e.g. with respect to exposure periods (dosing from GD7-PND 17 in Boberg et al. 2011 and GD12-PND14 in Clewell et al. 2013b), use of two different DINP variants and different rat strains in the two studies as well as normal biological variation.

As stated in the dossier, male reproductive system irreversible effects (e.g. sperm quality effects, structural abnormalities in reproductive organs, and decrease in anogenital distance) are linked to adverse effects in mammalian species, including humans. Overall, fetal disturbance of the developing male reproductive system can have multiple effects in mammalian species as described by Skakkebaek et al. (2001). Decreased AGD was seen for DINP only in neonatal or two week old rats (Clewell et al., 2013; Boberg et al., 2011), and indeed the early postnatal period is considered most sensitive to detect changes in AGD. Thus, even the positive control DBP did not affect AGD at PND 49-50, but only at PND 2 and 14 in the study by Clewell et al., 2013. The transient nature of the AGD changes in rodents do not discount the relevance as an indicator of adverse developmental changes in humans.

The observed changes showing impaired masculinization of rat offspring indicate endocrine changes that would likely also influence human male reproductive development. Therefore, the described findings are predictors of adverse male reproductive health effects also in humans.

The CLP Regulation states that if the only effects observed are considered to be of low or minimal toxicological significance classification may not necesarrily be the outcome (3.7.2.3.3.). The DS does not consider that the observed effects of DINP are of low or minimal toxicological significance. Several effects of DINP have been observed which are considered as important markers of reproductive toxicity including increased nipple retention, decreased AGD, decreased sperm motility and histological changes in testes and epididymis. As the observed pattern of is similar to those that are observed for other classified phthalates and as DINP is believed to share the same anti-androgenic mode of action, the observed findings cannot be discarded as being of low or minimal toxicological significance. It is recognized that the observed effects are only seen at relatively high doses for DINP and that some of the severe effects that are observed for other phthalates in addition (such as cryptorchidism, hypospadias, cleft palate, testicular tubular atrophy) have not been observed for DINP. The potency of DINP is thus much lower and the full scale of effects that are observed for other phthalates classified as reproductive toxicants

may not be expressed or be relevant for DINP, at least not when tested in concentrations relevant for classification.

Although it was concluded in the EU Risk Assessment from 2003 that the available studies did not justify a classification for reproductive toxicity, the one- and two generation studies however did show some treatment related effects in the highest doses (between approx. 550-1200 mg/kg bw, i.e. close to or above the limit dose relevant for classification). While these findings alone do not justify classification they are included in a total weight of evidence assessment where they are considered to support the conclusion of an effect of DINP on both development and fertility in those cases where effects are observed at concentrations below 1000 mg/kg/bw/day.

According to the criteria (CLP Annex I, section 3.7.2.3.1) both positive and negative results are assembled together into a WoE determination. Furthermore, a single, positive and reliable study with statistically or biologically significant positive results may justify classification. This supports the assessment by the DS that the observed positive findings observed in the key studies are sufficient to justify classification. Furthermore, DINP is considered to have the mode of action as that proposed for other phthalates classified as toxic to reproduction although it is recognised that the potency of DINP is lower than that of e.g. DEHP and other classified phthalates. .

In relation to the comment on adverse effects as defined by WHO/IPCS ("Principles For Evaluating Health Risks To Reproduction Associated With Exposure To Chemicals", 2001), these principles e.g. include the following examples of adverse effects that are considered relevant for reproduction, and which in turn are of direct relevance for the CLH proposal for DINP (citations with comment in brackets):

- "Factors that alter the level of testosterone, by decreasing synthesis, increasing metabolic clearance or blocking the androgen receptor, can adversely affect the amount or quality of semen" [decreased foetal testosterone levels shown for DINP by Borch et al. 2004; Hannas et al., 2011; Clewell et al., 2013a; Furr et al., 2014, Li et al., 2015 at doses < 1000 mg/kg bw/day]
- "Significant dose-related increases in histopathological damage of any of the male reproductive organs should be considered an adverse reproductive effect"[observed at for DINP by Gray et al. 2000 (750 mg/kg bw/day, one dose only) and Masutomi et al., 2003. In the latter study these findings were however assessed to be of minimal/slight severity and were only observed at doses > 1000 mg/kg bw/day and in the presence of maternal toxicity. However the dose-related histopathological effects observed by Masutomi et al. at the highest dose supports the relevance of the finding by Gray et al.]
- "The male reproductive system can be affected adversely by disruption of the normal endocrine balance" [see above references related to decresed foetal testosterone levels]
- "It should also be noted from a simple examination of the [*reproductive*] cycle that adverse effects due to exposure to a toxicant may not be immediate. Exposure in utero may result in latent reproductive deficits when the individual reaches adulthood and attempts to reproduce" [Changes in fetal testis histology and testosterone production and altered biomarkers AGD and nipple retention are indicators of disturbance of the developing

male reproductive system and thus indicate reproductive effects that may occur in adulthood (Clewell et al., 2013a and 2013b; Boberg et al., 2011)]

2) *Weight of Evidence assessment has not been performed*
The DS considers that indeed a total and robust weight of evidence assessment has been conducted. As neither the CLP Regulation nor the guidance provides specific guidelines or framework for how to perform a weight of evidence assessment, the WoE assessment performed in the CLH dossier is more of a "narrative" nature. Please also refer to the answer given above with respect to the comments on following the CLP criteria and guidance. The DS notes that reference is made to the quantitative weight of evidence methodology described by Dekant and Bridges (2016a and 2016b) which is based on the use of scoring systems for single observations. As decribed in the response to comment no. 1 the DS consideres that this methodology has some limitations.

3) *Reference to EU Risk Assessment from 2003*
It is recognised that the risk assessment from 2003 concluded that classification of DINP for reproductive toxicity was not warranted at the time. However, when taking into account the relevant information published for DINP since 2003 and hereunder integrating the existing information from the risk assessment and the proposed mode of action for DINP which is comparable to that of other, classified phthalates, the DS submitter concludes that a classification is justified.

4) *The CLH report does not perform a quality assessment of the studies on which the proposal is based*
The quality of each study has been evaluated and is reflected in the study description. Whereas there are no formal requirements of providing e.g. Klimisch scores of the studies used as the basis of a classification proposal, the Guidance on the preparation of dossiers for harmonised classification and labelling e.g. describes that "The relevant available information should be systematically evaluated in order to derive a classification" and "In the CLH report, the dossier submitter should clearly describe the relevant information. The dossier submitter should also include an analysis and discussion of the information, a comparison of the information against the classification criteria and a conclusion on classification for each relevant hazard class (and differentiation, if applicable)" (ECHA 2014).

- The DS considers that a systematic evaluation of the available data has been conducted. All the studies mentioned in the CLH report are considered valid and relevant but for some studies weaknesses and limitations have been identified and are described in the CLH dossier. Examples are e.g.: Kwack et al. 2009: Only one dose tested, not possible to assess dose-response relationship
- Waterman et al. (2000); one- and two generation studies: Sperm parameters not assessed
- Lee et al. 2006: Study associated with some limitations (as described by ECHA 2013), and although the findings of reduced AGD in males at PND 1 are acknowledged, lack of statistical method description means that less weight is given to the finding that AGD effect is seen already at doses from approx. 2 mg/kg bw/d

5) *Detailed comments on each of the key findings highlighted in the CLH dossier*
Please refer to response to comment 46 below which also includes detailed comments on the key findings highlighted in the CLH dossier. As more extensive

comments on the key findings are provided in comment no. 46 (from European Plasticisers) please refer to the answer given under comment no. 46.

References cited above that are not included in the CLH dossier:
Dekant W and Bridges J., 2016a: Assessment of reproductive and developmental effects of DINP, DnHP and DCHP using quantitative weight of evidence. Regulatory Toxicology and Pharmacology 81: 397-406.

Dekant W. and Bridges J., 2016b. A quantitative weight of evidence methodology for the assessment of reproductive and developmental toxicity and its application for classification and labeling of chemicals. Regulatory Toxicology and Pharmacology 82, 173-185.

ECHA 2014: Guidance on the preparation of dossiers for harmonised classification and labelling. Version 2.0.
WHO/IPCS 2001: Environmental Health Criteria 225. Principles For Evaluating Health Risks To Reproduction Associated With Exposure To Chemicals. WHO Geneva, 2001.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.05.2017	South Africa	The Southern African Vinyls Association	National NGO	3

Comment received

COMMENTS ON THE DANISH EPA DOSSIER PROPOSING CLASSIFICATION OF DINP BY THE SOUTHERN AFRICAN VINYLS ASSOCIATION OF SOUTH AFRICA (SAVA)

The Southern African Vinyls Association (SAVA) is the representative body for the local polyvinyl chloride (PVC) industry and through our Product Stewardship Commitment (PSC), we provide leadership and guidance towards transforming the PVC industry in relation to commerce, health and environmental issues.

SAVA is also represented on the Global Vinyls Council (GVC) and through our information sharing network we have been made aware of the fact that the Danish EPA has made its fourth re-submission in two years of a dossier proposing the classification of DINP as a reproductive agent. We have been informed that this was accepted by ECHA and the public consultation process has now been initiated.

SAVA supports peer reviewed scientific research and concur with current robust scientific data available on DINP and agree that it does not support this classification proposal by the Danish EPA. Any proposal or submission should be based on the weight of scientific evidence and not focus on a key study by Boberg and others in 2011 and 2016 (Corrigendum to "Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats") where the results have been shown not be reproducible for the large part, as is the case in the most recent Danish EPA dossier.

DINP is a major plasticiser for use in flexible vinyl (i.e. car underbody sealants, cabling, sheeting, footwear and hosing) and is of high importance to the members of SAVA. Based on international trends and product stewardship programmes, the South African

PVC industry voluntarily signed a Product Stewardship Commitment in 2011 to replace DEHP with DINP as a plasticiser and the replacement has been successfully concluded in the majority of PVC applications locally.

SAVA continuously review scientific data available on various chemicals including DINP and based on our research and understanding of the available peer reviewed data showing low hazards and safe use, we cannot support any proposed classification of DINP. The commitment shown by our industry to replace DEHP with DINP is based on this collection of sound and robust scientific data.

We agree with the conclusions made by various peer reviewed scientific studies that show that low phthalates (C3-C6 straight carbon backbones in the alkyl side chains) have adverse reproductive effects in animal studies and that high phthalates (C7-C13 straight carbon backbones in the alkyl side chains), do not show any adverse reproductive effects.

Given the high importance of this substance to our members, we can only support the current body of evidence based on peer reviewed and robust scientific research and urge ECHA and RAC to commit to a balanced and thorough scientific evaluation of all the relevant data on DINP.

We do not believe the classification dossier published by the Danish EPA supports any further classification of DINP or the substitution of DINP in PVC applications.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on the Danish EPA Dosier_DINP_By SAVA_15May2017.pdf

Dossier Submitter's Response

Thank you for your comments.

With regard to the concrete comments on the CLH proposal for DINP please refer to the answers given to comment no. 1 and 2, which also address the topics of

- Weight of scientific evidence (see answer to comment no. 2)
- Effects of phthalates in relation to the lenght of the carbon backbone in the alkyl side chains (see answer to comment no. 1, especially headline 1 and 4)

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2017	Italy	Istituto Superiore di Sanità	National Authority	4

Comment received

DEVELOPMENTAL TOXICITY. Upon integration of the available data from different studies, there is sufficient evidence to indicate that DINP induces adverse effects on male reproductive delopment; such effects are not secondary to maternal toxicity and are plausibly ue to the same (endocrine-related) mode of action as other phtalates, such as DEHP. Such adverse developmental effects can be elicited in experimental animals also at dose levels lower than 1000 mg/kg; wheares the available studies indicate that DINP has a weaker potency as compared to, e.g., DEHP, potency considerations are not relevant for classification. Therefore, the prposal for classification in category 1b for developmental toxicity can be supported.

EFFECTS ON FERTILITY. The available studies provide some suggestion that DINP may affect the reproductive function in both sexes. However, the evidence is too scattered and inconsistent Two examples of potentially relevant studies that do not allow to derive any firm conclusion:
i) the two-generation study (Waterman et al. 2000) did not find any significant adverse effects but sperm parameters (ass well as estrous cyclicity, as it seems) were not assessed;
ii) the study on juvenile rats by (Kwack et al., 2009) observed relevant adverse effects on sperm paramers, but with concomitant effect on liver weight (increased) and body weight (reduced). Since only one dose level (500 mg/kg bw) was tested, the dose responses for the reproductive and non-reprodyctive effects could not be compared.
Overall, the available data do not support any conclusion on a possible classification for reproductive toxicity of DINP, even in category 2.
Conversely, the available data warrant performing further studies.

Dossier Submitter's Response

Thank you for the support for the proposed classification for developmental effects of DINP. With regard to fertility effects it is acknowledged that that the proposed classification is based only on a few findings of fertility related effects caused by DINP. It was concluded in the EU RAR from 2003 that the effects in mice did not justify classification for fertility. However, as these studies did not examine sperm count or –quality, direct effects of DINP
on fertility were not fully elucidated at that time. The study by Kwack et al., 2009, provides
evidence for effects of DINP on sperm count and quality (although only one dose was tested). In the same study a reduction of sperm count to 34,2% of the controls was observed for DEHP (also at 500 mg/kg bw/d), a phthalate already associated with effects on fertility, and overall, DINP appeared to affect sperm motion in a similar manner as e.g. DEHP, DBP and BBP. As fertility assessment by breeding may not be considered a sensitive parameter in rats, the findings by Kwack et al., 2009, are not in conflict with the lack of effect on fertility in the Waterman et al., 2000, studies (which did not include an assessment of sperm parameters). Furthermore, also the reduction of sperm motility in rats after exposure during the sensitive perinatal period (Boberg et al., 2011) is considered key evidence that DINP may affect fertility of humans. As stated in the CLH dossier (cited form OECD guidance document no. 43) a dose-response trend and a statistically significant change in sperm motility would generally be interpreted as indicating a potential effect on fertility in humans.
Taking into account that the proposed mode of action for DINP is similar to that of other phthalates with demonstrated effects on reproduction and fertility, a classification for fertility effects in category 2 is overall considered justified.

RAC's response

Thank you for the comment. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2017	United Kingdom	<confidential>	Company-Downstream user	5

Comment received

We are a down steam user of DINP. It is a key raw material in the production of vinyl coated wallcoverings. We are a UK manufacturer and sell our products globally with a turnover of approx £57m and employ 500 people in the UK and International division. We

have tried alternative materials to DINP but the alternatives are not available in sufficient quantities to sustain supply.
We moved away from DOP to DINP as the toxicology tests indicated this to be safe to use.
We question the validity of the recent study as it is based upon oral toxicity in rats the dosage is excessive and is not directly comparable to the impact/risk to the human health. This test method does not reflect the likely exposure during installation or use of the wallcoverings.
We therefore oppose the proposal by the Danish authorities.

Dossier Submitter's Response

Thank you for your comment.

We note that the classification criteria under CLP only address the intrinsic hazardous properties of a substance and that exposure (such as likely exposure during installation or use of wallcoverings) is not a part of the hazard idenficitation. The exposure routes and dosages used in toxicity testing and for assessment of hazard do thus not necesarrily reflect the actual exposures connected with the use of a substance. Such elements are, however, taken into account when assessing the potential risk associated with the use. Please also refer to the answer given to comment no. 1 with regard to the potential socioeconomic aspects of a classification of DINP.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2017	Belgium	IGI - The Global Wallcoverings Association	Industry or trade association	6

Comment received

IGI – The Global Wallcovering Association – does not support the Danish proposal to classify DINP as a reproductive toxin.
DINP is a major raw material for vinyl wallcoverings, and approximately 50% of our member's products include the use of vinyls, so this classification would have a serious negative effect on our business throughout the EU. Business worth €1.2 billion, and employing 26,000 workers. We have no viable alternative to DINP that is currently freely available in the quantities required.
Our industry has discontinued use of lower phthalates since they were classified as reproductive toxins, and had moved to DINP following extensive evaluations that showed it to be of low hazard and safe to use.
We question the value of the recent studies put forward by Denmark, as they are based on oral ingestion by rats, and we see no relevance between this and the likely human exposure by consumers resulting from the handling of vinyl wallcoverings. Indeed, the levels of oral dosage given to rats in the recent studies, is excessive and disproportionate to the levels experienced by consumer contact. In our view these levels has been used to obtain the result that the Danish EPA required for this current proposal.
As previously stated, DINP is a raw material of high importance to our members, and we urge ECHA and the RAC to reject the Danish proposal, and ensure that any classification is only based on realistic and robust scientific evaluations.

Dossier Submitter's Response

Thank you for your comment. We note that the classification criteria under CLP only address the intrinsic hazardous properties of a substance and that exposure scenarios

(such as likely exposure during installation or use of wallcoverings) are not a part of the hazard idenficitation. The exposure routes and dosages used in toxicity testing and for assessment of hazard do thus not necesarrily reflect the actual exposures connected with the use of a substance. Such elements are, however, taken into account when assessing the potential risk associated with the use. With regard to the effects observed for DINP at high oral doses, the effects observed at doses up to 1000 mg/kg bw are considered relevant in the context of classification for reproductive toxicity according to the classification criteria. Please also refer to the answer given to comment no. 1 with regard to the potential socioeconomic aspects of a classification of DINP.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2017	Germany		MemberState	7

Comment received

The German CA does not want to question that the two substances that refer to the CAS numbers 68515-48-0 and 28553-12-0 are structurally very similar and marketed under the same name/abbreviation "DINP". The main component of 1,2-benzenedicarboxylic acid, di-C8-10-branched alkylesters, C9-rich (CAS 68515-48-0 is identical to the substance di-"isononyl" phthalate (CAS 28553-12-0). However, the only information about the concentration of the (identical) constituent can be derived from the name "C9-rich". Neither a typical concentration nor concentration ranges are provided. It is therefore not possible to assess the similarity of the two substances. We are convinced the DK CA correctly combined both substances for one harmonised C&L entry, but would appreciate to have more information about the substance identity.

Beyond that we think that it should be pointed out in the report that two substances are covered by the proposed entry and not one substance with two CAS and EC numbers

Dossier Submitter's Response

Thank you for the comment which address the substance identity of the two DINP variants and the specification of the proposed entry in Annex VI

1. *Substance identity*
   The below information obtained from Health Canada (2015b) may further clarify the composition and similarity of the two DINP variants included in the CLH proposal:

   "DINP with CAS RN 28553-12-0 is produced from n-butene that is converted primarily to methyloctanols and dimethylheptanols (CERHR 2003). The resulting mixed phthalate has side chains composed of 5 to 10% methyl ethyl hexanol, 40 to 45% dimethyl heptanol, 35 to 40% methyl octanol, and 0 to 10% n-nonanol (NICNAS 2008a). DINP with CAS RN 68515-48-0 is manufactured from octene that is converted to alcohol moieties of 3,4-, 4,6-,3,6-,3,5-, 4,5- and 5,6-dimethyl-heptanol-1, and has side chains comprised of 5 to 10% methyl ethyl hexanol, 45 to 55% dimethyl heptanol, 5 to 20% methyl octanol, 0 to 1% nonanol, and 15 to 25% isodecanol (CERHR 2003; NICNAS 2008a). [……..].While the two CAS RNs for DINP indicate different starting alcohols, the resulting isomeric phthalate mixtures share common constituents and cannot be differentiated through their physicochemical properties (ECJRC 2003). For this reason, the two CAS RNs are examined together in this SOS report."

2. *The proposed entry in Annex VI*
   We have tried to highlight in the CLH dossier (see e.g. section 1.1) that the proposal covers two distinctive phthalate mixtures each with their own name, EC no. and CAS no. We regret if it isn't stated clearly enough that the proposed entry covers two similar phthalate mixtures. In previous assessments and reviews (e.g. the Risk Assessment Report from 2003, The ECHA review from 2013, Health Canada 2015b) these two mixtures have (also) been grouped under the trivial name DINP.

Reference cited above that is not included in the CLH dossier:
Health Canada 2015b: State of the Science Report Phthalate Substance Grouping 1,2-Benzenedicarboxylic acid, diisononyl ester 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich (Diisononyl Phthalate; DINP). Environment Canada. Health Canada. August 2015.

RAC's response

Thank you for the comment. Your position has been noted. The substance identities have been clarified in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	United States	The Vinyl Institute	Industry or trade association	8

Comment received

"Dear ECHA,

The Vinyl Institute is a U.S. based trade association representing the producers of vinyl resins and additives, including plasticizers. It was recently brought to our attention that a proposal is being considered to require classification and labelling for di-isononyl phthalate (DINP) plasticizer. This plasticizer is widely used in U.S. flexible vinyl applications including certain flooring, wire and cable insulation, seals and gaskets, footwear, upholstery, and many other applications, some of which are exported from the U.S. to Europe. As such, it is an important ingredient to producers and consumers alike. Thus, it is critical that the health aspects be properly evaluated, understood, and communicated. The VI recently submitted comments* to the U.S. Consumer Products Safety Commission (CPSC) on their analysis of DINP by the Chronic Hazard Advisor Panel. In these comments which are attached for your review, two key characteristics of DINP were highlighted that must be weighed heavily when assessing potential exposure of this substance : 1.) DINP has an extremely low vapor pressure, and 2.) DINP has strong molecular bonds to the PVC molecule. Both of these characteristics are responsible for the low emissions and high retention of DINP in a finished article. For these reasons, the Vinyl Institute does not support the proposed classification. Given the high importance of this substance to our members, and the data supporting its retention and low exposure to consumers, we would urge that ECHA and RAC ensure a full and thorough scientific evaluation of all the relevant data on DINP.

*Comments of the Vinyl Institute to U.S. Consumer Products Safety Commission, RE: Estimated Phthalate Exposure and Risk to Pregnant Women and Women of Reproductive Age as Assessed Using 2013/2014 NHANES Biomonitoring Data, Docket Number CPSC-2014-0033, March 24, 2017"

ECHA note – An attachment was submitted with the comment above. Refer to public attachment VI Comments to CPSC on CHAP NHANES Information submitted 03-24-2017.pdf
Dossier Submitter's Response
Thank you for your comments. With respect to your comments on the key characteristics that must be weighed when assessing the exposure we note that the classification criteria under CLP only addresses the intrinsic hazardous properties of a substance and that exposure assessment is not a part of the hazard idenficitation under CLP (but rather a part of a risk assessment). So while we do not disagree that DINP show different characteristics in relation to vapour pressure and retention in vinyl products compared to DEHP these factors are not taken into account for classication purposes. Hazard assessment and classification is does not depend of the behaviour of the substance when integrated in finished articles. With regard to the comment on ensuring a full and scientific evaluation of all the relevant data in relation to exposure and potential risks, reference is also made to the previous evaluation of DINP done by ECHA in 2013 (in relation to the existing REACH restriction for DINP and DIDP) which have assessed most of the data contained in the CLH proposal for DINP although with a different purpose than performing a hazard assessment in relation to the CLP criteria. We are confident that RAC will ensure a full and thorough evaluation of this CLH proposal. *Reference:* ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	ExxonMobil Chemical Holland BV	Company-Manufacturer	9
Comment received				
ExxonMobil Chemical Holland BV – Comments on the CLH Report - Proposal for Harmonised Classification and Labelling of DINP (based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2; Substance Name:1,2-benzenedicarboxylic acid, di-C8-C10-branched alkylesters, C9-rich; [1] di-"isononyl"phthalate; [2] [DINP]; EC number: 271-090-9 and 249-079-5; CAS number: 68515-48-0 and 28553-12-0; Dossier Submitter – Danish EPA) ExxonMobil Chemical Holland BV (hereafter referred to as ExxonMobil) is a producer of DINP within the European Union. The summary comments below represent ExxonMobil's views on the classification proposal by the Danish EPA that is the object of this consultation. As a REACH Lead Registrant for DINP we have previously consulted with all members of the DINP Substance Information Exchange Fora (SIEF), as required by the REACH regulation, to agree classification and labelling, and to include that classification in the REACH registration dossier. Based on the scientific data and prior regulatory reviews (EU RAR, ECB, 2003), all SIEF members (over 200) agreed on the conclusion of "no				

classification" for all relevant CLP health and environmental hazards, and this was included as part of the REACH registration in 2010. The lack of classification was further confirmed in a major REACH registration dossier update in December 2015, which took into account the outcome of the ECHA re-evaluation which concluded that no further risk management measures are needed for DINP (existing restrictions in toys and childcare articles maintained). The CLH proposal on DINP (registry of intent November 10, 2014; final submission March 29, 2017) from the Danish EPA now effectively takes the regulatory evaluation process back to square one after a 10 year EU Risk Assessment under the Existing Substances Regulation (1995 – 2006), and a 4 year ECHA re-evaluation under REACH (2009 – 2013). In the absence of any significant new scientific data supporting classification this is very hard to understand for a REACH registrant supplying to an extensive value chain of downstream customers, who now face a further major period of uncertainty. The proposal is inconsistent with any measure of regulatory predictability to support business continuity and investment in a substance which is a major substitute for an SVHC within the EU and also a substitute globally. ECHA note – An attachment was submitted with the comment above. Refer to public attachment ExxonMobil DINP submission_May_19_2017_Final.pdf
Dossier Submitter's Response
Thank you for your comments. Please refer to the answer to comment no. 46 from European Plasticisers which address the same issues in further detail.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	France		Individual	10
Comment received				
If the DINP becomes classified as CMR our business will be drastically impacted ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Consultation publique DINP_V3.docx				
Dossier Submitter's Response				
Thank you for your comments. The confidential attachement is noted. As a general remark regarding the consequences of a classification we note that socioeconomic considerations adressing the impact of a potential harmonised classification is not part of this process and thus not for the DS to comment on.				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	China	AICM	Industry or trade association	11
Comment received				
DINP is one of the major substitutes for DEHP, which is a SVHC per REACH classification, in China and Asia Pacific. Hence it is very important to ensure a thorough robust assessment of all the scientific data on DINP, as classification will have a major impact on the substitution of DEHP by DINP throughout China and Asia Pacific, with the associated implications for articles being exported to the EU.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DINP_CLH_Summary comments_AICM comments May 2017 FINAL.docx

Dossier Submitter's Response

Thank you for your comments. We have grouped your comments and our response under the 6 main headlines below:

1. *Scientific basis for the proposal and comparison with CLP criteria (incl. adverse effects and significance of observed effects)*
   Please refer to the answer given under comment no. 2 (headline 1)

2. *Adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains*
   Please refer to the answer given under comment no. 1(headline 4)

3. *Weight of evidence assessment and lack of reference to the publications by Dekant and Bridges, 2016 in the CLH proposal*
   Please refer to the answers given under comment no. 1 (headline 2) and comment no. 2 (headline 2)

4. T*he use of the Boberg study and the re-analysis of the data by Morfeld et al., 2017*
   Please refer to the answer given under comment no. 1 (headline 3)

5. *Reference to previous reviews and assessments of DINP and lack of new evidence in the CLH proposal*
   The EU risk assessment from 2003 concluded that classification was not warranted for DINP based on the data available. However, new scientific data have been published for DINP since 2003. Based on the newer data (and considering findings from older studies) as well as considering the similar mode of action of DINP compared to other phthalates classified as reproductive toxicants, the DS submitter considers that the criteria for classification are fulfilled.

   With respect to the ECHA review from 2013 we note that the focus of this evaluation was solely to address the potential risk associated with the exposure to DINP and DIDP in toys, childcare articles and all other possible uses. Whereas the review describes all relevant information available incl. studies on effects on reproduction, this review does not contain an assessment of the available information against the CLP classification criteria. The review addresses risk taking into account the identified exposures and not hazard classification (i.e. the identification of intrinsic properties according to the CLP classification criteria). Although the review concludes that no further risks for DINP and DIDP were identified [besides that identified for mouthing of toys and childcare articles as already addressed by the existing REACH restriction, entry 52 in Annex XVII] the review does not as such contain a hazard assessment based on the CLP classification criteria nor does it exclude that DINP possibly fulfils the criteria for classification.

6. *Socioeconomic aspects of a classification of DINP*
   Please refer to the answer given under comment no. 1 (headline 5)

Reference

ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013

RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Brazil	Instituto do PVC	Industry or trade association	12

Comment received
Phthalates are plasticizers largely used in the Brazilian market in flexible PVC products, and DINP is one of the most used. This scenario is a result of many scientific studies which have been carried out for decades. Among those studies, there are strict risk analyses stating that its use is safe. In 2013, the reassessment carried out by ECHA itself and confirmed by RAC (Committee for Risk Assessment) contributes to this scenario, and it has concluded that it is not necessary to impose other restrictions to the use of DINP in products designed both to children and adults besides the existing ones. In case DINP rating under categories 1B and 2 is approved, the Brazilian market will surely have a negative impact, losing competitiveness, since many of the manufacturers of PVC flexible products follow the European guidelines and export products to that region. The replacement of a recognized safe plasticizer - which has been studied for a long time - by other ones whose effects on both human health and environment are not yet known, may bring serious future consequences. In addition, the national manufacturers of DINP will be impacted, which may cause possible plant shutdowns and unemployment in the sector. Therefore, it is of utmost importance that ECHA considers the available technical-scientific data, as well as its own ones, so that Denmark's request is not accepted, because we know these data show that the use of DINP is safe. The Brazilian PVC Institute is a class association whose aim is to gather and promote technical-scientific knowledge on PVC, and believes PVC versatility can provide sustainable solutions to health, housing, and well-being in society. Therefore, we seek to disclose the right perception of PVC sustainability in society.
Dossier Submitter's Response
Thank you for your comments. With regard to the reference to ECHAs review of DINP and DIDP from 2013 we note that the focus of this evaluation was solely to address the potential risk associated with the exposure to DINP and DIDP in toys, childcare articles and all other possible uses. Whereas the review describes all relevant information available incl. studies on effects on reproduction, this review does not contain an assessment of the available information against the CLP classification criteria. The review addresses risk taking into account the identified exposures and not hazard classification (i.e. the identification of intrinsic properties according to the CLP classification criteria). Although the review concludes that no further risks for DINP and DIDP were identified [besides that identified for mouthing of toys and childcare articles as already addressed by the existing REACH restriction, entry 52 in Annex XVII] the review does not as such contain a hazard assessment based on the CLP classification criteria nor does it exclude that DINP possibly fulfils the criteria for classification. We are confident that RAC will make a robust assessment of the proposal taking into account the available scientific information and considering the total weight of evidence in a balanced approach.

The CLH process under the scope of the CLP Regulation only addresses identification of the intrinsic properties of substances based on the available data and comparison with the criteria. Socioeconomic considerations adressing the impact of a potential harmonised classification is not part of this process and thus not for the DS to comment on. It is noted that a classification of DINP as toxic to reproduction does not in itself lead to a restriction of its use. *Reference:* ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Germany	Evonik Performance Materials GmbH on behalf of Evonik Degussa GmbH	Company-Manufacturer	13
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH for DINP CAS 28553-12-0_2017-05-19.pdf				
Dossier Submitter's Response				
Thank you for your comments which in turn refer to and support the comments submitted by European Plasticisers (comment no. 46). Please refer to our response to comment no. 46. With respect to the general comment on the legal validity of the proposal the DS considers that it is up to RAC to assess whether the criteria for classification have been adequately applied are considered to be fulfilled.				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	EuPC	Industry or trade association	14
Comment received				
Classification : the proposed classification is not based on a full robust weight of evidence evaluation of all the relevant data versus the CLP detailed criteria. Rather a selective approach, using mild transient effects not justifying per se a classification or based on studies of questionable quality is being taken.Our understanding of the available evidence is that a thourough evaluation should lead to the conclusion that classification is not required. DINP use and alternatives : DINP is one of the major general purpose plasticizer for PVC. According to European Plasticizers (www.europeanplasticisers.eu), the 3 general purpose plasticizers DINP, DIDP and DPHP represent 57% of the European plasticizer demand. We may confirm that DINP is the most commonly used plasticizer within this family. In our membership, it may be found mainly in the following applications : flooring, wire and				

cable, roofing/films and sheets, wall covering, coated fabrics, flexible profiles totalling close to 1 million tons. Other applications directly within the automotive industry may be considered as well.
It has been one of the main substitutes for low molecular weight phthalates such as DEHP, BBP, DBP and DiBP, based on the intrinsic properties of this alternative deemed as not classified for hazards and considered as safe for use by the EU risk assessment of 2003 and confirmed in 2013 by the Echa review . This substitution has become even more intensive since 2001 when DEHP and other low molecular weight phthalates were classified as reproductive agents and is now about complete within the European Union, although DEHP remains a major plasticisers outside the EU. Significant adaptations had to be made to processing techniques in order to achieve comparable performance. Today the only foreseeable alternative to phthalate plasticizers in the same price range is DOTP. Please note that application specific requirement may make this alternative less or not suitable in certain cases for which a more detailed assessment of suitability should be undertaken. There is currently not enough production capacity to replace this plasticizer.
Proportionality: Classification is an important risk management decision, which has broad regulatory impacts (e.g. reproductive classification triggers EU directive 92/85 EC on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding), which will need adaptation of work practices and could lead to potential discrimination of female workers (access to work). Most importantly, it will give ta signal to the market triggering requests for substitution whilst our industry has just gone through such a demanding process over the last 15 years, in replacing DEHP and other low molecular weight phthalates with DINP.
In light of the above and potential impact on industry competitiveness, it is important that the evaluation by Echa and RAC is made based on solid scientific ground relying on all relevant data enabling a proper evaluation based on weight of evidence.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20170519_EuPC_Position Paper on the Proposed classification of DINP as reprotox 1b.pdf

Dossier Submitter's Response

Thank you for your comments addressing the 3 main headlines below:

1. *The use of DINP and potential alternatives, incl. reference to previous assessments (EU 2003, ECHA 2013)*
   The CLH process under the scope of the CLP Regulation only addresses identification of the intrinsic properties of substances based on the available data and comparison with the criteria. Socioeconomic considerations adressing the impact of a potential harmonised classification, availability and compatibility of alternatives, is not part of this process and thus not for the DS to comment on.

   The EU risk assessment from 2003 concluded that classification was not warranted for DINP based on the data available. However, new scientific data have been published for DINP since 2003. Based on the newer data (and considering findings from older studies) as well as considering the similar mode of action of DINP compared to other phthalates classified as reproductive toxicants, the DS submitter considers that the criteria for classification are fulfilled.

   With respect to the ECHA review from 2013 we note that the focus of this evaluation was solely to address the potential risk associated with the exposure to DINP and DIDP in toys, childcare articles and all other possible uses. Whereas the review describes all relevant information available incl. studies on effects on

reproduction, this review does not contain an assessment of the available information against the CLP classification criteria. The review addresses risk taking into account the identified exposures and not hazard classification (i.e. the identification of intrinsic properties according to the CLP classification criteria). Although the review concludes that no further risks for DINP and DIDP were identified [besides that identified for mouthing of toys and childcare articles as already addressed by the existing REACH restriction, entry 52 in Annex XVII] the review does not as such contain a hazard assessment based on the CLP classification criteria nor does it exclude that DINP possibly fulfils the criteria for classification.

2. *The scientific basis for the CLH proposal incl. weight of evidence assessment*
   The key findings used for the classification proposal have each been commented by the EuPC as well as by other stakeholders. As more extensive comments on the key findings are provided in comment no. 46 (from European Plasticisers), please refer to the Dossier Submitters answer related to the key findings under comment no. 46.

   The DS considers that indeed a total and robust weight of evidence assessment has been conducted. As neither the CLP Regulation nor the guidance provides specific guidelines or framework for how to perform a weight of evidence assessment, the WoE assessment performed in the CLH dossier is more of a "narrative" nature. The CLH proposal is based on effects observed in different studies that have been performed under different conditions and concerning different lifestages of the tested animals (mostly rats). As a result a direct comparison of the findings is often not possible. Furthermore, while observations on sensitive parameters such as nipple retention, anogenital distance (AGD) and sperm quality are seen in some of the newer studies, the same endpoints/parameters have not been assessed in older studies. The fact that an observation of a certain effect in one study is not confirmed by other available studies that are comparable with respect to testing methodology and dosing regimes does not rule out its biological or toxicological validity. With regard to a more in-depth response to the comment on the scientific basis for the CLH proposal and weight of evidence evaluation you may also refer to the answers given to comment no. 1 and 2.

3. *Proportionality*
   According to the CLP Regulation substances fulfilling the criteria for classification as toxic to reproduction should normally be subject to a harmonised classification (CLP article no. 36 (1)). This is the basis and motivation for the classification proposal. While classification only addresses intrinsic hazards and does not on its own lead to restrictions of use, it is evident that a potential CMR classification of DINP will have consequences for further risk management e.g. when it comes to working environment legislation. However, as also stated above, the possible consequences of a classification and socioeconomic considerations are not part of the CLH process.

   We are confident that RAC will make a robust assessment of the proposal taking into account the available scientific information and considering the total weight of evidence in a balanced approach.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	The European Council of Vinyl Manufacturers	Industry or trade association	15

Comment received

To manufacture flexible PVC products, the European producers increasingly use and rely on high molecular weight phthalates such as DINP and DIDP. According to the European Plasticizers association these high molecular weight phthalates represent about 70% of the European plasticizers market.
Based on our understanding of the scientific data on DINP, ECVM does not support the proposed classification. We are aware of the established structure activity relationships for low (C3-C6 straight carbon backbones in the alkyl side chains) and high (C7-C13 straight carbon backbones in the alkyl side chains), with low phthalates showing adverse reproductive effects and high phthalates not showing adverse reproductive effects in animal studies. As a result, in the recent years the high molecular weight phthalates have undergone extensive evaluations, to confirm their safe use in numerous applications. This motivated the European PVC industry to switch massively from low molecular weight phthalates to the high molecular weight ones.
To our best knowledge, there are no suitable plasticizers available on the market which could fully replace high molecular weight phthalate plasticizers such as DINP when considering the price range and existing production volumes. Further, any substitution of such well known and highly scrutinized plasticizer by other, less analyzed plasticizer(s) could represent undesirable risks for human health and environment.
The fact that DINP is one of the phthalates restricted in toys is sometimes interpreted as a proof of hazardousness. However, the Directive 2005/84/EC clearly stipulates that this decision was based on the precautionary principle, and not on any definite evidence: "Scientific information regarding di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and di-n-octyl phthalate (DNOP) is either lacking or conflictual, but it cannot be excluded that they pose a potential risk if used in toys and childcare articles, which are by definition produced for children."
Given the high importance of this substance to our members, we would urge that ECHA and RAC ensure a full, exhaustive and, if possible, peer reviewed scientific evaluation of all the relevant data on DINP, to enable its further safe use.

Dossier Submitter's Response

Thank you for your comments which address the 3 main headlines below:

1. *Adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains*
   Please refer to the answer given to this topic under comment no. 1 (headline 4).

2. *The use of DINP and potential alternatives*
   The CLH process under the scope of the CLP Regulation only addresses identification of the intrinsic properties of substances based on the available data and comparison with the criteria. Socioeconomic considerations adressing the impact of a potential harmonised classification, availability and compatibility of alternatives, is not part of this process and thus not for the DS to comment on.

3. *Reference to the existing restriction for DINP in toys*
   We fully recognise that hazard identification under CLP (i.e. the identification of inherent properties) and risk assessment under REACH (i.e. a combined assessment of hazard and exposure) are two separate processes. The current

restriction under REACH Annex XVII is e.g. based on a review from ECHA (2013) concluding, that a risk from the mouthing of toys and childcare articles (containg DINP and DIDP) cannot be excluded if the existing restriction was lifted. The CLH proposal for DINP is solely based on the inherent properties of DINP including reference to effects observed for other classified phthalates and should not be confused with the existing restrictions of the substance in specific uses.

Reference:
ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2017	Belgium	ERFMI vzw, European Resilient Flooring Manufacturers' Institute	Industry or trade association	16

Comment received

ERFMI's comments on the proposed classification of DINP as toxic to reproduction 1b

ERFMI (European Resilient Flooring Manufacturers' Institute) represents the interests of the European producers of resilient floor coverings. Resilient floor coverings are based on plastics, mainly PVC, linoleum, rubber and cork. Its 17 members manufacture over 90% of the PVC floor coverings produced in the European Union and Switzerland.

ERFMI members employ close to 12.000 employees, in all EU and EFTA countries operating more than 50 manufacturing sites and a large number of sales companies. Altogether, these companies realise app. 250.000.000 m2 sales of floor coverings. The PVC floor covering market of our members represents at least €1.4 billion.

After huge efforts to substitute the low molecular weight phthalates, which had been carried out by the European manufacturers in the nearly last 20 years, DINP became a major plasticizer for the industry. The ERFMI members rely on the fact that DINP has been the subject of extensive regulatory evaluations with the conclusion that classification (Dangerous Substances Directive) is not required (EU Risk Assessment Report 2003), and that no further risk management measures are needed for children or adults (EU Risk Assessment Report - Completed 2003 (published in the Official Journal in 2006), ECHA Evaluation Report on New Data, 2013). These assessments included full hazard characterizations including the available reproductive studies.

Given the high importance of this substance to ERFMI's members, we would urge that ECHA and RAC ensure a full and thorough scientific evaluation of all the relevant data on DINP.
Best regards

ERFMI, European Resilient Flooring Manufacturers' Institute

Drs. A. J. Pluijmert, Managing Director ERFMI ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2017-05-17 DINP statement ERFMI final.pdf
Dossier Submitter's Response
Thank you for your comment. We note that the CLH process under the scope of the CLP Regulation only addresses identification of the intrinsic properties of substances based on the available data and comparison with the criteria. Socioeconomic considerations adressing the impact of a potential harmonised classification, availability and compatibility of alternatives, is not part of this process and thus not for the DS to comment on. We are confident that RAC will make a robust, scientific assessment of the proposal.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2017	France	GERFLOR	Company-Manufacturer	17
Comment received				
We are a PVC flooring producer, we use DINP as plasticizer. We can't take a scientific position on the ranking and teh tests which have been performed But it would be nice to clarify the situation in order to prevent demans and demands for updating DINP classification. It has to be definitiveli resolved, unless new data or element is coming. we would like to be sure that tests leading to the definition of reprotoxic 1B have been scrupulously followed. we would like to recall that European Commission has concluded on severals occasions that There is at present no need for further information or for risk reduction measures beyond those that are being applied already. more over Based on the risk assessment in this report, it can be concluded that no further risk management measures are needed to reduce the exposure of children to DINP and DIDP				
Dossier Submitter's Response				
Thank you for your comments. While we acknowledge the outcome of the latest evaluation of scientific evidence on the risk associated with DINP in toys and childcare articles (ECHA 2013), this assessment was done in a different context, namely an assessment of whether the current REACH restriction for DINP was considered adequate (REACH Annex XVII, entry 52). We note that hazard identification under CLP (i.e. the identification of inherent properties) and risk assessment under REACH (i.e. a combined assessment of hazard and exposure) are two separate processes. The current restriction under REACH Annex XVII is e.g. based on a review from ECHA (2013) concluding, that a risk from the mouthing of toys and childcare articles (containg DINP and DIDP) cannot be excluded if the existing restriction was lifted. The CLH proposal for DINP is solely based on the inherent properties of DINP including reference to effects observed for other classified phthalates, and does not take use and exposure into account. According to the CLP Regulation substances fulfilling the criteria for classification as toxic to reproduction should normally be subject to a harmonised classification.				

Reference:
ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Germany	Arbeitsgemeinschaft PVC und Umwelt e.V. (AGPU)	Industry or trade association	18

Comment received

Wednesday, May 17, 2017
Comments by Arbeitsgemeinschaft PVC und UMWELT e.V. (AGPU) on the proposed classification of DINP as toxic to reproduction.

AGPU is a German industry association representing companies from the full PVC supply chain from a salt mine via PVC and additives manufacturers to converters and recyclers. DINP is a major plasticiser for our industry, it is produced by some of our member companies, it is used by many of our member companies and finally it can be contained in PVC-wastes that some of our member companies recycle. Therefore, it is of high importance to our members. We have only limited access to the full reports of the toxicological studies undertaken by the plasticiser producers. However, we are constantly monitoring the scientific/regulatory topics including evaluations by ECHA, member states, independent third party experts or regulatory reviews undertaken in other regions.
The evidence presented by this CLH report fails to present a sufficient justification for the classification and labelling of DINP as toxic to reproduction.

Dossier Submitter's Response

Thank you for your comment. It is the view of the Dossier Submitter that the substance DINP does fulfil the criteria for classification as toxic to reproduction. According to the CLP Regulation substances fulfilling the criteria for classification as toxic to reproduction should normally be subject to a harmonised classification (CLP article 36(1)). Please also refer to the response provided to some of the more detailed comments in this dossier with regard to the scientific justification for the proposal (e.g. answers given to comment no. 1 and 2).

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	United Kingdom	INOVYN	Company-Downstream user	19

Comment received

General Comments

We find that the description of manufacturing methods is covered in very little detail, presumably since this is adequately described in the EU risk assessment document. However it is important to note that different manufacturing methods exist in the

plasticiser industry and these can impart different properties to the end products. It is of note that registrants of the C9 (and C10) phthalates have registered these as multi-constituent substances whereas the CLH dossier refers to DINP as a UVCB substance. Under modern analytical techniques the composition of these substances can be determined. A great deal is known about the distributions and these have been the subject of widespread intellectual property dossiers (see for example reference (1) and references cited therein). Such details have been presented to EFSA as part of the application for food contact status of these substances under EU Regulation 10/2011 (where the assigned PM Reference Numbers refer to the different CAS identities) as well as to EChA in the REACH registration dossiers. Since there is a direct link between manufacturing method and isomer distribution, and thus to physico-chemical properties, the identification of the distribution is important. We do not understand why the CLH dossier authors appear to think that these distributions are somehow "unknown" when the knowledge of them leads to the direct understanding of the properties of the molecules. The details of the composition are an important part of standardisation work and as such are well reviewed. The effects of carbon chain distribution of plasticisation properties can be seen in the well-used text of the flexible polymers industry (2). As an extreme example we can give the case of a highly branched DINP manufactured until the early 1990s (and thus not registered under REACH) which had an inherent viscosity some 25% higher than the corresponding DINP. This is well understood.

Consequences of (an unwarranted) change in DINP classification

The PVC resin industry has embarked upon numerous studies and statistical significance analysis over the past ten years to transfer its QC determination of PVC resins from DEHP to DINP since DINP is more representative of the plasticisers in use by the industry and is the nearest thing to an industry reference material. Additionally resin manufactures had concerns as to their ability to use DEHP in QC analysis without a REACH authorisation from the DEHP supplier. Since resins are sold into flexible applications where they will be blended with plasticiser it is vital to know that the resin in question meets a series of specified properties when blended with an industry representative plasticiser. Owing to the different manufacturing technologies available for the manufacture of DINP – a fact not present for selection of DEHP in the past - the replacement has required extensive study to identify which DINP to use for QC determinations and to ensure that our methodology is statistically robust. These are linked to company's ISO 9001 registrations and link into several key markets which will use such registrations as a starting point for material qualification.

The use of DINP in the range of flexible applications has also been reviewed in the recently developed ISO 16000-33 standard (4) since it is seen as an important component of articles and as such needs to be have details of composition understood. The importance of this substance to this industry is clearly evident.

While the above two facts should not be used as reasons to reject a change in classification where the law requires it, it does stress the importance of such a decision being based on sound understanding and a review of all relevant literature. This makes this consultation different to the recent one on di-iso-octyl phthalate for which there was no market significance owing to the fact that the substance is not in commercial production.

References

(1) References US Patent Application US 08/991,005

(2) J.K. Sears and J.R. Darby: "The Technology of Plasticizers" J.R. Wiley and Sons, 1982
(3) ISO/FDIS 16000-33, Indoor air - Part 33 Determination of phthalates with gas chromatography/mass spectrometry (GC/MS)

Dossier Submitter's Response

Thank you for the comments.

With regard to the manufacturing methods of the two DINP variants, we have used the information available in the EU Risk Assessment from 2003, in the public part of the REACH registration dossiers and from other relevant open sources. The DS understands that the isomer distribution is important in relation to the physico-chemical properties. However, as the aspect of substance identification has been elucidated in previous assessments, additional weight has not been allocated to this subject in the current proposal. It is noted that data submitted to EFSA as part of an application for food-contact status are confidential and not readily available for the authorities for other legislative purposes.

With regard to the consequences of a classification we note that socioeconomic considerations adressing the impact of a potential harmonised classification is not part of this process (as also indicated in your comment) and thus not for the DS to comment on.

We also agree that a decision on classification should be based on a through scientific assessment and evaluation of all relevant literature. We are confident that RAC will make a robust assessment of the current proposal.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Germany	REHAU AG + Co.	Company-Downstream user	20

Comment received

I have not found any new information in this CLH report compared with former versions. I cannot identify any realistic pathway to absorb or to ingest DINP-doses comparable to the doses applied in the studies quoted for reproduction toxicity. I have a suspicion that the Danish national authority is misapplying the CLH classification to make the use of DINP more difficult because they had no such success with the implementation of their national tax on phthalates.

Dossier Submitter's Response

The CLH report summarises the information available for DINP and the proposal is to a large extent based on studies published after the EU Risk Assessment of DINP from 2003. The majority of the studies used in the CLH proposal have also recently been evaluated by ECHA in their "Evaluation of new scientific evidence concerning DINP and DIDP from 2013". A few additional recent publications have also been included in the CLH proposal. In this light it can be argued that most of the information used for the CLH proposal is not new. However, the ECHA review from 2013 did not contain an assessment of the available information against the CLP classification criteria. The review addressed the potential risk of DINP and DIDP taking into account the identified use and exposure and not hazard classification (i.e. the identification of intrinsic properties according to the CLP classification criteria). Hence, the review does not contain a hazard assessment based on the CLP classification criteria nor does it exclude that DINP possibly fulfils the criteria for classification.

The exposure routes and dosages used in toxicity testing and for assessment of hazard do thus not necesarrily reflect the actual exposures connected with the use of a substance. Such elements are, however, taken into account when assessing the potential risk associated with the use. With regard to the effects observed for DINP at high oral doses, the effects observed at doses up to 1000 mg/kg bw are considered relevant in the context of classification for reproductive toxicity according to the classification criteria.

Reference:
ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	France		Individual	21

Comment received

DINP is a major plasticiser for use in flexible vinyl and is of high importance to the members of Alkor Draka.Based on our understanding of the scientific data on DINP, Alkor Draka does not support the proposed classification.

Dossier Submitter's Response

Thank you for your comment. Please refer to some of the more detailed answers in this document addressing the scientific basis for the proposal, e.g. answers to comment no. 1 and 2.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Japan	Japan Plasticizer Industry Association	Industry or trade association	22

Comment received

Di-isononyl phthalate (DINP) is a phthalate ester used as a plasticizer of plastics consisting primarily of polyvinyl chloride (PVC). In response to and according to the CLP Regulation, the hazard category of DINP's reproductive toxicity was inferred as of 29th September 2015 (Study No. P150412). In this report, the CLP hazard category was reassessed by considering the content and classification (Repr. 1B; H360Df) of the CLH Report (Proposal for Harmonized Classification and Labelling) issued by the Danish Environmental Protection Agency on 1st December 2017.

For DINP classification inferred in accordance with CLP Regulations, more data was thought needed for reliable assessment. Therefore, at this time, as the DINP hazard category, 'not classified' was judged more appropriate than the 1B proposed in the CLH Report.

Working for better regulation of chemical substances in Europe and more meaningful application of CLP Rules, we have the following tow comments. They are made entirely to avoid the excessive precautionary principle.

i) Judgements to regulate all chemicals should be based both on a set of MoA of endocrine disruption and the 'degree of disorder/effect' induced.

ii) According to the Hazard Statement (H360Df), DINP "may damage the unborn child" and "is suspected of damaging fertility." Since aberrations seen before birth may disappear after birth, human health should be judged by viewing through the entire life cycle as described in b, c and d above.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on DINP classification in CLP by JPIA (15th May, 2017).docx

Dossier Submitter's Response

Thank you for your comments.

The attachment provides an thorough examination of the data used as the basis for the CLH proposal and ultimately concludes that

- The literature available and used as the basis of the CLH proposal was equally valuable as weight of evidence
- The available data almost only includes rats and is thus considered insufficient for assessing species differences
- More data – such as multigeneration reproductive studies – are considered necessary for a reliable assessment, as endpoints relating to endocrine action were not sufficiently evaluated in the available generation reproduction studies and as the studies on endocrine action do not discover if the changes observed in pups would lead to impairment of the reproductive function in adulthood.

Although the DS agrees that a generation study conducted according to present day standards (e.g. including endpoints related to endocrine effect parameters) would be useful to shed further light on the reproductive toxicity of DINP and possibly support the existing evidence and add to the understanding of the long-term endocrine related effects of DINP, we consider the total weight of evidence considering all the available data provide a sufficient basis for proposing a classification.

RAC's response

Thank you for the comments. Your position has been noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	Australia	Vinyl Council of Australia	Industry or trade association	23

Comment received

Comments on the proposal by the Danish EPA for harmonized classification and labelling of Di-isononyl phthalate (DINP) as a reproductive toxicant - Category 1B Developmental - Category 2 – Fertility

The Vinyl Council of Australia (VCA) is the peak association representing the PVC value chain in Australia. Our members include both local manufacturers and importers/distributors of raw materials and PVC products.

The VCA would like to provide information relevant to the Australian PVC industry for the technical consultation on the above proposal. We have concerns about the proposal and its ramifications for the global and our local vinyl and plasticiser industries. It is our view

that scientific data does not support this classification proposal of DINP as a Reproductive toxicant Category 1B (Development), nor as a Reproductive toxicant Category 2 (Fertility).

DINP is a major plasticiser for use in flexible vinyl and is of high importance to the members of the Vinyl Council. We are aware of the extensive prior evaluations of DINP showing low hazards and safe use, and these evaluations have been the basis for the current use of DINP by our members.

Based on our understanding of the scientific data on DINP, the Vinyl Council of Australia does not support the proposed classification.

Under the Australian vinyl industry's PVC Stewardship Program, we constantly monitor scientific and regulatory information and developments regarding plasticisers to keep our members and Australian stakeholders well informed. We are aware of the established structure activity relationships for low molecular weight (C3-C6 straight carbon backbones in the alkyl side chains) and high molecular weight (C7-C13 straight carbon backbones in the alkyl side chains) phthalates, with low phthalates showing adverse reproductive effects and high phthalates - such as DINP - not showing adverse reproductive effects in animal studies.

DINP has been the subject of extensive regulatory evaluations with the conclusion that classification is not required. ECHA's Evaluation Report on New Data, in 2013, found that no further risk management measures were needed for children or adults. A study by Boberg et al. (2011) that is heavily relied upon in the Danish EPA's dossier, was assessed as part of the ECHA Restriction Evaluation and did not change the conclusion that no further risk management measures were needed.

Since the publication of Boberg et al. (2011), the paper has been critiqued by peers and the statistical methods used, questioned since the results of statistical significance for the effects of DINP in animals cannot apparently be reproduced for several parameters. The dossier submitter has not included consideration of these critiques in its proposal.

It is our understanding that the dossier submitter has been selective in referring to some observations in certain studies which do not represent adverse effects warranting classification, while neglecting the extensive evidence which supports the absence of adverse effects on sexual function and fertility or on development for DINP.

A cumulative risk assessment undertaken by Australia's chemical regulatory agency, NICNAS (2012) aimed to assess public health risk from use of DINP in consumer products such as cosmetics, children's toys and childcare articles. Its conclusions did not support the need for restrictions on the use of DINP in Australia. NICNAS had identified a weak anti-androgenic pattern observed with DINP at high doses but concluded that the risks from exposure were low.

Reversible endocrine activity is not sufficient grounds for determining adverse effects.

In February 2015, NICNAS concluded that classification for adverse reproductive effects under the Global Harmonised System is not justified. In its 2015 review, NICNAS stated [1]:
"NICNAS does not consider reversible effects on components of the endocrine system or reversible outcomes of these hormonal perturbations or other related measurements to be necessarily adverse. Where these changes can be shown to lead to adverse outcomes

affecting the ongoing functioning of the organism, it is these adverse outcomes that are used as the driver for recommending risk management measures. The available data do not conclusively demonstrate the presence of adverse effects."

Based on the scientific evidence, we do not agree with the Danish EPA's proposal for classification of DINP. A robust weight of evidence evaluation by the ECHA Risk Assessment Committee (RAC) should lead to the conclusion that classification is not supported.

Given the high importance of this substance to our members, we would urge that ECHA and RAC ensure a full and thorough robust scientific evaluation of all the relevant data on DINP.

Please do not hesitate to contact us if you have any questions.

Yours sincerely

Sophi MacMillan
Chief Executive

[1] NICNAS Response to Public Comment, Assessment ID 1178: Human Health Tier II IMAP Assessment for diisononyl phthalates (DINPs) and related compounds.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 170516 DINP_ECHA_DK.pdf

Dossier Submitter's Response

Thank you for your comments. Please refer to the answers given to comment no. 1, 2 and 11 which we belive address all the same issues as described in your above comments and attachment, namely:

1. *Adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains*
   Please refer to the answer to comment no. 1 (headline 4)

2. *The reliance of the CLH dossier on the Boberg study from 2011*
   Please refer to the answer to comment no. 1 (headline 3)

3. *The CLH proposal is based on selective/reversible findings in certain studies not representing adverse effects*
   Please refer to the answer to comment no. 2 (headline 1)

4. *Reference to EHCAs review from 2013 concluding that no further risk management measures were needed for children and adults*
   Please refer to the answer to comment no. 11 (headline 5)

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	United Kingdom	British Coatings Federation	Industry or trade association	24

Comment received

The effects of DINP are not comparable with those seen with the classified lower molecular weight phthalates (DBP, BBP, DEH and DIBP) and this point is also made in the dossier in 4.11.4.2 ''In comparison with DEHP, DPB and BBP the overall evidence for effect of DINP on fertility is limited'' and yet the dossier then tries to say there is correlation. There are no similar effects shown by DINP to those shown by the other classified phthalates.

Similarly in 4.11.5 (4.11.4.1 overview of data) it clearly states that ''Human…. studies did not show any clear association between adult exposure to DINP and fertility measures….'' This we believe was borne out by the review of all data carried out by Dekant and Bridges published in 2016 (see: http://www.sciencedirect.com/science/article/pii/S027323001630280X) which concludes that there is no justification to classify DINP. It is noted that this important publication is not included in the Danish dossier, which raises concerns over the selectivity of the information given in the dossier.

The Danish dossier relies on the study by Dr Boberg to support its proposal to classify DINP, however this study (in 2011) has been brought into question and Dr Boberg has herself admitted that she did not follow strict protocols or calculate statistics correctly. The data were questioned by Morfeld and this was acknowledged by Boberg.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment BCF comments on DINP reclassification May 17.docx

Dossier Submitter's Response

Thank you for your comments. Please refer to the answer to comment no. 1 which addresses the above points.

RAC's response

Thank you for the comments. Your position has been noted. The reported statistical weaknesses of the Boberg study were considered in the RAC assessment.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	Germany		Individual	25

Comment received

Specific comments on effects cited as supportive for classification in the CLH proposal:
The following points are listed as scientific justification for the classification of DINP as a Category 1B reproductive toxicant for development and Category 2 for fertility in the CLH proposal:
"DINP induces effects on the developing male reproductive system. Key findings in animal studies on reproductive effects of DINP are:
a) Structural abnormalities: skeletal effects (rudimentary ribs) were seen two developmental toxicity studies (Hellwig et al., 1997;Waterman et al., 1999) (1000 mg/kg bw/day),
b) Effect on altered growth: decreased body weight in offspring in a two-generation study (Waterman et al, 2000) (from 159 mg/kg bw/day),
c) Functional deficiency: dose-dependent long-lasting decrease in sperm motility in rat

offspring exposed perinatally (Boberg et al., 2011) (from 600 mg/kg bw/day),
d) Structural abnormalities: increased nipple retention and decreased anogenital distance in infant or prepubertal male rats exposed perinatally (Boberg et al., 2011; Gray et al., 2000, Lee et al., 2006; Clewell et al., 2013b) (mostly from 750 mg/kg bw/day),
e) Structural abnormalities: increased incidence of permanent changes (permanent nipples, malformations of testes and epididymis, histological changes in testes and epididymides) in rats exposed perinatally (Gray et al., 2000; Masutomi et al., 2003) (at 750 and 1165 mg/kg bw/day, respectively),
f) A comparable pattern of adverse effects and of mode of action as seen for other phthalates classified as reproductive toxicants in category 1B, e.g. DEHP, DBP, DIBP and BBP (Boberg et al., 2011; Borch et al., 2004; Hannas et al., 2011; Clewell et al., 2013a, Li et al., 2015).
….Key findings for effects of DINP on fertility are:
g) reduced absolute and relative testes weights at high doses in a 2-year study in mice (Aristech Chemical Corporation, 1995) (742 and 1560 mg/kg bw/day), and at higher doses in studies with shorter durations of exposure, i.e. a 4-week study in mice (Hazleton 1991) (1377 mg/kg bw/day), and a 13-week study in mice (Hazleton 1992) (2600 and 5770 mg/kg bw/day),
h) reduced sperm count and effects on sperm motion parameters after 28 days of exposure of juvenile rats (Kwack et al., 2009) (one dose only, 500 mg/kg bw/day),
i) dose-dependent long-lasting reduced sperm motility in rats exposed perinatally (Boberg et al., 2011) (from 600 mg/kg bw/day)."

The following comments apply to the scientific justifications put forward in support of the individual points a) to j) in the CLH proposal.
a) "Structural abnormalities". Rudimentary ribs are not an "abnormality", but a variation (Carney and Kimmel, 2007; Kimmel et al., 2014). The incidence of these variations in rat offspring is variable and these changes are reversible within days after birth. Therefore, they do not represent an adverse effect as defined by WHO/IPCS that may serve as a basis for classification. Increases in the incidence of these variations usually represent delays in ossification due to maternal or fetal toxicity. The presence of such variations after very high doses of DINP thus cannot be used to justify classification as category 1B for development.

b) "Effect on altered growth". The following text is the result of the detailed analysis in the EU RAR: "These findings were considered by the laboratory as the results of maternal stress and/or direct effects of DINP via exposure through lactation. Other studies with phthalates concluded that these decreases were apparently due to decreased food consumption by the dams and changes in the quality or quantity of milk (Dostal et al., 1987). Thus the laboratory concluded that the lower body weights in the pups might have resulted from decreased milk consumption". Palatability issues are caused by the high concentrations of DINP present in food. In addition, treatment related effects on body weight were only observed after doses of approximately 1,000 mg/kg/day at PND 0 (1.5% DINP in diet) which is at the limit dose to be considered in classification. Based on the guidance and criteria of the CLP regulation, this "effect on altered growth" cannot be used to justify classification.

c) "Functional deficiency". The CLH proposal cites "decrease in sperm motility" observed in one study (Boberg et al., 2011) in offspring after in utero exposure to DINP. As discussed several times below, raw data from this study (publicly available through the US EPA Hero database) have been reanalyzed using the statistical approach outlined in the publication (Boberg et al., 2017; Morfeld et al., 2017). Several of the sperm changes (and other changes) reported as significant in Boberg et al, 2011 could not be reproduced

when relying on the raw data and applying the statistical procedures described in Boberg et al., 2011. Furthermore, several additional issues question the reliability of the conclusions regarding sperm paramters after DINP-administration made in the CLH proposal. Sperm analyses in Boberg et al., 2011 examined only 1 - 3 animals per litter, changes in sperm parameters were small, and dose-response could not be established. In well-performed studies, sperm motility in controls is > 80 %, but motility in controls in Boberg et al., 2011 was only 60 % suggesting a general issue with the applied procedures. According to the guidance Document (OECD, 2008), in general, 200 sperm should be analyzed and a minimum of 70% motility is acceptable in controls (OECD, 2008). Sperm motility in the DINP-exposed animals in Boberg et al., 2011 also remained within the historical control range of the laboratory at all DINP doses (53.1 to 66.9 %). In addition, a dose-response regarding sperm parameter effects and adverse changes in testes histology are required to determine whether an effect on sperm parameters is adverse since testes histology is considered the most sensitive endpoint indicative of adverse effects on male fertility (Mangelsdorf et al., 2003). Testes histology and weights were not changed in the DINP-exposed animals at the time point when sperm was analyzed (Boberg et al., 2011). Therefore, the information presented regarding sperm motility is inconclusive and cannot serve as indication for an adverse effect. The CLH proposal does not integrate the results of the two-generation study performed with DINP according to the respective OECD-guideline. Since no effects on fertility were observed in this 2-generation study with DINP, there is no support for a "functional deficiency" as claimed in the CLH proposal.

d) "Structural abnormalities" (nipple retention and anogenital distance). Nipple retention occurs in juvenile male rats at low frequencies and the significance of small increases in nipple retention as observed in one study with DINP is highly questionable. As the effect is reversible, it does not qualify as adverse and thus cannot be used to support classification. The changes in anogenital distance reported by Boberg et al., 2011 in the publication could not be confirmed in the reanalysis of the raw data applying the statistical methods described in the publication. Therefore, only one study (Clewell et al., 2013b) in the database (seven studies assessed this parameter) observed a small change in anogenital distance in juvenile rats exposed in utero to DINP. The magnitude of the change remained within the range of historical controls in the laboratory. The six other studies that determined anogenital distance did not observe an effect of DINP-administration. Therefore, the support for a change in anogenital distance due to DINP-exposure is highly inconsistent and a weight of evidence analysis does not support the claims made in the CLH proposal. In addition, the small and reversible (i.e. not adverse) change in anogenital distance cannot serve as a basis for classification.

e) "Structural abnormalities: increased incidence of permanent changes". Effects summarized here in the CLH proposal are inconsistent over studies for all the endpoints cited. In addition, the changes covered under this heading were not consistently observed in studies with DINP. Small increases in nipple retention were reported in two studies (Gray et al., 2000; Boberg et al., 2011), but nipple retention was not observed in another study (Clewell et al., 2013b) with higher statistical power or in Masutomi et al. (Masutomi et al., 2003). Regarding additional support for adverse effects, the CLH-proposal cites an increased incidence of "structural abnormalities" (apparently two offspring with retained nipples, one with bilateral testicular atrophy and one with unilateral epididymal agenesis) following DINP administration (Gray et al., 2000). In this study, statistical significance was only reached when the different types of effects were summed for statistical analysis. This is inappropriate. In addition, areolae incidence at PND13 (0 % to 14 % in controls) seems to have been highly variable in the laboratory (Ostby et al., 2001). Effects reported in Masutomi et al (2003) are different from those in Gray et al. 2000 and

consisted of minimal to slight changes (degeneration of meiotic spermatocytes and Sertoli cells, scattered cell debris in ducts in epididymis) that reached statistical significance only at DINP-doses of > 1,165 mg/kg/day. The CLH proposal does not integrate the absence of such "permanent changes" in the two-generation study with DINP or in adult males exposed to DINP in utero (Boberg et al., 2011). Due to the inconsistent information from the studies and the remaining database on DINP, the effects reported cannot be used to justify classification.

f) "A comparable pattern of adverse effects and of mode of action as seen for other phthalates". Several low molecular weight phthalates, for example DEHP, dibutyl phthalate and benzylbutyl phthalate, clearly showed reduced male reproductive capacity and increased incidences of malformations in multigeneration studies. It is claimed that such effects should also be observed with DINP since a decrease in testicular testosterone production is considered an early key event in the "phthalate syndrome" in rats and some studies showed a decrease in fetal testes testosterone after DINP-exposure (Hannas et al., 2012; Furr et al., 2014). However, results from DINP toxicity studies regarding testosterone production are inconsistent over studies and changes in testosterone production induced by DINP were only induced at dose levels that induced maternal toxicity. It should be noted that the liver is the major target organ for DINP. Given the important role of the maternal liver during pregnancy (providing metabolites and precursors for the developing fetuses) the effects on testosterone seen in some studies may be secondary to effects on the maternal liver (e.g. disturbance of cholesterol metabolism which provides precursors for testosterone). There also seems to be no apparent connection between the reversible reductions in testosterone induced by DINP and adverse phenotypes since, despite reducing testosterone in some studies, adverse effects on reproductive organs or reproductive performance were not seen. DINP does not impair fertility, affect the onset of puberty or male mating behavior, does not induce cryptorchidism, hypospadias, general reproductive tract malformations, and permanent nipple retention, or permanent decreases of AGD (Waterman et al., 2000; Boberg et al., 2011; Clewell et al., 2013b). These effects were observed in appropropriate studies with other low molecular weight phthalate esters such as DEHP, but not with DINP (EFSA, 2005 a, b; Lhuguenot, 2009). The absence of these effects demonstrate that DINP does not cause the permanent histopathological alterations considered as hallmarks of the "phthalate syndrome" in rats (Johnson et al., 2012).

g) "reduced absolute and relative testes weights at high doses". Histopathological changes were not observed in the testes and the high doses of DINP applied caused a significant depression of body weight gain. Therefore, the testis/epididymis weights were not decreased relative to body weight. These studies cited in the CLH proposal applied doses well above the limit dose of 1,000 mg/kg bw/day for classification and several studies have shown adverse effects of DINP on target organs other than the male reproductive tract, even at much lower dose levels. These effects occurred at much higher doses than those causing hepatotoxicity (the NOAEL for liver effects of DINP has been identified by ECHA as 15 mg/kg bw/day).
h) "reduced sperm counts". In support of this claim, the CLH proposal cites Kwack et al., 2009. This publication assessed sperm parameters after administration of a number of phthalates to rats and reported significantly lowered sperm counts (app. 25 % lower as in controls) and motility of epididymal sperm after a four-week treatment of adult rats with a single dose level of 500 mg DINP/kg bw/day administered by gavage. The study suffers from the use of a single dose level of DINP and unclear reporting regarding use of concurrent controls. Testes histology and weights, which are more appropriate to conclude on an effect of DINP on male fertility (see above), were not assessed. Moreover, the changes in sperm number only had a statistical significance level of < 0.05 and

general toxicity of DINP is evident from several observations in DINP-treated animals in this study. The limited information provided (Kwack et al., 2009) indicates DINP treatment-related general toxicity such as body weight reduction, increases in relative organ weights, and effects on clinical chemistry and hematology parameters. Thus, the effects on sperm count and sperm motility may be interpreted as secondary to systemic toxicity and should not be used to support the claim of "reduced sperm counts" when effects on fertility have not been observed in a two-generation study.

j) "dose-dependent long-lasting reduced sperm". This claim in the CLH-proposal is only supported by the study of Boberg et al., 2011. Issues with this study and the sperm counts reported have been outlined above under comments to c). There is clearly no dose-dependence of the changes reported in Boberg et al., 2011 and the statistical significance of several of the reported sperm changes is not reproducible.
Conclusions
A number of studies with different study designs applying different types of DINP and using different rat strains are available for evaluation (see table 1 in attached document). The results of these studies demonstrate that DINP does not cause permanent effects considered as the hallmarks of the "phthalate syndrome". Malformations and permanent histopathological changes of the male reproductive tract were not observed in any of these key studies. Effects on reproductive organs observed after DINP administration were only transient and did not persist to adulthood. In addition, these transient effects observed occurred at doses in a range where a number of other studies have demonstrated maternal toxicity. Thus, some of the reported effects may be secondary to liver toxicity in the maternal animals. Moreover, some of the effects (sperm motility, nipple retention) in Boberg et al., 2011 are of questionable significance (see above) and only partly reproducible by reanalysis of the raw data (Boberg et al., 2016; Boberg et al., 2017; Morfeld et al., 2017). When reported in supporting studies, effects of DINP on testes weight and testicular histology and other endpoints assessed (AGD, testosterone reduction) were inconsistent.
A weight of evidence approach based on the results of the studies in table 1 concludes that DINP does not impair fertility, affect the onset of puberty or male mating behavior, does not induce cryptorchidism, hypospadias, general reproductive tract malformations, and permanent nipple retention, permanent decreases of AGD. The absence of these effects demonstrate that DINP does not cause the permanent histopathological alterations considered as hallmarks of the "phthalate syndrome" in rats (Johnson et al., 2012). Several other phthalates, for example DEHP, dibutyl phthalate and benzylbutyl phthalate, showed reduced male reproductive capacity and increased incidences of malformations in multigeneration studies (Lhuguenot, 2009).
In conclusion, as detailed elsewhere (Dekant and Bridges, 2016b), DINP does not induce permanent effects on sexual function and fertility and thus a classification is not supported since a consistently observed "adverse effect on sexual function and fertility" is required as a basis for classification by the CLP regulation.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment DINP-WolfgangDekant.zip

Dossier Submitter's Response

Thank you for your comments. Please refer to response to comment 46 below which also includes detailed comments on the key findings highlighted in the CLH dossier. As more extensive comments on the key findings are provided in comment no. 46 (from European Plasticisers) please refer to the answer given under comment no. 46.

Please also refer to the comment provided under comment no 2 (also from Individual, Germany) which includes the same attachment.

RAC's response
Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
15.05.2017	France	SFEC	Industry or trade association	26
Comment received				
As users, we (Sfec, company) can not take a scientific position on the ranking. On the other hand : • A clear position on the situation is needed. On a regular basis, the demand for the DINP classification returns. It has to be definitly settled. Compliance with the test criteria leading to the definition of a reprotoxic 1B must be scrupulously followed. It is recalled that the European Commission had concluded, on 2014 that: " « There is at present no need for further information or for risk reduction measures beyond those that are being applied already ».				
Dossier Submitter's Response				
Thank you for your comments. We agree that the question of the classification for DINP needs to be settled. According to the CLP Regulation substances fulfilling the criteria for classification as toxic to reproduction should normally be subject to a harmonised classification (CLP article 36 (1)). This is the basis and motivation for the classification proposal. The conclusion of the European Commission is based on a risk assessment which takes all identified uses and exposure into account. The conclusion that no risk is identified or that no further risk reduction measures are needed does not leave the provisions of the CLP Regulation regarding harmonised classification redundant.				
RAC's response				
Thank you for the comments.				

Date	Country	Organisation	Type of Organisation	Comment number
15.05.2017	South Africa	The Southern African Vinyls Association	National NGO	27
Comment received				
COMMENTS ON THE DANISH EPA DOSSIER PROPOSING CLASSIFICATION OF DINP BY THE SOUTHERN AFRICAN VINYLS ASSOCIATION OF SOUTH AFRICA (SAVA) The Southern African Vinyls Association (SAVA) is the representative body for the local polyvinyl chloride (PVC) industry and through our Product Stewardship Commitment (PSC), we provide leadership and guidance towards transforming the PVC industry in relation to commerce, health and environmental issues. SAVA is also represented on the Global Vinyls Council (GVC) and through our information sharing network we have been made aware of the fact that the Danish EPA has made its fourth re-submission in two years of a dossier proposing the classification of DINP as a reproductive agent. We have been informed that this was accepted by ECHA and the public consultation process has now been initiated.				

SAVA supports peer reviewed scientific research and concur with current robust scientific data available on DINP and agree that it does not support this classification proposal by the Danish EPA. Any proposal or submission should be based on the weight of scientific evidence and not focus on a key study by Boberg and others in 2011 and 2016 (Corrigendum to "Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats") where the results have been shown not be reproducible for the large part, as is the case in the most recent Danish EPA dossier. DINP is a major plasticiser for use in flexible vinyl (i.e. car underbody sealants, cabling, sheeting, footwear and hosing) and is of high importance to the members of SAVA. Based on international trends and product stewardship programmes, the South African PVC industry voluntarily signed a Product Stewardship Commitment in 2011 to replace DEHP with DINP as a plasticiser and the replacement has been successfully concluded in the majority of PVC applications locally. SAVA continuously review scientific data available on various chemicals including DINP and based on our research and understanding of the available peer reviewed data showing low hazards and safe use, we cannot support any proposed classification of DINP. The commitment shown by our industry to replace DEHP with DINP is based on this collection of sound and robust scientific data. We agree with the conclusions made by various peer reviewed scientific studies that show that low phthalates (C3-C6 straight carbon backbones in the alkyl side chains) have adverse reproductive effects in animal studies and that high phthalates (C7-C13 straight carbon backbones in the alkyl side chains), do not show any adverse reproductive effects. Given the high importance of this substance to our members, we can only support the current body of evidence based on peer reviewed and robust scientific research and urge ECHA and RAC to commit to a balanced and thorough scientific evaluation of all the relevant data on DINP. We do not believe the classification dossier published by the Danish EPA supports any further classification of DINP or the substitution of DINP in PVC applications. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on the Danish EPA Dosier_DINP_By SAVA_15May2017.pdf
Dossier Submitter's Response
Thank you for your comments. Please refer to the answer to comment no. 3 (also from SAVA) which is based on the same attachement.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.05.2017	Italy	Istituto Superiore di Sanità	National Authority	28
Comment received				
EFFECTS ON FERTILITY. The available data do not support per se any conclusion on a possible classification for reproductive toxicity of DINP, even in category 2. Conversely, they wwarrant performing further studies, To this purpose, d hoc protocols might be envisaged. For instance a study starting				

exposure in the pre-pubertal period till adulthood, and examining in detail both sexes (histopathology of reproductive organs, including quantitative measurements, sperm parameters, estrous cyclicity, hormone measurements) in comparison with endpoints of general/systemic toxicity: this protocol may provide a robust basis to conclude whether DINP specifically impairs male and/or female reproductive funcyion. Last but not least, the use of in vitro assays investigating mechanisms and/or fnctional markers (e.g., steriodogenesis) should support classification.
Dossier Submitter's Response
Thank you for your comments. Please refer to the answer to comment no. 4 (also from Istituto Superiore di Sanità) concerning the comment on fertility.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2017	United Kingdom	<confidential>	Company-Downstream user	29
Comment received				
We question the validity of the recent study as it is based upon oral toxicity in rats the dosage is excessive and is not directly comparable to the impact/risk to the human health. This test method does not reflect the likely exposure during installation or use of the wallcoverings.				
Dossier Submitter's Response				
Thank you for your comments. Please refer to the answer to comment no. 5 (also from a UK based Company-Downstream user).				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.05.2017	Belgium	IGI - The Global Wallcoverings Association	Industry or trade association	30
Comment received				
We question the value of the recent studies put forward by Denmark, as they are based on oral ingestion by rats, and we see no relevance between this and the likely human exposure by consumers resulting from the handling of vinyl wallcoverings. Indeed, the levels of oral dosage given to rats in the recent studies, is excessive and disproportionate to the levels experienced by consumer contact. In our view these levels has been used to obtain the result that the Danish EPA required for this current proposal.				
Dossier Submitter's Response				
Thank you for your comments. Please refer to the answer to comment no. 6 (also from IGI – The Global Wallcoverings Association).				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.05.2017	Germany		MemberState	31
Comment received				
A former EU risk assessment report from 2003 concluded that no classification under Directive 67/548/EC for DINP is warranted. The available new data which have been published since then demonstrate developmental effects of DINP in particular on male offspring exposed perinatally. Key findings include increased nipple retention, decreased anogenital distance, histological changes in testes and epididymis, and decreased sperm motility. The observed effects show a comparable pattern as other phthalates which have been classified as reproductive/developmental toxicants and there is indication for a similar anti-androgenic mode of action (decrease of testicular testosterone production in several studies; weak-positive in one Hershberger assay). Decreased sperm counts and motility after adult or perinatal exposure furthermore indicate possible consequences for male fertility. Regarding the above mentioned effects, DINP is certainly less potent than other phthalates such as DEHP. Nonetheless, the observed effects of DINP are not considered to be secondary to non-specific toxicity. In conclusion, the proposed classification of DINP as Repr. 1B (H360Df) is supported.				
Dossier Submitter's Response				
Thank your for your support.				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	United States	American Chemistry Council	Industry or trade association	32
Comment received				
Please see the attached comments from the High Phthalates Panel of the American Chemistry Council. ECHA note – An attachment was submitted with the comment above. Refer to public attachment ACC Comments re Classification and Labelling of DINP May 2017.pdf				
Dossier Submitter's Response				
Thank you for your comments. Please refer to the answers given to comment no. 2 and 11 which we belive address all the same issues as described in your above comments and attachment, namely: 1. *The CLH proposal is based on selective/reversible findings in certain studies not representing adverse effects, interpretation of and comparison with criteria* Please refer to the answer to comment no. 2 (headline 1) 2. *Reference to EHCAs review from 2013 concluding that no further risk management measures were needed for children and adults* Please refer to the answer to comment no. 11(headline 5)				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	United States	The Vinyl Institute	Industry or trade association	33
Comment received				
To the VI's knowledge, DINP has not shown adverse reproductive effects in certain animal studies. ECHA note – An attachment was submitted with the comment above. Refer to public attachment VI Comments to CPSC on CHAP NHANES Information submitted 03-24-2017.pdf				
Dossier Submitter's Response				
Thank you for your comment. Please refer to the answer to comment no. 8 (also from The Vinyl Institute) which refers to the same attachment.				
RAC's response				
Thank you for the comments. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	ExxonMobil Chemical Holland BV	Company-Manufacturer	34
Comment received				
Based on the extensive scientific data on DINP, ExxonMobil respectfully disagrees with the decision from the dossier submitter to propose harmonized classification (CLH). ExxonMobil proposes that no classification is required for DINP for adverse reproductive effects (development and fertility). This extensive data on DINP includes 30 animal studies of direct relevance to inform reproductive classification. While these animal studies show that a reduction in testosterone is consistently observed following exposure to DINP, the empirical evidence on DINP collectively supports that this reduction is insufficient to culminate in adverse effects, i.e. the multitude of studies on DINP consistently fail to report the adverse effects which are seen in studies on low molecular weight phthalates (i.e. those with C3-C6 straight chain backbones in the alkyl side chains), namely, hypospadias, cryptorchidism, under developed prostate and seminal vesicles, changes in secondary reproductive organ weights, and underdeveloped Wolffian Duct. Other observations have also been sporadically reported in the scientific literature on DINP. These observations require careful consideration as to whether they are indeed treatment related based on dose responsiveness, high variability or imprecision of the endpoint, incidence within normal range of variation and historical controls, replicability across studies and study quality; as well as careful consideration of toxicological significance based on the level of biological organization with which the observation is associated (e.g. biochemical, cellular, whole organism), severity, incidence, correlation with other in-study observations, (both positive and negative outcomes), and occurrence below limit doses. Using this type of weight of evidence approach as described in CLP (Annex I, Section 3.7.2) our conclusion is that the CLP criteria are not met and that classification is not warranted for some or clear adverse effects on reproduction (i.e. consistent and identifiable toxicologically significant changes which affect function or morphology of a tissue/organ or produce serious changes to biochemistry relevant to human health are not supported by the evidence). This conclusion is supported by the quantitative weight of evidence assessment taking into account the CLP criteria conducted by Bridges and Dekant (2016), as well as by prior regulatory reviews (ECB, 2003) and well established structure activity relationships for low and high molecular weight				

phthalates. Human epidemiological data is also consistent with the conclusion that classification for adverse reproductive effects (development and fertility) is not required.

With regard to the use of the CLP criteria and the legality of the dossier, the Danish decision to propose the harmonized classification (i.e. basic legal act) is legally void in our opinion because the detailed CLP criteria (re: CLP Regulation, Annex I, Section 3.7.2.) are not applied or demonstrated, formally and materially in the review of the data and in determining whether classification is required or not.

With respect to the scientific quality, the dossier has a number of serious shortcomings which could mislead the reader towards a conclusion which is not scientifically supported:
• Selective reporting of studies and study outcomes with emphasis placed on observations representing endocrine activity (e.g. testosterone change) versus the downstream negative outcomes (e.g. hypospadias, cryptorchidism)
• Lacks a clear and objective scientific explanation for concluding observed effects are treatment related (e.g. does not explain how a minimal magnitude change in AGD that is rarely observed is considered chemically mediated; does not explain why permanent nipples that are within literature control ranges and are not dose responsive are concluded as treatment related).
• Lacks a clear and objective scientific explanation for concluding why effects representing changes at low levels of biological organization are considered adverse despite a lack of occurrence of the events downstream.
• Does not transparently assess study quality and how study limitations affect conclusions with regard to classification, particularly for key studies. For example, Boberg et al (2011) – one of the main studies used to support the case for classification – the dossier does not transparently assess significant flaws in the statistical methods applied in the original paper and in a subsequent Corrigendum (http://doi.org/10.1016/j.reprotox.2016.07.001) published by the authors in 2016, as highlighted in a letter (https://doi.org/10.1016/j.reprotox.2017.03.013) to the editor sent by Morfeld et al (2017) to the journal where Boberg et al (2011) was originally published, with a rebuttal letter (https://doi.org/10.1016/j.reprotox.2017.03.014) from Boberg et al (2017). These two letters to the editor receive no acknowledgment in the CLH dossier presumably because they were published shortly after the time of resubmission of the dossier to ECHA. These letters are now "in press" and available via the website (links are provided in these comments) and we would respectfully request that they should be taken into account in the RAC process.
• Some of the studies cited by the dossier submitter have already been extensively assessed by regulators in the past and have been found not to support classification (EU Risk Assessment Report, ECB 2003). The effects which regulators concluded previously did not support classification are now used to support classification and no explanation or justification as to why this is now the case has been provided (e.g. testes weights in chronic mouse study – Aristech 1995).
• As already noted the dossier submitter does not refer to and evaluate the scientific data versus the detailed CLP criteria under 3.7.2., which is essential to make a determination on classification under the CLP regarding adverse effects, total weight of evidence, toxicological significance, nature, severity and consistency of effects, and effects seen below or above limit doses.
• Furthermore the dossier submitter does not objectively depict the fundamental differences in observed effects between DINP and low molecular weight (LMW) phthalates such as DEHP (see Table 1a in Part 1 of European Plasticisers comments). This lack of adverse effects for high molecular weight phthalates such as DINP and the crucial differences in this respect with LMW phthalates is well documented in the scientific literature based on structure activity relationships (Fabjan et al. 2006; OECD 2004,

Saillenfait et al. 2014). In this context it is noted that over half of the 82 references in the dossier are not related to DINP, but many rather relate to low molecular weight phthalates.

The points above are further analyzed in detail in the submission by European Plasticisers (formerly ECPI) - the CEFIC sector group of which ExxonMobil is a member - to the public consultation. We would respectfully request the RAC to take the full weight of evidence on DINP into account in line with the CLP criteria, and to clearly identify what are the consistently observed effects for DINP in reproductive animal studies, and on what basis these are considered as adverse or non-adverse, and thereby ensure a thorough, robust and transparent assessment and opinion on the proposed classification of DINP.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment ExxonMobil DINP submission_May_19_2017_Final.pdf

Dossier Submitter's Response

Thank you for your comments. Please refer to the answer to comment no. 46 from European Plasticisers which address the same issues in further detail.

RAC's response

Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	France		Individual	35

Comment received

No specific comments

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Consultation publique DINP_V3.docx

Dossier Submitter's Response

Thank you for your comments. Please refer to the answer given to comment no. 10 (referring to the same confidendial attachment).

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	China	AICM	Industry or trade association	36

Comment received

The evidence and rationale brought forward by the dossier submitter does not justify classification of DINP as a reproductive toxicant according to the criteria of the CLP. Based on the extensive scientific evidence demonstrating a lack of adverse reproductive effects following exposure to DINP, per the CLP criteria as detailed in section 3.7.2. of Annex I of the CLP, AICM proposes that classification for development and fertility effects is not required. This proposal for no classification is consistent with the statement in the current DINP IUCLID REACH registration dossiers (updated December 2015) which uses IUCLID standardized language – that is, the reason for no classification is that the reproductive data on DINP is "conclusive but not sufficient for classification".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DINP_CLH_Summary comments_AICM comments May 2017 FINAL.docx

Dossier Submitter's Response
Thank your for your comments. Please refer to the answer to comment no. 11 (also from AICM) which refers to the same attachment.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Brazil	Instituto do PVC	Industry or trade association	37
Comment received				
As representative of the Brazilian PVC production chain, we would like to declare our position against Denmark's proposal to rate DINP under categories 1B and 2 as toxic for reproduction, development and fertility, respectively.				
Dossier Submitter's Response				
Thank you for your comment. Please refer to the answer to comment no. 12 (also from Instituto do PVC)				
RAC's response				
Thank you for the comment. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	France		MemberState	38
Comment received				
There is no reporting of the quality of the studies in the tables. Could you please clarify if all the studies are considered of adequate reliability? Page 29: There are some discrepancies between findings reported in the table and in the text. For example, for the one generation study, reduced live birth pups and pup survival are noted in the text but not in the table. Could you please clarify? Page 56: For developmental toxicity, it was stated that decreased AGD occurred mostly from 750 mg/kg bw/day. However, it should be noted this effect can occurred at much lower doses since Lee et al., 2006 reported reduced AGD at all doses tested starting from 2 mg/kg bw/day. Page 60: Mode of action: effects on male reproductive system reported with phthalates are not only linked to an anti-androgenic effect. In particular, multinucleated gonocytes can be due to a direct effect on germ cells. Decrease of insulin like 3 can also be involved in reduced sperm production and cryptorchidism. Page 66: In addition to effect on sperm, the occurrence of malformations in the male reproductive system reported in the prenatal and perinatal toxicity studies can be used as supportive data to classify the substance for fertility (category 2). Page 67: It would have been interesting to assess the potency of DINP with the setting of SCL (specific concentration limit) for developmental toxicity by calculating ED10 for the effect considered the most sensitive in all studies and choose the resulting lower value. Overall, we agree with the proposed classification.				

Dossier Submitter's Response
Thank you for your comments and support. With regard to the quality of the studies, please refer to the answer provided in the answer to comment no. 2. With regard to the one-generation study (p. 29) and the effects observed in the highest dose on no. of live birth pups and pup survival it is clearly a mistake that these parameters are not reported in table 10. In Annex I to the CLH report these findings are described in more detail (page 84 of the CLH report/page 227 in the EU Risk Assessment Report/): "*The mean live birth index (95.2%), Day 4 survival index (85.6%), Day 14 survival index (92.7%) and lactation index (87.2%) of the high-dose offspring were statistically significantly decreased compared with controls (live birth: 98.2%, Day 4: 93.1%, Day 14: 98.5% and lactation index: 93.9%). The historical control range from this laboratory was the following: live birth: 99.1-95.2%, Day 4: 99.5-89.0%, Day 14: 100-93.7% and lactation index: 100-86.9%."* With regard to the Lee et al. study from 2006 reporting reduced AGD at doses starting from 2 mg/kg bw/day (page 56) we note that this study is associated with some limitations (described in the ECHA review of DINP and DIDP from 2013 and commented in the CLH dossier). As stated in the CLH dossier, this study was not considered sufficient by ECHA 2013 to change the developmental NOAEL. No details on statistical corrections for litter effects were presented, and therefore it cannot be determined at which dose the observed dose-dependent effect on AGD would be statistically significant using appropriate methods. We agree with your comments regarding pages 60 and 66 and thank you for these clarifications. In relation to the possible setting of an SCL an assessment of the ED10 for the key findings has been made. However, it was concluded by the DS that a single representative ED10 could not be derived based on the available data as the classification proposal is based on different types of effects observed in different studies and as comparison with other classified phthalates also forms part of the total weight of evidence. It is thus our opinion that a robust SCL cannot be derived.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Germany	Evonik Performance Materials GmbH on behalf of Evonik Degussa GmbH	Company-Manufacturer	39
Comment received				
see attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on CLH for DINP CAS 28553-12-0_2017-05-19.pdf				

Dossier Submitter's Response
Thank you for your comment. Please refer to the answer given to comment no. 13 (also from Evonik Performance Materials GmbH, relating to the same attachment as above), and to the answer to comment no. 46 from European Plasticisers.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	EuPC	Industry or trade association	40

Comment received

The dossier proposes2 types of reproductive effects warranting classification. We herewith comment point per point the summary justifications provided in page 8 to 10 of the dossier, commenting each indent.

1. Developmental toxicity effects

a) Observation of skeletal effect (rudimentary ribs) found in Hellwig et al 1997 and Waterman et al 1999, such foetal variations are not per se considered significant criteria for classification as per the CLP Regulation Annex I, Section 3.7.2.2.2.

b) Decreased weight of offspring in a two-generation study (Waterman et al 2000) is quoted, but it is not so clear what is the cause of this reduced weight : effects seen are likely related to palatibililty and not due to the inherent toxicity of DINP. In addition effects were only seen above the limit dose and were reversible. These effects do not meet the CLP criteria for classification.

c) Functional deficiency decrease in sperm motility observed by Boberg et al 2011 : limited number of specimen , control rats were not fulfilling OECD quality requirements for sperm motility (minimum 70% motility), the sperm motility for rats within the same lab varied greatly and the statistical approach is questioned (Morfeld et al 2017)

d) Structural abnormalities and anogenetical distance in infant and prepubertal rats : one has to note that such changes were only transient, are of probably low biological consequence (hence not meeting CLP annex 1 section 3.7.2.3.3. : significance of effect) and furthermore occur at levels where there is a clear toxicity from other effects to mothers. It is therefore not possible to distinguish an effect different from others as required by CLP annex 3.7.2.1.1.

e) Likewise for bullet point e, Dekant et al 2016 questions the reliability of Gray et al 2000 and also the statistical significance of the findings.

f) Regarding similar effects of low molecular weight phthalates (mode of action), one should note that this is not consistent with known structure activity relationships showing differences between C3-to C6 phthalates and C7 to C13 (OECD SIAM 2004 and Clewell 2013b)

Reproductive fertility effects

g) Reduced testes weight quoted in g) occur at doses typically above the limit doses and well above those inducing toxicity for the liver (NOAEL set at 15mg/kg.bw by Echa in 2013).

h) Kwack et al 2009 reports a reduced sperm count , but there are several flaws in the study : single dose of 500 mg.kg.bw, unclear concurrent controls, the study is of low reliability in view of inconsistent results for sperm counts and motility, for example showing effects for MEP for which other studies have clearly shown not to cause reproductive effects. Boberg et al 2011. reports dose dependent long lasting effect on sperm motility in rats exposed perinatally. For limitations of this study see above point c.

Conclusions on classification of DINP EuPC would note that the CLP criteria have not been applied in the DINP CLH dossier in reviewing the data. As indicated above, when the criteria are applied the conclusion is that the criteria are not met and classification is not required. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20170519_EuPC_Position Paper on the Proposed classification of DINP as reprotox 1b.pdf
Dossier Submitter's Response
Thank you for your comments. Please refer to the answer given to comment no. 14 (also from EuPC) which refers to the same attachment as above.
RAC's response
Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
19.05.2017	Belgium	The European Council of Vinyl Manufacturers	Industry or trade association	41
Comment received				
Based on our understanding of the scientific data on DINP, ECVM does not support the proposed classification.				
Dossier Submitter's Response				
Thank you for your comments. Please refer to the answer given to comment no. 15 (also from The European Council of Vinyl Manufacturers).				
RAC's response				
Thank you for the comment. Your position has been noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2017	Belgium	ERFMI vzw, European Resilient Flooring Manufacturers' Institute	Industry or trade association	42
Comment received				
After huge efforts to substitute the low molecular weight phthalates, which had been carried out by the European manufacturers in the nearly last 20 years, DINP became a major plasticizer for the industry. The ERFMI members rely on the fact that DINP has been the subject of extensive regulatory evaluations with the conclusion that classification (Dangerous Substances Directive) is not required (EU Risk Assessment Report 2003), and that no further risk management measures are needed for children or adults (EU Risk Assessment Report - Completed 2003 (published in the Official Journal in 2006), ECHA Evaluation Report on New Data, 2013). These assessments included full hazard characterizations including the available reproductive studies. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 2017-05-17 DINP statement ERFMI final.pdf				

Dossier Submitter's Response
Thank you for your comments. Please refer to the answer given to comment no. 16 (also from ERFMI) which refer to the same attachment as above.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2017	Netherlands		MemberState	43
Comment received				
Several other classification proposals for ortho- phthalates have been discussed in the last period. The overall conclusion is that ortho-phthalates with a backbone length of C3-6 are associated with reproductive and developmental toxicity, whereas ortho-phthalates with a shorter (<C3) or longer (C7-C13) do not induce such effects. For these effects, a category approach has been proposed (see a.o. Fabjan et al., 2006 and Saillenfait et al., 2011). Since DINP has a backbone length of C7, classification for reproductive and developmental toxicity is unexpected. The current proposal for DINP is partly based on data for the substance itself and partly on similarities with other phthalates. In our opinion, due to the fact that DINP is a borderline case between C3-C6 and longer backbone length ortho-phthalates, classification should be based on the observed effects with DINP and only the type of effects can be compared to other ortho-phthalates. In general, an assessment of the observed effects in relation to the limit dose of normally 1000 mg/kg bw/day, the severity and the reversibility of the effects, and thus the relevance of the observed effects, seems to be limited. Also the consistency of the effects between the studies should be considered. Please include this in your assessment for example by providing an overview table(s) for the main effects. Below, we will comment on the key findings as indicated in 4.11.4.1 Overview of data. Development a) An increased incidence of rudimentary ribs as observed in two developmental toxicity studies is not sufficient for classification. b) When controlled for litter size, a significant reduction in pup weight is only observed in high-dose males on PND 0, in males and females of the mid and high-dose levels on PND 7 and 14 and in all treated animals on PND 21. The effects on PND 21 may be caused by direct intake of DINP by the pups and are thus not considered to be an effect on development. In addition, the weights of all F1 and F2 treated offspring were within the historical control range of the laboratory with the exception of the F2 high-dose males and females on PND 0 and the F2 high-dose males on PND 1. It can therefore be questioned whether the effects are biologically relevant. In addition, general toxicity (liver and kidney) can be expected at this dose level. c) A significantly reduced percentage of motile sperm was observed in juveniles after exposure to dose levels ≥600 mg/kg bw during development in the study by Boberg et al. 2011. However, there are some questions on the methods of analysis of the sperm parameters (see Boberg 2016, Morfeld 2017 and Boberg 2017) which reduce the reliability of the data. In addition, it is noted that the percentage of motile sperm in the control animals (59%) is also very low, and even below the quality criteria of the OECD (OECD 2008), which states a minimum of 70%. Further, the decreased % of motile sperm was within the range of the historical control data. Also, the % of progressive sperm cells, which is more relevant then % motile sperm, was not significantly affected at most dose levels.				

d) In contrast to what is mentioned in point d, DINP did not affect nipple retention or AGD in the study by Gray et al (2000). Decreased anogenital distance was observed in the study by Boberg, at a dose levels of 900 mg/kg bw, but only when analysed with non standard methods (see Boberg 2016 and Morfeld 2017). Furthermore, as for an effect on nipple retention (≥750 mg/kg bw), a very high dose is needed for the effects to occur. In the study by Clewell, a decreased AGD was only observed at a relatively high dose level (750 mg/kg bw). No effects on nipples was observed at this dose. Further, these effects are likely reversible as no effect on AGD was observed on day 90 in Boberg. In addition, nipple retention is not a relevant effect in humans as all human males retain their nipples but more an indicator of reduced systemic testosterone.
Decreased anogenital distance was observed at dose levels from 1 mg/kg bw in the study by Lee et al.However, this is inconsistent with all other available studies and ECHA already noted that no firm conclusions could be drawn from this study due to its limitations.
e) In the study by Masutomi et al., testicular histology was only slightly affected, and only at a dose level > 1000 mg/kg bw, which also induced maternal toxicity. This is not considered relevant for classification. The effects in the study by Gray et al. (malformations of testis, epididymis, accessory reproductive organs and external genitalia, 4 out of 52 pups and statistically significant, 3 out of 14 litters and not statistically significant, differences between the observed type of reproductive malformation) occur at a slightly lower dose (750 mg/kg bw) and should be considered. Could you provide information on historical control values to have an indication whether these types of male reproductive organ abnormalities occur spontaneously?
f) As already mentioned, DINP does not belong to the group of ortho-phthalates that is generally accepted to cause effects on development (and fertility), because of its backbone of C7. Whereas the observed effects are not comparable to other C7-C13 backbone phthalates (which do not cause effects on fertility or development), they are also not completely comparable to the shorter, reprotoxic ortho-phthalates with a backbone of C3-C6, which amongst others clearly show hypospadias and cryptorchidism. Therefore, DINP should be assessed based only on the observed effects.

Overall, the available data shows that DINP induces a reduction in fetal testicular testosterone production due to an effect on steroidogenesis as do other phthalates. However, the available comparisons with other phthalates show a reduced potential for DNIP. The primary effect occurs at dose levels clearly below the limit dose. Histopathological changes of the fetal and pup testis, secondary or related to the reduction in fetal testicular testosterone, occur (increased Leydig cell clustering and multinucleated gonocytes). These effects are also observed with other phthalates but the potency of DINP is lower. However, the observed fetal and pup histopathological effects are at least partially reversible as in adult rats treated in utero or peri-natal structural effects are only observed at incidences without statistical significance even at dose levels above the limit dose, small increase with a doubtful significance (Gray) and no structural histopathological testis effects (Boberg day 90), or only minimal to slight at dose levels above the limit dose (Masutomi). A possible reduction in sperm motility, but not in sperm count or sperm progression, was observed on day 90 PND after exposure from GD 7 to PND 17 is considered of doubtful biological significance as the % of progressive sperm cell (moving in a direction) is considered more relevant than the % of motile sperms (moving) and the observed changes in motility were within the historical control range of the lab. It can therefore be questioned whether these effects warrant classification in category 1B. Other phthalates show irreversible effects on the male reproductive organs such as hypospadias at dose levels at or below the limit dose. In addition, in some studies more general effects secondary to the reduction in testosterone production were observed in the form of an increase in nipple/areola retention in males (low incidence) and a decrease

in male anogenital distance mainly around PND 14. These type of effects are under control of T3. However, no significant increase in nipple/areola retention was observed in adult animals exposed perinatal indicating that this effect is reversible. Also, there was no significant effect on male AGD on day 90. Therefore it is concluded that DINP induces comparable developmental effects as other phthalates but with a lower potency and without conclusive evidence for irreversible structural/functional effects on the adult male. In addition, based on the reduced potency it cannot be concluded that such effects are likely to occur at dose levels at or below the limit dose. Therefore, classification in category 1B is not considered justified. However, as there are some indications of structural/functional effects (Grey, 2000) supported by the observation of effects in line with the proposed AOP that could induce such effects classification in category 2 is warranted.

The effects on male developmental testes are considered not secondary to the general toxicity and there is insufficient evidence that these effects are not relevant to humans.

Fertility
g) Results occurring only at dose levels > 1000 mg/kg bw are normally not considered relevant for classification. Therefore, only the reduced testis weight observed at a dose level of ≥ 742 mg/kg bw in the 2 year mouse study by Aristech (1995) at dose levels also inducing a reduction in body weight could be relevant. However, since no histopathological changes in the testes were observed in this study, the results are not considered biologically relevant. In addition, no such effects were observed in repeated dose and generation studies at dose levels below 1000 mg/kg bw/day.
h) The effects of DINP on sperm count and sperm velocity were only observed at a dose that also reduced body weight (by 12%). As the dossier submitter also indicates, this implies that the effect on sperm velocity may be secondary to a delay in general development in a sensitive period for spermatogenesis. Sperm production in rats starts at day 50 and increases up to day 100 (Robb, 1978, J. Repro. Fert. 54:103-107). A reduction in body weight and body weight gain resulting in a delay in general developmental can therefore have a strong effect on the development of sperm production and parameters. The observed reduction in sperm count and change in sperm parameters is therefore not considered evidence of a direct effect of DINP on the testis. It is however noted that sperm motion was affected in a similar manner as by other ortho-phthalates (e.g. DEHP, DBP and BBP) and therefore, that a direct effect cannot totally be excluded. This is further supported by the study of Glass (1986, Pediatric Research 20(11)) showing that limited feed reduction does not reduce daily sperm production per gram testis and only limitedly reduces total sperm production (results day 51) but somewhat more for the day 81 results.

i) See point c. Furthermore, an effect due to peri-natal exposure would be more relevant for classification for effects on development than for classification for effects on sexual function and fertility.

In conclusion, DINP induces comparable effects on the sexual function of rodents as other phthalates. However, mainly at dose levels above the limit dose of 1000 mg/kg bw/day. The only effects observed at or below the limit dose are of questionable biological relevance or possible secondary to the general toxicity. The proposed classification in category 2 is justified mainly on the decrease in sperm counts and sperm motility in the presence of general toxicity in the study by Kwack (2009).

With regard to the derivation of an SCL it is suggested to derive ED10 values for the different effects warranting classification. If the lowest ED10 still indicates a low potency,

a higher SCL then the GCL could be considered.

Dossier Submitter's Response

Thank you for your comments. The DS notes that the NL MSCA is of the opinion that the evidence for reproductive effects of DINP are not strong enough for a classification in Category 1B, and that classification in Category 2 is warranted for developmental effects. It is not clearly stated in the comments whether the proposed Cat 2 classification for fertility is considered justified.

In your comments the following main issues are highlighted:

1. *Category approach for ortho-phthalates, DINP is considered a borderline case between C3-C6 and longer backbone length orthphthalates*
   Please refer to the answer given to comment no. 1 (headline 4)

2. *Severity, reversibility, relevance and consistency of the observed effects*
   It is true that the observed effects of DINP and on which the CLH proposal is based are seen at relatively high doses close to the limit dose of 1000 mg/kg bw/day. In the opinion of the DS this is a consequence of the much lower potency of DINP compared to other (C3-C6) ortho-phthalates. The observed effects of DINP (on e.g. AGD, nipple retention and sperm quality) are considered to be associated with the decrease in fetal testicular testosterone, which has been shown in a number of studies. This same mechanism is also proposed for other phthalates, which are classified for reproductive toxicity. Besides from the setting of specific concentrations limits the classification criteria do not take potency into account, and a substance may be classified as a reproductive toxicant if adverse effects on development and/or fertility are observed at doses below 1000 mg/kg bw/day and these effects are not considered to be a secondary effect of maternal toxicity or of a general toxic effect. When seen in isolation the effects observed for DINP are less marked when compared to the C3-C6 phthalates and do not cover the complete spectrum of adverse effects associated with other, already classified (C3-C6) phthalates. Thus, effects like hyperspadia, cryptorchidism, undescended testes etc. have not been observed for DINP in the available studies. As the mode of action is expected to similar for DINP and the classified phthalates, the lack of full overlap and consistency in the findings is considered to be due to the much lower potency of DINP.

   Please also refer to the answer to comment no. 2 (headline 1) which address some of the same issues.

3. *Specific comments related to the key findings in section 4.11.4.1 in the CLH proposal*

   a) and b) Although it was concluded in the EU Risk Assessment from 2003 that the available studies (including those showing rudimentary ribs and reduced pup weight) did not justify a classification for reproductive toxicity, the one- and two generation studies however did show some treatment related effects in the highest doses (between approx. 550-1200 mg/kg bw, i.e. close to or above the limit dose relevant for classification). When these findings alone do not justify classification (c.f. CLP Annex I, section 3.7.2.3.3) they are included in a total weight of evidence assessment where they are considered to support the conclusion of an effect of DINP on both development and fertility in those cases where effects are observed at concentrations below 1000 mg/kg/bw/day.

c) With regard to the questions on the Boberg study related to methods of analysis and control values for motile sperm, please refer to the answer to comment no. 1 (under the issue "The reliance of the CLH dossier on the Boberg study from 2011", headline 3). Please note that these offspring were not juveniles, but young adults (3 months old).

d) With respect to the comment on the Gray et al. study, the list of key findings in the CLH report refer to the observed effect of DINP on areola retention, not to reductions in AGD. According to Gray et al. (2000) a significantly increased number of aereolas (with or without nipples) were observed in males as well as increased incidence of malformations of male reproductive organs (at 750 mg/kg bw/day). This is also what is reflected from table 12 and the description of the Gray study in the text. We agree that nipple retention is an indicator of reduced systemic testosterone – as is neonatal AGD - and reduced systemic testosterone will likely influence human male reproductive development. Therefore, rodent nipple retention is a predictor of adverse male reproductive health effects also in humans.

With regard to the Lee et al. study from 2006 reporting reduced AGD at doses starting from 2 mg/kg bw/day (page 56) we note that this study is associated with some limitations (described in the ECHA review of DINP and DIDP from 2013 and commented in the CLH dossier). As stated in the CLH dossier, this study was not considered sufficient by ECHA 2013 to change the developmental NOAEL. No details on statistical corrections for litter effects were presented, and therefore it cannot be determined at which dose the AGD would be affected using appropriate methods. Nevertheless, the clearly dose-dependent reduction in male AGD and AGDi (AGD divided by cube root of body weight) seen in the Lee et al., 2006, study provide evidence for an effect of DINP on male neonatal AGD.

e) Unfortunately, no historical control values can be provided to indicate whether the listed male reproductive organ abnormalities occur spontaneously.

f) We agree that DINP differs from (some of) the other C7-C13 backbone phthalates, and also from the shorter C3-C6 backbone phthalates. Please refer to answers given to comment no. 1 in this regard.

Please also refer to the response to comment 46 (from European Plasticisers) which address the key findings in more detail.

RAC's response
Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.05.2017	France	GERFLOR	Company-Manufacturer	44
Comment received				
page 7/369 ECHA document DINP.				
Dossier Submitter's Response				
Thank you for your comments. Please refer to the answer to comment no. 17 (also from GERFLOR).				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Belgium	European Plasticisers	Industry or trade association	45
Comment received				
We provide attached the extensive quantitative weight of evidence report prepared by W. Dekant, J. Bridges and G.M.H. Swaen on reproductive and developmental effects of DINP, DnHP and DCHP. This project was sponsored by ECPI (now European Plasticisers). ECHA note – An attachment was submitted with the comment above. Refer to public attachment DINP-WOE Report-final.pdf				
Dossier Submitter's Response				
Please refer to the answer given with regard to the quantitative WoE assessment by Dekant and Bridges under comment no. 1 (headline 2).				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Belgium	European Plasticisers	Industry or trade association	46
Comment received				
European Plasticisers – Comments on the CLH Report Proposal for Harmonised Classification and Labelling – Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2; Substance Name: 1,2-benzenedicarboxylic acid, di-C8-C10-branched alkylesters, C9-rich; [1] di-"isononyl"phthalate; [2] [DINP]; EC number: 271-090-9 and 249-079-5; CAS number: 68515-48-0 and 28553-12-0; Dossier Submitter – Danish EPA European Plasticisers1 represents the major producers of plasticisers in Europe (BASF, Evonik, ExxonMobil, Deza, Grupa Azoty, Lanxess, Perstorp, and Proviron). The opinion of European Plasticisers on the classification proposal is as follows: 1. Based on the scientific evidence, European Plasticisers does not agree with the proposal for classification of DINP as a Reproductive toxicant Category 1B (Development). 2. Based on the scientific evidence, European Plasticisers does not agree with the proposal for classification of DINP as a Reproductive toxicant Category 2 (Fertility). 3. European Plasticisers would note that the endpoints brought forward by the dossier submitter have not been interpreted and/or documented in the dossier versus the detailed criteria established under the CLP for effects warranting classification (see Section 3.7.2.2. – Basis for classification). In the attached comments scientists from European Plasticisers member companies have applied these detailed criteria to the data with the conclusions shown under point 5. 4. European Plasticisers would note that a key study central to the CLH dossier is by Boberg et al (2011). This study is used in four of the nine key points in the "Short scientific justification" which the dossier submitter includes to support the classification proposal. A re-analysis of the raw data from this study using the methods in the published paper (Boberg et al. 2011) has shown that the results of statistical significance for the effects of DINP in animals cannot be reproduced for several parameters (Morfeld et al., 20172). A Corrigendum3 from Boberg et al. in 2016 and letters to the editor (Morfeld et al., 2017; Boberg et al. 20174) have confirmed that the original published methods were not in fact followed and that non-standard methods are now proposed, thereby maintaining the original				

results. When the statistics are performed according to the original methods, the statistical significance of AGD, histopathology outcomes, and sperm parameters is lost in almost all instances, calling into question the statistical and toxicological significance of these observations. A Data in Brief article (Chen et al., submitted) and a letter to the editor (Morfeld et al. 2017) have been written by scientists from European Plasticisers member companies, which clarify the reproducibility discrepancies and their significance to interpretation of this particular study. The editor and an independent reviewer engaged by the editor confirmed in writing their agreement with nearly all of the points in the European Plasticisers letter (Morfeld et al, 2017). European Plasticisers would also note that according to the metadata in the dossier, Dr. Boberg is also the author of the classification dossier.
5. The evidence and rationale brought forward by the dossier submitter does not justify classification of DINP as a reproductive toxicant according to the criteria of the CLP. Based on the extensive scientific evidence demonstrating a lack of adverse reproductive effects following exposure to DINP, per the CLP criteria as detailed in section 3.7.2. of Annex I of the CLP and the detailed criteria in section 3.7.2.2. (Basis for classification), European Plasticisers proposes that classification for development and fertility effects is not required. This proposal for no classification is consistent with the statement in the current DINP IUCLID REACH registration dossiers (updated December 2015) which uses IUCLID standardized language – that is, the reason for no classification is that the reproductive data on DINP is "conclusive but not sufficient for classification".
The above opinion is supported by the attached detailed comments which are provided in five parts:
Part 1 – Short Summary of the Scientific Justification for No Classification
Part 2 – Structured Summary on Danish EPA Reproductive Classification Proposal – DINP does not fulfill the criteria of Annex I of the CLP and therefore does not warrant classification
Part 3 – Detailed comments on the dossier
Part 4 – Scientific Appendices providing detailed information relevant to Parts 1 and 2
Part 5 – Additional Background Information
The above comments (Parts 1 to 5) are provided as 5 individual pdf documents in the zip file attached to this submission to the ECHA web page.
1 www.europeanplasticisers.eu
2 https://doi.org/10.1016/j.reprotox.2017.03.013
3 http://doi.org/10.1016/j.reprotox.2016.07.001
4 https://doi.org/10.1016/j.reprotox.2017.03.014

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DINP CLH comments pdfs May 17.zip

Dossier Submitter's Response

Thank you for your comments. The attachments (part 1-5) provide a very detailed summary of comments to the CLH dossier as well as in depth analysis of the CLH dossier including proposals for text revisions. Please note that at this stage the DS is, however, not supposed to revise the CLH report. It is noted that many of the comments provided by European Plasticisers are in their essense similar to those provided in comment no. 1, 2 and 47 and the answers to these comments are thus overlapping in many aspects.

For clarity the answers to the comments are grouped under the same headlines as those used in the comments in Part 1 – "Short Summary of the Scientific Justification for No Classification". In addition answers to each of the specific comments in Part 2 – "Structured summary on Danish EPA Reproductive Classification Proposal – DINP does not

fulfill the C&L criteria of Annex I section 3.7.2 of the CLP and therefores does not warrant classification" are given subsequently.

General response (grouped under the same headlines as used in Part 1 of the attached detailed comments):

A1: Adverse effects on development are not observed following treatment with DINP during the period of organogenesis.
Although it was concluded in the EU Risk Assessment from 2003 that the available studies (including those showing rudimentary ribs and reduced pup weight) did not justify a classification for reproductive toxicity, the one- and two generation studies however did show some treatment related effects in the highest doses (between approx. 550-1200 mg/kg bw, i.e. close to or above the limit dose relevant for classification). While these findings alone do not justify classification (c.f. CLP Annex I section 3.7.2.3.3) – as also stated in the comments provided - they are, however, included in a total weight of evidence assessment where they are considered to support the conclusion of an effect of DINP on both development and fertility in those cases where effects are observed at concentrations below 1000 mg/kg/bw/day.

A2: Adverse effects on development are not observed in studies assessing in utero exposures to DINP during the androgen sensitive male-programming window.
The CLP Regulation states that if the only effects observed are considered to be of low or minimal toxicological significance classification may not necessarily be the outcome (3.7.2.3.3.). The DS does not consider that the observed effects of DINP are of low or minimal toxicological significance. Several effects of DINP have been observed which are considered as important markers of reproductive toxicity including increased nipple retention, decreased AGD, decreased sperm motility and histological changes in testes and epididymis. As the observed pattern of is similar to those that are observed for other classified phthalates and as DINP is believed to share the same anti-androgenic mode of action, the observed findings cannot be discarded as being of low or minimal toxicological significance. It is recognized that the observed effects are only seen at relatively high doses for DINP and that some of the severe effects that are observed for other phthalates in addition (such as cryptorchidism, hypospadias, cleft palate, testicular tubular atrophy) have not been observed for DINP. The potency of DINP is thus much lower and the full scale of effects that are observed for other phthalates classified as reproductive toxicants may not be expressed or be relevant for DINP, at least not when tested in concentrations relevant for classification. Besides from the setting of specific concentrations limits the classification criteria do not take potency into account, and a substance may be classified as a reproductive toxicant if adverse effects on development and/or fertility are observed at doses below 1000 mg/kg bw/day and these effects are not considered to be a secondary effect of maternal toxicity or of a general toxic effect.

While some of the key findings (e.g. effects on sperm quality, increased nipple retention and reduced AGD) are not observed consistently when looking across the available data for DINP and while the some of the effects may be transient, this does not neglect the importance of the findings. With respect to the older one- and two-generation studies, parameters like sperm quality, AGD and presence of nipple/aereola were not examined as these parameters were simply not included in the former guidelines. This explains why impact on sperm quality, reduced AGD and nipple retention is only seen in some of the newer studies published after the EU Risk assessment as these parameters were not examined in previous guideline studies. The lack of confirmatory findings can thus partly be explained the different study designs used. The findings on e.g. AGD and nipple retention are not found consistently in comparable studies where these parameters have

been assessed at comparable dose levels (e.g. increased nipple retention at two weeks of age and decreased neonatal male AGD was demonstrated by Boberg et al., 2011 but in the study by Clewell et al., 2013b, AGD reduction was only seen at two weeks of age). This could be due to minor differences in assessment methods, the test design e.g. with respect to exposure periods (dosing from GD7-PND 17 in Boberg et al. 2011 and GD12-PND14 in Clewell et al. 2013b), use of two different DINP variants and different rat strains in the two studies as well as normal biological variation.

As stated in the dossier, male reproductive system irreversible effects (e.g. sperm quality effects, structural abnormalities in reproductive organs, and decrease in anogenital distance) are linked to adverse effects in mammalian species, including humans. Overall, fetal disturbance of the developing male reproductive system can have multiple effects in mammalian species as described by Skakkebaek et al. (2001). Decreased AGD was seen for DINP only in neonatal or two week old rats (Clewell et al., 2013; Boberg et al., 2011), and indeed the early postnatal period is considered most sensitive to detect changes in AGD. Thus, even the positive control DBP did not affect AGD at PND 49-50, but only at PND 2 and 14 in the study by Clewell et al., 2013. The transient nature of the AGD changes in rodents do not discount the relevance as an indicator of adverse developmental changes in humans.

A3: DINP does not cause adverse reproductive effects comparable to LMW phthalates
While recognizing the difference in potency of DINP compared to phthalates with alkyl side chain lengths between C3-C6, we find that reproductive effects of phthalates are not considered exclusively related to phthalates with alkyl side chain lengths between C3-C6. Recent studies have shown that also phthalates with backbones C7 are able to reduce fetal testosterone production (Furr et al., 2014; Saillenfait, 2011), whereas no effects on fetal anogenital distance were found in studies on phthalates with a backbone of 8 carbon atoms or more (Saillenfait et al, 2013a; Saillenfait, 2013b). Rat studies have shown that di-n-heptyl phthalate (with C7 backbone) reduces fetal testosterone (Furr et al., 2014), and reduce male AGD and AGDi (Saillenfait et al., 2011). The observed changes showing impaired masculinization of rat offspring indicate endocrine changes that would likely also influence human male reproductive development. Therefore, the described findings are predictors of adverse male reproductive health effects also in humans.
In a recent publication Health Canada (Health Canada 2015a) has proposed a different subgrouping/category definition of phthalates for human health assessment. This approach is related to effects on the developing male reproductive system in rats. DINP has thus been included in the subgroup of intermediate chain length phthalates (between C3-C7) based on specific lines of evidence (gene expression changes related to steroidogenesis in the fetal testes, foetal testicular testosterone production in rats and decreased AGD as an indicator of androgen deficiency during early development in male rat offspring) that are considered to be related to the proposed mode of action (MOA) behind the rat phthalate syndrome. The rat phthalate syndrome is characterised by malformations of male reproductive organs and incomplete masculinisation which in turn can lead to adverse effects on development and fertility. This supports that not only C3-C6 phthalates are associated with reproductive effects. However, a lower potency may be associated with phthalates with alkyl side chain lengths ≥C7.

A4: Human data provide further scientific justification for no classification
It is correct that the epidemiological evidence in relation to showing associations between DINP exposure and adverse reproductive outcome is weak. This inability to show clear support for classification is, however, generally often the case for epidemiological studies. This is also reflected in the CLP criteria stating that "even well-designed and conducted epidemiological studies may lack a sufficient number of subjects to detect relatively rare

but still significant effects, to assess potentially confounding factors" (CLP Annex I, section 1.1.1.4). The guidance on the application of the CLP criteria further state that "However, normally positive results that are adequate for classification should not be overruled by negative findings (section 3.2.2.3.3 on Weight of Evidence, ECHA 2015). As stated in the CLH dossier the evidence for lack of human relevance of phthalate effects is weak as further elaborated in section 4.11.4.4 of the CLH report.
The available human data are thus not considered to provide scientific justification for no classification.

B1: The extensive evidence in adult animals following repeat exposure to DINP (sub-chronic, chronic, and sub-acute) do not provide some or clear evidence of an adverse effect on sexual function or fertility following exposure to DINP ad exposures below the limit dose,

B2: DINP does not impair fertility in one- and two-generation studies,

B4: DINP does not induce adverse effects on fertility observed with DEPH and DBP

Collective answer to B1, B2 and B4: It is acknowledged in the dossier that there are only few studies on DINP showing effects on the male reproductive system indicating effects on fertility (impact on sperm count and velocity in juvenile rats, 28 d; impact on sperm motility in rats exposed perinatally, adverse effects on reproductive organs in a 2 year study).
It was concluded in the EU RAR from 2003 that the effects in mice did not justify classification for fertility. However, as these studies did not examine sperm count or –quality, direct effects of DINP on fertility were not fully elucidated at that time. The study by Kwack et al., 2009, provides evidence for effects of DINP on sperm count and quality (although only one dose was tested). In the same study a reduction of sperm count to 34,2% of the controls was observed for DEHP (also at 500 mg/kg bw/d), a phthalate already associated with effects on fertility, and overall, DINP appeared to affect sperm motion in a similar manner as e.g. DEHP, DBP and BBP. As fertility assessment by breeding may not be considered a sensitive parameter in rats, the findings by Kwack et al., 2009, are not in conflict with the lack of effect on fertility in the Waterman et al., 2000, studies (which did not include an assessment of sperm parameters). Furthermore, also the reduction of sperm motility in rats after exposure during the sensitive perinatal period (Boberg et al., 2011) is considered key evidence that DINP may affect fertility of humans. As stated in the CLH dossier (cited form OECD guidance document no. 43) a dose-response trend and a statistically significant change in sperm motility would generally be interpreted as indicating a potential effect on fertility in humans.
Based on the findings mentioned and the proposed mode of action for DINP, which is similar to that of other phthalates with demonstrated effects on reproduction and fertility, a classification for fertility effects in category 2 is thus proposed as there is some evidence from experimental animals of an adverse effect on fertility, but this evidence is not sufficiently convincing to place the substance in Category 1.

B3: The existing data on sperm are unreliable and do not support at DINP-mediated effect on fertility
Regarding the use of data on sperm motility in the study by Boberg et al., 2011, it is confirmed that control values in the DINP study were below 70%, but within the range of control values in other studies on Wistar Han rats performed using the same methods in the same laboratory. Morfelt et al., 2017, conclude that changes in sperm motility for DINP exposed animals do not differ substantially from historical controls, but in fact the

mean value in the high dose DINP group are 47.4%, whereas the lowest mean value in a historical control group is 12% higher, i.e. 53.1% (Boberg et al., 2017).
The study of Kwack et al., 2009, includes only one dose, and this is listed as a limitation in the CLH dossier. More weight would have been given to a study showing dose-dependent effects at more than one dose level, but no other studies on sperm quality assessment in adult males have been reported for DINP. Bearing this limitation in mind, the reported findings are overall considered valid. As would be expected, the magnitude of the effect of DINP is less than the magnitude of the effects of e.g. DEHP, MEHP and DBP. Effects of some of the monoesters differ in effect magnitude from the results seen for diesters, and this would warrant further investigation. Regarding the study by Kwack et al, please see also response to comment number 47.

Specific response to the comments on each of the key findings (a-i) presented in the CLH dossier and as commented in detail in Part 2 of the attached detailed comments:

Development
a) Structural abnormalities: skeletal effects (rudimentary ribs) were seen two developmental toxicity studies (Hellwig et al., 1997;Waterman et al., 1999) (1000 mg/kg bw/day),
b) Effect on altered growth: decreased body weight in offspring in a two-generation study (Waterman et al, 2000) (from 159 mg/kg bw/day)
Repsonse to a) and b) (same answer provided above under A1): Although it was concluded in the EU Risk Assessment from 2003 that the available studies (including those showing rudimentary ribs and reduced pup weight) did not justify a classification for reproductive toxicity, the one- and two generation studies however did show some treatment related effects in the highest doses (between approx. 550-1200 mg/kg bw, i.e. close to or above the limit dose relevant for classification). While these findings alone do not justify classification (c.f. CLP Annex I section 3.7.2.3.3) they are included in a total weight of evidence assessment where they are considered to support the conclusion of an effect of DINP on both development and fertility in those cases where effects are observed at concentrations below 1000 mg/kg/bw/day.

c) Functional deficiency: dose-dependent long-lasting decrease in sperm motility in rat offspring exposed perinatally (Boberg et al., 2011) (from 600 mg/kg bw/day),
Response to c): Regarding the use of data on sperm motility in the Boberg et al., 2011, study, as control values are below 70% motile sperm, which is considered a standard requirement in OECD guidance document. We can confirm that control values in the DINP study were below 70%, but within the range of control values in other studies on Wistar Han rats performed using the same methods in the same laboratory. Morfelt et al., 2017, conclude that changes in sperm motility for DINP exposed animals do not differ substantially from historical controls, but in fact the mean value in the high dose DINP group are 47.4%, whereas the lowest mean value in a historical control group is 12% higher, i.e. 53.1% (Boberg et al., 2017). With regard to the specific comment on the increased sperm counts at the highest dose level per g cauda epididymis observed in the Boberg study there is no apparent explanation for this observation.

d) Structural abnormalities: increased nipple retention and decreased anogenital distance in infant or prepubertal male rats exposed perinatally (Boberg et al., 2011; Gray et al., 2000, Lee et al., 2006; Clewell et al., 2013b) (mostly from 750 mg/kg bw/day),
Response to d) Nipple retention is an indicator of reduced systemic testosterone – as is neonatal AGD - and reduced systemic testosterone will likely influence human male

reproductive development. Therefore, rodent nipple retention is a predictor of adverse male reproductive health effects also in humans.
Reduced AGD is not seen in only one, but in several studies (Boberg et al., 2011, Lee et al., 2006, Clewell et al., 2013). As also described in the CLH, AGD was reduced at PND 14, but not in neonatal males in the Clewell study, and no change in AGD was seen in the study by Gray et al., 2000. The finding of AGD in the study by Lee et al., 2006, should not be disregarded although this study has some limitations. However, no details on statistical corrections for litter effects were presented, and therefore it cannot be determined at which dose the observed dose-dependent effect on AGD would be statistically significant using appropriate methods.

e) Structural abnormalities: increased incidence of permanent changes (permanent nipples, malformations of testes and epididymis, histological changes in testes and epididymides) in rats exposed perinatally (Gray et al., 2000; Masutomi et al., 2003) (at 750 and 1165 mg/kg bw/day, respectively),
Response to e): The observed permanent structural effects in offspring observed after perinatal DINP exposure are considered to be specific and not secondary non-specific consequences of maternal or other toxic effects. This is also in line with the conclusions of the ECHA review from 2013, stating that low incidences of permanent changes are seen with high doses of DINP. As noted in the CLH report, the Clewell et al., 2013 study did not show permanent changes at PND 49, but a few cases of incomplete or flaccid epididymides (6% of pups), interstitial edema in epididymides, undescended testis, and slight hypospadias were seen in the DINP exposed groups. It is not clear whether these effects were dose related as the incidence was low and a few controls also had flaccid epididymides (2% of pups) and slight hypospadias. With regard to the incidences and severity of nipple retention observed for DINP and compared to that observed in studies with DBP and DEHP this is regarded as a consequence of the differences in potency between these substances.

f) A comparable pattern of adverse effects and of mode of action as seen for other phthalates classified as reproductive toxicants in category 1B, e.g. DEHP, DBP, DIBP and BBP (Boberg et al., 2011; Borch et al., 2004; Hannas et al., 2011; Clewell et al., 2013a, Li et al., 2015).
Response to f): Reproductive effects of phthalates are not considered as exclusively related to phthalates with alkyl side chain lengths between C3-C6. Recent studies have shown that also phthalates with backbones C7 are able to reduce fetal testosterone production (Furr et al., 2014; Saillenfait, 2011), whereas no effects on fetal anogenital distance were found in studies on phthalates with a backbone of 8 carbon atoms or more (Saillenfait et al, 2013a; Saillenfait, 2013b). Rat studies have shown that di-n-heptyl phthalate (with C7 backbone) reduces fetal testosterone (Furr et al., 2014), and reduce male AGD and AGDi (Saillenfait et al., 2011).
In a recent publication Health Canada (Health Canada 2015a) has proposed a different subgrouping/category definition of phthalates for human health assessment. This approach is related to effects on the developing male reproductive system in rats. DINP has thus been included in the subgroup of intermediate chain length phthalates (between C3-C7) based on specific lines of evidence (gene expression changes related to steroidogenesis in the fetal testes, foetal testicular testosterone production in rats and decreased AGD as an indicator of androgen deficiency during early development in male rat offspring) that are considered to be related to the proposed mode of action (MOA) behind the rat phthalate syndrome. The rat phthalate syndrome is characterised by malformations of male reproductive organs and incomplete masculinisation which in turn can lead to adverse effects on development and fertility. This supports that not only C3-

C6 phthalates are associated with reproductive effects. However, a lower potency may be associated with phthalates with alkyl side chain lengths ≥C7.

Fertility:
g) reduced absolute and relative testes weights at high doses in a 2-year study in mice (Aristech Chemical Corporation, 1995) (742 and 1560 mg/kg bw/day), and at higher doses in studies with shorter durations of exposure, i.e. a 4-week study in mice (Hazleton 1991) (1377 mg/kg bw/day), and a 13-week study in mice (Hazleton 1992) (2600 and 5770 mg/kg bw/day),
h) reduced sperm count and effects on sperm motion parameters after 28 days of exposure of juvenile rats (Kwack et al., 2009) (one dose only, 500 mg/kg bw/day),
Response to g) and h): It is acknowledged in the dossier that there are only few studies on DINP showing effects on the male reproductive system indicating effects on fertility (impact on sperm count and velocity in juvenile rats, 28 d; impact on sperm motility in rats exposed perinatally, adverse effects on reproductive organs in a 2 year study). The older 1- and 2-generation studies have not assessed sperm parameters. Based on the findings mentioned and the proposed mode of action for DINP, which is similar to that of other phthalates with demonstrated effects on reproduction and fertility, a classification for fertility effects in category 2 is thus proposed as there is some evidence from experimental animals of an adverse effect on fertility, but this evidence is not sufficiently convincing to place the substance in Category 1.

i) dose-dependent long-lasting reduced sperm motility in rats exposed perinatally (Boberg et al., 2011) (from 600 mg/kg bw/day)."
Response to i): It is not correct that "*as specified in CLP section 3.7.1.4, for pragmatic reasons, effects induced during in utero exposure are not considered for classification for sexual function and fertility . Such effects are rather evaluated under the developmental toxicity endpoint*." In CLP section 3.7.1.3 regarding Adverse effects on sexual function and fertility, it is explicitly stated that such effects include any effect of substances that has the potential to interfere with sexual function and fertility and does not specifically exclude effects induced during in utero exposure. Likewise the text in the ECHA Guidance on the Application of the CLP criteria (version 5.0, July 2017) does not include this limitation of what cannot be considered for classification for sexual function and fertility.

The responses provided above are considered to addres the main issues in the substantial comments provided by European Plasticisers. Answers to many of the remarks are also reflected elsewhere in this RCOM document. When going through the page by page detailed comments it is clear that European Plasticisers have different interpretations and observations related to many of the statements and findings in the dossier. The DS considers that RAC will take the comments provided into account when preparing the opinion on the classification proposal.

With regard to the comment on test substance identity in Part 3 (Detailed comments on proposal) the DS would like to clarify this specific issue: In the datasheet for DINP CAS no. 28553-12-0, product number 376663 (used in the Boberg et al., study from 2011), it is noted that <0.15 % may be dioctyl phthalate as an impurity. This is different from the information obtained by European Plasticisers and listed in Part 3. It may be noted that even if 0.3% of the test substance was DEHP (and not dioctyl phthalate, as listed as a possible impurity), the dose of 600 mg/kg bw/day of DINP affecting sperm motility would correspond to 1.8 mg/kg bw/day of DEHP, a low dose that would not be expected to affect sperm motility.

References cited above that are not included in the CLH dossier:
Boberg, et al. (2017). Rebuttal to letter by Morfeld et al., Boberg et al. (2011) – Corrigendum (2016): Further significant modifications needed. Reproductive Toxicology 2017. http://www.sciencedirect.com/science/article/pii/S0890623816304099

Health Canada 2015a: Proposed Approach for Cumulative Risk Assessment of Certain Phthalates under the Chemicals Management Plan. Health Canada Environment Canada. August 2015.

Morfeld et al. (2017). Boberg et al. (2011) – Corrigendum (2016): Further significant modifications needed. Reproductive Toxicology 2017. http://www.sciencedirect.com/science/article/pii/S0890623816303719Saillenfait AM, Roudot AC, Gallissot F, Sabate JP (2011). *Prenatal developmental toxicity studies on di-n-heptyl and di-n-octyl phthalates in Sprague-Dawley rats.* Reprod Toxicol. 32:268-76.

Saillenfait AM, Roudot AC, Gallissot F, Sabate JP (2011). *Prenatal developmental toxicity studies on di-n-heptyl and di-n-octyl phthalates in Sprague-Dawley rats.* Reprod Toxicol. 32:268-76.

Saillenfait AM, Gallissot F, Sabaté JP, Remy A (2013). *Prenatal developmental toxicity studies on diundecyl and ditridecyl phthalates in Sprague-Dawley rats.* Reprod Toxicol. 37:49-55.

Saillenfait AM, Sabaté JP, Robert A, Cossec B, Roudot AC, Denis F, Burgart M (2013). *Adverse effects of diisooctyl phthalate on the male rat reproductive development following prenatal exposure.* Reprod Toxicol. Dec;42:192-202.

RAC's response

Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Germany	Arbeitsgemeinschaft PVC und Umwelt e.V. (AGPU)	Industry or trade association	47

Comment received

Please find hereunder our comments/rationale:
We focus our comments on the summary on page 8 (but realize that the same arguments have also been used on other places in the document).
a) "Structural abnormalities: skeletal effects (rudimentary ribs) were seen [in] two developmental toxicity studies (Hellwig et al., 1997; Waterman et al., 1999) (1000 mg/kg bw/day),"
What is the reason that DK is bringing up this topic again?
To our understanding, there is no significant difference between the evaluation criteria for effects toxic to reproduction between the old Directive 67/548/EEC, Annex I and the CLP (Regulation (EC) No 1272/2008.
The effects described in these publications have already been evaluated within the EU RAR (2001/2003) with the conclusion that no classification was warranted.
b) "Effect on altered growth: decreased body weight in offspring in a two-generation study (Waterman et al, 2000) (from 159 mg/kg bw/day),"
What is the reason that DK is bringing up this topic again?

To our understanding, there is no significant difference between the evaluation criteria for effects toxic to reproduction between the old Directive 67/548/EEC, Annex I and the CLP (Regulation (EC) No 1272/2008.
The effects described in these publications have already been evaluated within the EU RAR and concluded not to be sufficient for classification.
c) "Functional deficiency: dose-dependent long-lasting decrease in sperm motility in rat offspring exposed perinatally (Boberg et al., 2011) (from 600 mg/kg bw/day),"
Boberg et al. (2011) seems to be essential to support the CLH proposal. However, we notice that this study is not undisputed but even under massive scrutiny.
In a most recent letter to the editor, Morfeld et al. (2017) expresses serious doubts on the validity of this study. Having read the letter to the editor and the poor response of the authors, we share this view, i.e. Boberg et al (2011) seems to suffer from various flaws and therefore may be of ambiguous validity.
Further, it is hard to understand how a substance that is claimed by DK to act via an antiandrogenic mode of action leads to statistically significantly increased sperm counts at the highest dose level.

f) "a comparable pattern of adverse effects and of mode of action as seen for other phthalates classified as reproductive toxicants in category 1B, e.g. DEHP, DBP, DIBP and BBP."
We are not at all convinced that this statement is a proper representation of the data. Low molecular weight phthalates result in cleft palates, cleft prepuce, hypospadias, mal positioned testes and testicular damage, e.g. Saillenfait (2008) describe malformations and other adverse effects as a result of DBP and DiBP dosing: "Preputial separation (onset of puberty) was delayed in male offspring at 500 and 625mg DIBP/(kg day).
Hypospadias, cleft prepuce, and undescended testis were observed in males (11–12 or 16–17 weeks old) exposed in utero to 500 and 625 mg DIBP/(kg day). Histopathological lesions were also present in adult testes, mainly consisting in seminiferous tubule degeneration."
To our knowledge, none of these malformations are reported from valid studies with DINP.
Page 64: "Species similarities are seen between mice, rats and marmosets in the foetal germ cell effects seen with prenatal exposure in vivo (McKinnell et al., 2009; Gaido et al., 2007)."
Again, this statement is strange as e.g. McKinnell (2009) report significant differences; their conclusion says: "Fetal exposure of marmosets to MBP does not measurably affect testis development/function or cause testicular dysgenesis, and no effects emerge by adulthood. Some effects on germ cell development were found, but these were inconsistent and of uncertain significance."

Also, the second quote, Gaido et al. (2007) , reports differences and not similarities as in the mouse, gonocyte multinucleation is not associated with decreased testicular testosterone.

g) "reduced absolute and relative testes weights at high doses in a 2-year study in mice (Aristech Chemical Corporation, 1995) (742 and 1560 mg/kg bw/day), and at higher doses in studies with shorter durations of exposure, i.e. a 4-week study in mice (Hazleton 1991) (1377 mg/kg bw/day), and a 13-week study in mice (Hazleton 1992) (2600 and 5770 mg/kg bw/day)"

The US CEHRH Monograph on DINP notes that the testicular weight decreases coincide with decreased body weights.

Further, what about limit dose aspects? The majority of effects described here are related to dose levels exceeding 1000 mg/kg bw./day – what is the reason to suggest to take them into account?

h) "reduced sperm count and effects on sperm motion parameters after 28 days of exposure of juvenile rats (Kwack et al., 2009) (one dose only, 500 mg/kg bw/day),
What about the validity of this study? There are ambiguous results presented for very short chain phthalates, i.e. Dimethylphthalate (DMP) and Diethylphthalate (DEP) including the respective monoesters, which actually do not show toxicity to reproduction.

While the report cited Habert (2009) to claim species similarities, it unfortunately fails to include the more recent findings presented by Habert et al. (2014); this review should be included for discussion on the validity of data selected in the report:
Habert R. et al. (2014), Concerns about the widespread use of rodent models for human risk assessments of endocrine disruptors, Reproduction (2014) 147 R119–R129.
The CLH report needs to deal with the doubts regarding the relevance of the effects seen with rodents for human hazard assessment.
Already the abstract of this excellent review concludes: "…For instance, MEHP and DES affect steroidogenesis in rodents, but not in human fetal testis. These species differences raise concerns about the extrapolation of data obtained in rodents to human health risk assessment and highlight the need of rigorous comparisons of the effects in human and rodent models, when assessing ED risk."
While this applies to DEHP, the doubts should also work for DINP.

Our Conclusion
Overall, AGPU concludes that the CLH report presented by DK has several flaws and presents a very selective view on the data with DINP.
AGPU urges ECHA/RAC to critically evaluate this report and ultimately reject the proposal as unfounded.
References:
1) Morfeld P et al. (2017): Letter to the Editor, Boberg et al. (2011) – Corrigendum (2016): Further significant modifications needed. Reprod Toxicol, online first: http://www.sciencedirect.com/science/article/pii/S0890623816303719
2) Saillenfait, A. M. et al. (1998): Assessment of the developmental toxicity metabolism, and placental transfer of di-n-butyl phthalate administered to pregnant rats. Toxicol. Sci., 45, 212–224.
3) Saillenfait A.-M et al. (2008): Diisobutyl phthalate impairs the androgen-dependent reproductive development of the male rat, Reproductive Toxicology 26 , 107–115
4) McKinnell C. et al. (2009): Effect of fetal or neonatal exposure to monobutyl phthalate (MBP) on testicular development and function in the marmoset. Human Reproduction, Vol.24, No.9 pp. 2244–2254,
5) Gaido KW et al. (2007) Mouse phthalate exposure shows that gonocyte multinucleation is not associated with decreased testicular testosterone. Toxicological Sciencies 97, 491–503

Dossier Submitter's Response

Thank you for your comments. Below we have responded to your comment on the key findings in the CLH report and reference to the Habert et al. report from 2014. You may also refer to the answers given to comment no. 1 and 2 which address some of the common, general comments from other stakeholders e.g. on the scientific basis for the classification proposal and comparison with criteria etc.

1) *Comments on Key Findings in CLH report*

a) and b) Although it was concluded in the EU Risk Assessment from 2003 that the available studies (including those showing rudimentary ribs and reduced pup weight) did not justify a classification for reproductive toxicity, the one- and two generation studies however did show some treatment related effects in the highest doses (between approx. 550-1200 mg/kg bw, i.e. close to or above the limit dose relevant for classification). When these findings alone do not justify classification (c.f. CLP Annex I section 3.7.2.3.3) they are included in a total weight of evidence assessment where they are considered to support the conclusion of an effect of DINP on both development and fertility in those cases where effects are observed at concentrations below 1000 mg/kg/bw/day.

With respect to the comment on the classification criteria under the old DSD Directive and the present CLP Regulation it is not the change of legislative framework that has lead to the proposal for a classification of DINP. Additional information has been published about the effects of DINP since the risk assessment from 2003. The proposal is thus based on an assessment on the relevant information available for DINP (up until 2016) which in the view of the DS justifies a proposal for classification.

c) With regard to the reliance of the CLH dossier on the Boberg study from 2011 please refer to the answer provided under comment no. 1 (headline 3). (With regard to the specific comment on the increased sperm counts at the highest dose level per g cauda epididymis observed in the Boberg study there is no apparent explanation for this observation.)

f) When seen in isolation the effects observed for DINP are less marked when compared to the C3-C6 phthalates and do not cover the complete spectrum of adverse effects associated with other, already classified (C3-C6) phthalates. Thus, effects like hyperspadia, cryptorchidism, undescended testes etc. have not been observed for DINP in the available studies. As the mode of action is expected to similar for DINP and the classified phthalates, the lack of identical full consistency or more completely overlapping findings is considered to be due to the much lower potency of DINP. Please also refer to the comments on adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains given in the answer to comment no. 1.

g) The effects on reproductive organs observed in repeated dose studies are seen just below and well above the normal dose limit of 1000 mg/kg bw/d for the assessment of effects on reproduction in relation to classification. However, the effects observed in shorter term studies by Hazleton 1991 and 1992 at doses > 1000 mg/kg bw/day are considered to support the dose related decreases in both absolute and relative testis weight seen in the 2 year study by Aristech 1995 (at 742 and 1560 mg/kg bw/day). That is why these studies are mentioned although the effects are only seen at doses higher than 1000 mg/kg bw/day.

h) The study of Kwack et al., 2009, includes only one dose, and this is listed as a limitation in the CLH dossier. More weight would have been given to a study showing dose-dependent effects at more than one dose level, but no other studies on sperm quality assessment in adult males have been reported for DINP. Bearing this limitation in mind, the reported findings are overall considered valid. As would be expected, the magnitude of the effect of DINP is less than the magnitude of the effects of e.g. DEHP, MEHP and DBP. Effects of some of the

monoesters differ in effect magnitude from the results seen for diesters, and this would warrant further investigation.
The comment here that short chain DMP and DEP and metabolites "actually do not show toxicity to reproduction". DMP and its metabolite MMP did not show effects on sperm count or quality in the Kwack study, whereas DEP metabolite MEP did reduce sperm count and VCL. In guideline two-generation studies fertility effects of DEP are only seen at very high doses, whereas reduction in sperm count and quality are seen at lower doses. Overall, findings for other phthalates tested in the Kwack study are in line with other relevant studies on those substances.

2) *Reference to the Habert et al. report from 2014 regarding use of rodent models for human risk assessment of endocrine disrupters*
The CLH dossier does indeed "deal with the doubts regarding the relevance of the effects seen with rodents for human hazard assessment " and includes a section particularly on human relevance and species differences and similarities (section 4.11.4.4 of the CLH report). Thank you for notifying us on the Habert et al., 2014, paper. You may also refer to the answer given to comment no. 46 with regard to human data (more specifically the answer provided under headline A4).

RAC's response

Thank you for your detailed comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	United Kingdom	INOVYN	Company-Downstream user	48

Comment received

Specific Comments

Based on our understanding of the science INOVYN does not support the classification proposal and considers that no classification for DINP still remains the appropriate status. Given that the substance was extensively reviewed under previous legislation (DSD and EU Risk Assessment programmes) and recently by Dekant and Bridges (1) and found to not require a change of classification we think that, given that the studies considered in the CLH document were also considered in the previous consultations, we see no reason for a change in the classification.

Since DINP remains a very important product for the flexible polymer industry we feel that studies must be viewed in the context of an overall weight of evidence approach taking into account all robust studies, particularly those previously assessed by regulators and found to support a not classified conclusion. No measure appears to have been made by the CLH authors to review the overall quality of the studies cited (a requirement that is placed on registrants when submitting their REACH dossiers) nor do we see reference to the basis for classification as described in section 3.7.2.2. of the CLP regulation (for example, nature of adverse effects, their toxicological significance and severity, and the fact that the effects seen below or above limit doses). We are also aware that the publication of Dr Boberg (2), regarded as significant by the CLH authors, was the subject of a corrigendum in the journal in which it was originally published since strict protocols for the calculation of statistics were not followed. Moreover the well-established relationship between alkyl chain length and degree of branching of phthalate esters and their reproductive toxicology properties has not been discussed.

Hence we conclude that the findings of the previous reviews and, including, importantly, the more recent review of weight of evidence of studies on DINP (which included the Boberg paper) (1), that no new classification is warranted, remain applicable.

(1) W. Dekant and J. Bridges, regulatory toxicology and Pharmacology, Vol. 81, November 2016, pages 397 – 406
(2) Boberg J, Christiansen S, Axelstad M, Kledal TS, Vinggaard AM, Dalgaard M et al. Reproductive and behavioral effects of diisononyl phthalate (DINP) in perinatally exposed rats. Reprod Toxicol 2011; 31(2):200-209

Dossier Submitter's Response

Thank you for your comments. Please refer to the answers to comment no. 1 and 2 in this document, which also address the issues highlighted in your comments above, namely

- Reference to previous reviews of DINP under previous legislation (EU Risk Assessment incl. classification according to DSD)
- The review by Dekant and Bridges and weight of evidence assessment
- Quality of the studies
- Nature of adverse effects, significance and severity
- Reliance of the CLH proposal on the study by Boberg et al.
- Adverse effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Germany	REHAU AG + Co.	Company-Downstream user	49

Comment received

The proposal for classification is H360 Df which refers to hazards for females. The summary for justification refers to efects on males which is very curious. I cannot understand why adverse effects of other phthalates with much lower molecular weight should be sufficient to classify this substance DINP with H360 Df even if studies performed with DINP don't lead to such a classification. Most studies were performed using rats and mice which are known to have a weakness on excretion of phthalates and their metabolites. This make most of the studies quoted worthless.

Dossier Submitter's Response

Thank you for your comments. The proposal to classify DINP H360 Df does not refer to hazards for females (capital letter "D" refers to the proposed category 1B classification for developmental effects, small letter "f" refers to the proposed category 2 classification for fertility effects). Rather, the key findings described for DINP are related to effects on males.
The comparison of the findings for DINP with those of other (lower molecular weight) phthalates is considered relevant due to the anti-androgenic effects observed for DINP that show a similar pattern compared to those of other phthalates already classified for reproductive toxicity (please also refer to the answer to comment no. 1, headline 1 and 4).

It is evident that effects observed for DINP (e.g. sperm parameters, AGD and nipple retention) occur at much higher doses compared to some of the other classified phthalates. DINP thus has a lower potency. It is also evident that some of the most

severe effects of the other, already classified phthalates (e.g. cryptorchidism, hypospadias, general reproductive tract malformations) are not observed for DINP under the dose regime investigated and at doses relevant for classification. However, under the classification system potency is not reflected in the actual classification (i.e. the hazard class and category). Only when it comes to the setting of an SCL is the potency taken into account, but the available data to not allow a robust conclusion on an SCL.
RAC's response
Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	France		Individual	50
Comment received				
We ask that the classification of the DINP is definitively established and not discussed again in the future as well as the application of the criteria which defines a reprotoxique 1B. We recall that the European Commission had concluded that: « There is at present no need for further information or for risk reduction measures beyond those that are being applied already. » Voir page 301/302 du DINP report. « Based on the risk assessment in this report, it can be concluded that no further risk management measures are needed to reduce the exposure of children to DINP and DIDP » Voir page 7/369 du document Echa DINP.				
Dossier Submitter's Response				
Thank you for your comments which refers to the EU Risk assessment of DINP from 2003 and ECHAs review of new scientific evidence concerning DINP and DIDP in relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006 Both reports contain an evaluation of the available data on the toxicological properties of DINP within the scope of a risk assessment. With regard to the assessment from 2003 this concludes that a classification for reproductive toxicity is not warranted. New data have, however, has been published since then. Based on these new data as well of taking the fidings in older studies into account and integrating this information with present day knowledge of the mode of action of certain phthalates, a new assessment of the hazardous properties and the classification according to the CLP Regulation is considered justified. While we acknowledge the outcome of the latest evaluation of scientific evidence on the risk associated with DINP in toys and childcare articles (ECHA 2013), this assessment was done in a different context, namely an assessment of whether the current REACH restriction for DINP was considered adequate (REACH Annex XVII, entry 52). We note that hazard identification under CLP (i.e. the identification of inherent properties) and risk assessment under REACH (i.e. a combined assessment of hazard and exposure) are two separate processes. The current restriction under REACH Annex XVII is e.g. based on a review from ECHA (2013) concluding, that a risk from the mouthing of toys and childcare articles (containg DINP and DIDP) cannot be excluded if the existing restriction was lifted. The CLH proposal for DINP is solely based on the inherent properties of DINP including reference to effects observed for other classified phthalates, and does not take use and				

exposure into account. According to the CLP Regulation substances fulfilling the criteria for classification as toxic to reproduction should normally be subject to a harmonised classification.

Reference:
Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.05.2017	Japan	Japan Plasticizer Industry Association	Industry or trade association	51

Comment received

a) Based on the results obtained from generation reproductive studies in rats using oral exposure, DINP did not adversely affect rat reproduction (generation reproduction) because of no changes in indices of reproductive toxicity (mating index, male fertility index, female fertility index, fecundity index, gestation index, gestation length, etc.) or male reproductive system organs (organ weight, necropsy and histopathological examination) in F0 or F1 parental animals.

b) As for the developmental toxicity in rats, non-specific changes were seen in skeletal/visceral examinations of fetuses (increase in skeletal variations, etc., which are frequently seen also among control animals) and suppression of body weight gain in pups, but these changes were all considered secondary effects of maternal toxicity. In addition, nipple retention and histopathological changes of the testis observed were inferred to probably be very minor.

c) In classifying the hazardousness, although the above literature and their results were all equally valuable as weight of evidence, data seemed to be lacking to assess the hazardousness of DINP in more detail. That is, the endpoints to examine the endocrine action (AGD, nipple retention, sexual maturation, sperm function test, etc.) were not seemed to be sufficiently evaluated in generation reproduction studies.

d) To supplement this deficiency, studies assessing endocrine action were conducted; AGD, testosterone level in the testis and histopathology were evaluated. However, in order to discover if the changes seen in fetuses would remain to affect the reproductive function in adulthood, more comprehensive assessment appears to be required by conducting multi-generation reproductive studies, etc., not by examining only the adverse effects at the fetal stage.

e) Moreover, since almost all the reproductive developmental toxicity studies used rats and no studies used non-rodents such as rabbits, for example, to assess the developmental toxicity, particularly teratogenicity, the data was considered insufficient to discuss species differences.

f) In addition, toxicological effects on the testis reported from general toxicity studies were very likely secondary ones associated with other toxicological changes because many other studies did not report any findings indicating testicular toxicity.

For DINP classification inferred in accordance with CLP Regulations, more data was thought needed for reliable assessment. Therefore, at this time, as the DINP hazard category, 'not classified' was judged more appropriate than the 1B proposed in the CLH Report.

See attached in detail

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments on DINP classification in CLP by JPIA (15th May, 2017).docx

Dossier Submitter's Response

Thank you for your comments. Please refer to the answer to comment no. 22 (from JPIA) which refer to the same attachment.

RAC's response

Thank you for the comments. Your position has been noted.

Date	Country	Organisation	Type of Organisation	Comment number
16.05.2017	Italy	Polynt S.p.A	Company-Manufacturer	52

Comment received

Based on the extensive scientific evidence demostrating a lack of adverse reproductive effects following exposure to DINP, per CLP criteria as detailed in section 3.7.2 of Annex I of the CLP, we propose that classification for development and fertility effects is not required.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment DINP_CLH_Polynt Comments.pdf

Dossier Submitter's Response

Thank you for your comments. We have grouped your comments and our response under the 6 main headlines below:

1. *Scientific basis for the proposal and comparison with CLP criteria (incl. adverse effects and significance of observed effects)*
   Please refer to the answer to comment no. 2 (headline 1)

2. *Adverse reproductive effects of phthalates in relation to the length of the carbon backbone of the alkyl side chains*
   Please refer to the answer to comment no. 1 (headline 4)

3. *Weight of evidence assessment and lack of reference to the publications by Dekant and Bridges, 2016 in the CLH proposal*
   Please refer to the answer to comment no. 1 (headline 2) and 2 (headline 2)

4. T*he use of the Boberg study and the re-analysis of the data by Morfeld et al., 2017*
   Please refer to the answer to comment no. 1 (headline 3)

5. *Reference to previous reviews and assessments of DINP and lack of new evidence in the CLH proposal*
   The EU risk assessment from 2003 concluded that classification was not warranted for DINP based on the data available. However, new scientific data have been published for DINP since 2003. Based on the newer data (and considering findings

from older studies) as well as considering the similar mode of action of DINP compared to other phthalates classified as reproductive toxicants, the DS submitter considers that the criteria for classification are fulfilled.

With respect to the ECHA review from 2013 we note that the focus of this evaluation was solely to address the potential risk associated with the exposure to DINP and DIDP in toys, childcare articles and all other possible uses. Whereas the review describes all relevant information available incl. studies on effects on reproduction, this review does not contain an assessment of the available information against the CLP classification criteria. The review addresses risk taking into account the identified exposures and not hazard classification (i.e. the identification of intrinsic properties according to the CLP classification criteria). Although the review concludes that no further risks for DINP and DIDP were identified [besides that identified for mouthing of toys and childcare articles as already addressed by the existing REACH restriction, entry 52 in Annex XVII] the review does not as such contain a hazard assessment based on the CLP classification criteria nor does it exclude that DINP possibly fulfils the criteria for classification.

6. *Socioeconomic aspects of a classification of DINP*
   Please refer to the answer to comment no. 1 (headline 5)

Reference
ECHA 2013: Evaluation of new scientific evidence concerning DINP and DIDP In relation to entry 52 of Annex XVII to REACH Regulation (EC) No 1907/2006. Final review report. European Chemicals Agency, 2013

RAC's response

Thank you for the comments. Your position has been noted.

PUBLIC ATTACHMENTS
1. ACC Comments re Classification and Labelling of DINP May 2017.pdf [Please refer to comment No. 32]
2. VI Comments to CPSC on CHAP NHANES Information submitted 03-24-2017.pdf [Please refer to comment No. 8, 33]
3. ExxonMobil DINP submission_May_19_2017_Final.pdf [Please refer to comment No. 9, 34]
4. DINP_CLH_Summary comments_AICM comments May 2017 FINAL.docx [Please refer to comment No. 11, 36]
5. Comments on CLH for DINP CAS 28553-12-0_2017-05-19.pdf [Please refer to comment No. 13, 39]
6. 20170519_EuPC_Position Paper on the Proposed classification of DINP as reprotox 1b.pdf [Please refer to comment No. 14, 40]
7. 2017-05-17 DINP statement ERFMI final.pdf [Please refer to comment No. 16, 42]
8. DINP-WOE Report-final.pdf [Please refer to comment No. 45]
9. DINP CLH comments pdfs May 17.zip [Please refer to comment No. 46]
10. Comments on DINP classification in CLP by JPIA (15th May, 2017).docx [Please refer to comment No. 22, 51]
11. DINP_CLH_Polynt Comments.pdf [Please refer to comment No. 52]
12. 170516 DINP_ECHA_DK.pdf [Please refer to comment No. 23]
13. BCF comments on DINP reclassification May 17.docx [Please refer to comment No. 1, 24]
14. Comment DINP-WolfgangDekant.zip [Please refer to comment No. 2, 25]

15. Comments on the Danish EPA Dosier_DINP_By SAVA_15May2017.pdf [Please refer to comment No. 3, 27]

CONFIDENTIAL ATTACHMENTS
1. Consultation publique DINP_V3.docx [Please refer to comment No. 10, 35]