Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

diisohexyl phthalate

EC Number: 276-090-2
CAS Number: 71850-09-4

CLH-O-0000001412-86-158/F

Adopted
9 June 2017

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: diisohexyl phthalate
EC number: 276-090-2
CAS number: 71850-09-4
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
19.09.2016	Germany		MemberState	1
Comment received				
The German CA agrees to the proposed classification of Repr. 1B; H360FD according to the CLP-Regulation (CLP). There is clear evidence of reproductive toxicity as an intrinsic and hazardous property of the phthalates with a carbon backbone of 3-6 carbon atoms and a total number of 4-8 carbon atoms in the side chain which DIHP belongs to. It is agreed that the coherence of the data of reproductive toxicity of these phthalates allows for read-across to fill data gaps for DIHP and supports the conclusion that DIHP is a reproductive toxicant.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
29.09.2016	France		MemberState	2
Comment received				
Category approach: We support the proposed classification mainly based on read-across with DHP (CAS 68515-50-4). For the category approach, please note that not all the cited C4-C6 phthalates have harmonized classified Repr. 1B for fertility endpoint. Indeed DIBP and DBP are classified Repr. 1B-Df. Mode of action: Recent publications have questioned the relevance of anti-androgenic effects of phthalates in humans. Indeed, some experimental studies using in vitro or xenograft				

models did not show any decrease of testosterone by different phthalates (such as DBP, MEHP and MBP) in human foetal testis although this effect was clearly observed in rat foetal testis. Could you please consider these data and discuss the weight of evidence for the classification proposal?

DIOP:
In page 42, references to DIOP are made stating that this phthalate has 8 carbons in total in the side chain. However, it should be clarified that technical DIOP is usually present as mixtures, which may contain isomers with a linear portion from 4 to 6 carbons. The composition of DIOP commercial mixture is commonly 70-75% of isomers with C4-C6 ester backbone and less than 25% of isomers with C7 backbone or more. DEHP and DnOP are isomers of DIOP (Saillenfait, 2013).

Dossier Submitter's Response

Thank you for your support.

Yes, we are aware that not all the C4-C6 phthalates in the chemical grouping have harmonized classification as Repr. 1B for adverse effects on sexual function and fertility. The category members with the shortest side chain lengths (DIBP and DBP) are classified as Repr 1B; H360Df. However, since we strongly consider the chemical grouping as valid for read-across we consider that diisohexyl phthalate should be classified in Repr. 1B on the basis of both adverse effects on fertility and sexual function, and adverse effects on the development of the offspring similar to the reference chemicals DPP, DnHP and DEHP in the category which are closer in carbon chain length and where data on both end points are sufficient for classification.

Regarding Mode of action and human relevance:
It would have been helpful if specific references had been indicated in the comment by the FR CA for us to be able to consider the data.
Although human data from epidemiological studies and case studies are presently considered insufficient to determine a causal association between reproductive effects and phthalate exposure there are some studies (although not conclusive) indicating effects on e.g. semen quality, testosterone levels and anogenital distance in humans. It is therefore reasonable to assume that the identified pattern of reproductive effects reported in animal studies may also be of human relevance. Phthalates have been associated with the development of testicular dysgenesis syndrome (TDS) in rats after in utero exposure where deficiency of androgen action is strongly implicated. In *in vitro* studies of human fetal testis recovered from the first trimester of pregnancy (a critical period for testicular differentiation) MEHP exposure caused reductions in the number of germ cells but had no effect on testosterone synthesis and there were no effects on the expression of steroidogenic genes (Lambrot et al., 2009). However, it is noted that technical challenges in the study may have obscured the results. In an attempt to refine models for studying the human fetal testis response to phthalates Mitchell et al., 2012 and Heger et al., 2012 have studied species differences in phthalate-induced endocrine disruption using transplantation of human fetal testis tissue into mice or rats. The chosen endpoints for studying endocrine disruption in human fetal testis in these studies were testosterone levels and seminal vesicle weight (Mitchell et al); and formation of multinucleated germ cells (MNG) and steroidogenic gene expression (Heger et al). There was a significant increase in the number of MNG content in human fetal testis xenografts after DBP exposure compared to control indicating phthalate-specific effects. In contrast, expression of steroidogenic gene was not altered in human fetal testis xenografts exposed to DBP. The masculinization programming window is critical for effects on normal male reproductive development and TDS disorders may only occur if there is a reduction in androgen production/action in this period. The xenograft studies by Mitchell et al. and Heger et al. do not take into account in utero exposure to phthalates throughout the the

male programming window and are therefore not strong enough to disregard the proposed mode of action as relevant for humans.
Moreover, the study by Furr et al. (2014) which used a short-term in vivo protocol to screen phthalates for their ability to disrupt testis endocrine function in utero demonstrated that decreased fetal testicular testosterone levels in rats and mice is an early key event with no qualitative species differences observed. However, there are differences in sensitivity between rats and mice as a result of the dose levels of phthalate esters required to trigger the effect.
In summary, these studies indicate that there are differences in response to phthalates between human and rat (and between rat and mouse) and that humans seem not to be more sensitive than rats, but the evidence is not considered to be conclusive at present.

References:
Furr JR,Lambright CS, Wilson VS, Foster PM, Gray LE Jr. A short-term in vivo screen using fetal testosterone production, a key event in the phthalate adverse outcome pathway, to predict disruption of sexual differentiation. Toxicol Sci. 2014 Aug 1;140(2):403-24.

Heger NE, Hall SJ, Sandrof MA, McDonnell EV, Hensley JB, McDowell EN, Martin KA, Gaido KW, Johnson KJ, Boekelheide K. Human fetal testis xenografts are resistant to phthalate-induced endocrine disruption. Environ Health Perspect. 2012 Aug;120(8):1137-43.

Lambrot R, Muczynski V, Lécureuil C, Angenard G, Coffigny H, Pairault C, Moison D, Frydman R, Habert R, Rouiller-Fabre V. Phthalates impair germ cell development in the human fetal testis in vitro without change in testosterone production. Environ Health Perspect. 2009 Jan;117(1):32-7.

Mitchell RT, Childs AJ, Anderson RA, van den Driesche S, Saunders PT, McKinnell C, Wallace WH, Kelnar CJ, Sharpe RM. Do phthalates affect steroidogenesis by the human fetal testis? Exposure of human fetal testis xenografts to di-n-butyl phthalate. J Clin Endocrinol Metab. 2012 Mar;97(3):E341-8.

Thank you for the clarification regarding the constituents of the common composition of technical DIOP.

RAC's response

RAC concurs with the response from the DS.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2016	Netherlands		MemberState	3

Comment received

Because
• 1,2-Benzenedicarboxylic acid, diisohexyl ester is expected to be rapidly metabolized to the mono-ester;
• Phthalates with a backbone length of of C4-6 have been associated previously with reproductive and developmental toxicity;
• Read-across information obtained from 7 reference ortho-phthalates with ester side-chain lengths within the interval of 3-6 carbon atoms as included in the current CLH dossier shows that the transitional phthalates have similar reproductive and developmental adverse effects.;
• All reference phthalates included in the dossier have a harmonised classification in Repr. 1B (for DHP, CAS nr 68515-50-4, the proposal is also Repr. 1B). All reference substances are classified as Repr 1B; H360 FD, except for 2 of the shorter side chain length (C3 and C4) substances, which are classified as Repr 1B; H360 Df;
it is expected that also 1,2-Benzenedicarboxylic acid, diisohexyl ester can cause an adverse effect on reproduction and on development and therefore we agree with the proposed classification as Repr. 1B; H360FD. However, it is suggested to exclude DHP from the justification, as grouping/read-across should be based on substances with

relevant data and not based on a substance with a certain classification already mainly based on read-across.
Dossier Submitter's Response
Thank you for your support. We agree that grouping/read-across should be based on substances with relevant data. DHP is merely included as a supporting member and considered relevant since diisohexyl phthalate and DHP (1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear) are to a large extent based on the same constituents, i.e. branched and linear C6 isomers to a varying extent. Diisohexyl phthalate is one of the branched constituents of DHP.
RAC's response
RAC concurs with the response from the DS.