Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

diisooctyl phthalate

EC Number: 248-523-5
CAS Number: 27554-26-3

CLH-O-0000001412-86-193/F

Adopted

9 March 2018

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: diisooctyl phthalate
EC number: 248-523-5
CAS number: 27554-26-3
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Denmark		MemberState	1
Comment received				
DK agrees with the proposed classification for DIOP as Repr. 1B; H360DF. We appreciate the clear argumentation provided for the category approach. In spite of the relatively few data available for DIOP itself we believe that the CLH report provides a well-founded basis for the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Belgium	European Plasticisers	Industry or trade association	2
Comment received				
Please read specific comments in public attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment European Plasticisers_Comments_DIOP_Annex XV_CLH.pdf				
Dossier Submitter's Response				
We note your support regarding classification Repr. 1B for development. Composition: Thank you for the additional information on substance composition. In the absence of registration dossier for this substance, information on composition was based on literature and in particular on Saillenfait (2013) publication. We understand that the composition				

cited in this publication specifically refers to the tested substance and may not be representative of the whole production of DIOP.

Justification / Identified uses:
We agree that there is no justification for the self-classifications reported in the ECHA C&L inventory list.

We note that you state that DIOP is not manufactured commercially in the EU anymore. Indeed, apparently, according to ECHA website, the envisaged registration deadline was 30/11/2010, but without any official action of registration at this time. However, since DIOP may be potentially used in the future as an alternative of other currently classified phthalates, a classification process is considered needed in order to avoid possible substitution.

Page 11 2nd para from bottom:
The Lefaux (1972) reference is: *Lefaux R (1972) Les matieres plastiques dans l'industrie alimentaire, p161* as indicated in the NICNAS report (2008).

The choice of the upper boundary for the category of reproductive toxicant phthalates is not so clear considering the reproductive effects reported with DIOP and DINP for example. In this mind, we can cite the Health Canada report (2015) considering phthalates with C3-C7 backbone as toxicant for development. In addition, Lioy et al (2015) referred to phthalates with C3-C8 backbone as "active" phthalates (related to "phthalate syndrome"). In the context of this CLH report, the category for reprotoxic phthalates including at least C3-C7 backbones in the alkyl side chains is considered more relevant than C3-C6, in order to include DIOP.

Page 12 reference to Health Canada, 2015:
Please note that DINP shows adverse reproductive effect that are mainly consistent with medium chain group. This supports the fact that some phthalates with carbon backbones > 6C can have reprotoxic effects.

Page 13 Table 8.1:
DIOP is defined as diisooctyl phthalate and therefore with a backbone of 7 carbons, as confirmed in the ECHA website.

We agree that phthalates considered for read-across are all phthalates with C3-C6 backbone.

Page 19, 1st paragraph, last line:
The CLH report will not be amended after public consultation. Anyway, we do not agree to delete "…… it cannot be excluded the presence of a more sensitive effect at lower doses" considering the very limited database with DIOP.

Page 21, 3rd paragraph:
The CLH report will not be amended after public consultation. The category including C3-C7 backbones in the alkyl side chains is more relevant than C3-C6 for reprotoxicant phthalates (see responses above).

Page 22, 1st paragraph:
See responses above.

Page 27, 1st paragraph:
We agree that reproductive effects reported with phthalates are not only due to anti-androgenic disruption.

Even if there is no fertility study with DIOP, cryptorchidism and hypospadias observed after in utero exposure are risk factors for a decreased fertility at adulthood. Considering the composition of DIOP, its effects on male reproductive tract after in utero exposure and based on the data on other medium chain phthalates, the evidence is considered sufficient to classify DIOP as Repr. 1B for fertility rather than Repr. 2.

RAC's response

Noted.

As regards the category approach, RAC considers that DIOP should be included in the medium chain length group due to the close similarity between effects observed on male reproductive tract following exposure to DIOP and other C3-C6 phthalates. However, we acknowledge that the proposed Health Canada category approach was made for cumulative risk assessment of certain phthalates, and not for hazard classification purposes.

See also response to comment no 5.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Denmark		MemberState	3

Comment received

For developmental toxicity the available and reliable pre-natal and peri-/postnatal studies of DIOP (Saillenfait 2013) provide clear dose-response relationships and cover a wide spectrum of effects that are comparable to those observed for other C3-C7 phthalates that are included in the category approach. For fertility it is considered justified to expect that DIOP will have similar effects as the other classified phthalates in the category and thus to classify DIOP based on read-across. The effects of DIOP on the male reproductive organs observed in the developmental toxicity studies could furthermore be considered indicative of fertility effects.

With respect to the considerations of the Mode of Action and relevance for humans the CLH proposal for DIOP states that recent publications have questioned the relevance of anti-androgenic effects induced by phthalates in rats to humans. However, we also note that in relation to both the previous and the present restriction proposal for "the four phthalates" (2012 and 2017) RAC has concluded that there is too much uncertainty about the available data (on the four phthalates) to conclude whether humans are less, equally or more sensitive than rats (RAC/SEAC 2012, Opinion on the Annex XV proposal on the four phthalates). Further, in their opinion of the current restriction proposal RAC acknowledges the dossier submitters view that the currently available scientific evidence in male animals and epidemiological studies shows that these effects (i.e. the wide spectrum of anti-androgenic effects observed) are relevant for male humans (RAC/SEAC 2017, Opinion on the Annex XV proposal on the four phthalates). We suggest that these considerations are also taken into account in the current CLH proposal for DINP.
Although it is recognized that DIOP seems to be of lower potency than some of the other phthalates in the category we agree that the data are not sufficient for the setting of an SCL. This is primarily due to the lack of information of possible additional sensitive endpoints such as effects on germ cells in male adult offspring (and mammary gland development in female adult offspring), which have been observed at low doses for other

phthalates covered by the category approach. It can thus not be ruled out that additional effects of DIOP would be evident at even lower doses than those listed in table 9.1 in the CLP dossier (calculation of ED10 for DIOP based on developmental effects).
Dossier Submitter's Response
Thank you for your comment. We agree that there is too much uncertainties to conclude whether humans are less, equally or more sensitive than rats. We agree that it cannot be ruled out that additional effects of DIOP would be evident at even lower doses than those listed in table 9.1 in the CLH dossier.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.04.2017	Belgium	European Plasticisers	Industry or trade association	4
Comment received				
Please read specific comments in public attachment ECHA note – An attachment was submitted with the comment above. Refer to public attachment European Plasticisers_Comments_DIOP_Annex XV_CLH.pdf				
Dossier Submitter's Response				
See response to comment 2.				
RAC's response				
Noted. See response to comment 2.				

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2017	Netherlands	RIVM/BR	National Authority	5
Comment received				
Reproduction toxicity · We question whether the classification Repr. 1B for effects on the reproductive system/fertility based on lesions of the male reproductive tract (in particular hypospadias, undescended testis and hypospermatogenesis) reported in the absence of significant maternal toxicity is justified as the effects on the male reproductive tract can be seen as an as a developmental effect, relevant for classification as Repr. 1B; H360 D because this effect was observed after in utero exposure. In addition, the category approach is based on a group of source substances ranging in side chain length from C3 to C6. This means that read-across to DIOP, with a chain length of C7, is based on extrapolation. The side chain length is considered important because it is stated that a chain length above 8 is considered not reprotoxic according to the Health Canada report. In addition, a number of phthalates with longer chain lengths in the range of C7 to C11 have been discussed by TC-C&L (September 2002) and some were not classified. This should be taken into account for the justification of the borders of the group and the justification for the read-across. · Information on the classification of DIPP is also available from the TC C&L meeting in September 2002 and related documents. · We agree with classification Repr. 1B for effects on development based on embryotoxicity (decreased pup weight and skeletal variations), embryolethality (post-implantation losses and resorptions) and malformations of the male reproductive tract,				

reported in the absence or with minimal maternal toxicity. In addition, also a lower quality study indicates that prenatal exposure to DIOP in mice can increase the number of resorptions, late fetal deaths, and dead and malformed foetuses
Dossier Submitter's Response
We agree that the data from medium chain phthalates provided in the CLH report are related to phthalates with C3-C6 backbones. The read-across is not completely considered as an extrapolation considering that DIOP is a mixture of isomers with a large percentage of C4-C6 ester backbone, including DEHP. Cryptorchidism and hypospadias are risk factors for a decreased fertility at adulthood. Considering the composition of DIOP, its effects on male reproductive tract after in utero exposure and based on the data on other medium chain phthalates, the evidence is considered sufficient to classify DIOP as Repr. 1B for fertility. The choice of the upper boundary for the category of reproductive toxicant phthalates is not so clear considering the reproductive effects reported with DIOP and DINP for example. In this mind, we can cite the Health Canada report (2015) considering phthalates with C3-C7 backbone as toxicant for development. In addition, Lioy et al (2015) referred to phthalates with C3-C8 backbone as "active" phthalates (related to "phthalate syndrome"). In the context of this CLH report, the category for reprotoxic phthalates including at least C3-C7 backbones in the alkyl side chains is considered more relevant than C3-C6, in order to include DIOP. For DIPP classification, we only have access to public data. The data is not publicly available in ECHA website. Thank you for your support for Repr. 1B for effects on development.
RAC's response
In the CLP Regulation, Annex I, section 3.7.1.3 "Adverse effects on sexual function and fertility" there is no reference to the exposure period for induced effects on sexual function and fertility. In one of the studies by Saillenfait *et al.* (2013a) with exposure on GD 12-21, it was shown that DIOP induced permanent postnatal alterations of the male reproductive system at PNW 10-12 that may have an effect on fertility. However, more importantly, it is noted that when comparing with other C3-C6 *ortho*-phthalates, there is similar toxicity to male reproductive organs after DIOP exposure. RAC therefore consideres that classification of DIOP as Repr. 1B, H360F, is justified. Thank you for your support for classification for Repr. 1B for effects on development.

PUBLIC ATTACHMENTS
1. European Plasticisers_Comments_DIOP_Annex XV_CLH.pdf [Please refer to comment No. 2, 4]