Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Di-n-hexyl phthalate (DnHP)

ECHA/RAC/CLH-O-0000001541-83-03/A2

Adopted

13 September 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Di-n-hexyl phthalate (DnHP)
CAS number: 84-75-3
EC number: 201-559-5

General comments

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
16/02/2011	Netherlands / RIVM / National Authority	Proposed textual changes At several places in the document an open space should be added between the name of the author and 'et al.' P15 table 11 second columnline 9 from the bottom: epithetlium → epithelium P18, table 12: The percentage of fertile females should read 74% (14/19) instead of 82% in the 0.3% DnHP dose group P24, table 19: The table-heading should be placed above the table. P26 line 3-5: 'Thus …DEHP': change the words 'than those' in 'like the ones' P27, line 4: the hyphen between the numbers 9 and 12 is missing P31, table 26: - In the table at the line 'left testis' the number 22/9 and 17/8 are not clearly placed. - in legend b under the table 26 one reads 3 times DIBP instead of DnHP P33 para 4.11.3.2 line 3-end:	 Modified Modified Modified Modified Modified Modified Modified	The text is revised

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		-P33 last line: n-diethylhaxyl → diethylhexyl P34 line 6: 7.2 mmol/kg/gay → /day P36 first last sentence: : the word 'although'should be replaced by also	Modified Modified Not modified because it would change the meaning of the sentence	
01/03/2011	Germany / Franziska Wittmann / MSCA	We agree to the proposed classification Repr. 1B – H360D according to CLP-regulation (CLP) and Repr. Cat.2; R61 according to directive 67/548/EEC (DSD), respectively. There is clear evidence in rats that in utero exposure to Di-n-hexyl phthalate (DnHP) causes developmental toxicity in terms of high intrauterine resorption rates of the progeny, teratogenicity and pre-/postnatal developmental disorder of the male reproductive system at concentration levels below 1000 mg/kg bw/d. We also agree that there is clear evidence for fertility impairment in male mice and rats after postnatal repeated oral exposure to DnHP at concentration levels above 1000 mg/kg bw/d. Based on the findings on substance related decrease in litter production per pair we also think that there is strong evidence for fertility impairment at concentration levels below 1000 mg/kg bw/d. Therefore we support the proposed classification Repr. 1B – H360F (CLP) and Repr. Cat. 2; R60. Readability of the document could be improved by checking language and spelling. It is recommended to include consecutive numbering on Tables. References in text should be named consistently. Abbreviations should be explained (e.g. DNHP, DnOP, DPP, DNPP etc.). The term various in combination with phthalates should be specified. Section 4.11.4 (Summary and discussion of reproductive toxicity) p. 36. The paragraph starting with "Regarding its impact… " should be reworded. It is hardly understandable.	Thanks for your support Thanks for your support Special care has been given to number the tables. Modified Modified	The support is noted

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		Table 31, page 37: the information given in table 31 is a repetition of information from other tables, omission of this table should be considered.	This table give information that are partly similar than others. However, it comes from ANOTHER publication and we tried to be exhaustive.	There is similar information in the two tables (11 and 33) and they could be merged, but as it involves additional work, it is not considered a priority.
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	We agree with the classification proposal Repro Cat 1B (H360FD). We only have a few minor comments; Page 11. Section 4.1 Toxicokinetics Radiolabelled DnHP was used (Elsisi et al, 1989), but there is no mentioning of where on DnHP the 14C-radiolabel was located. Whether it is on the ring or on the side-chain will make a big difference.	This text has been added within our proposal: "The radioactive isotope was synthesized using 14C-radiolabeled phtalic acid (uniformly labelled on the ring) and the appropriate alcohol."	The text is revised.
03/03/2011	Belgium / Maggie Saykali / ECPI European Council for Plasticisers and Intermediaes / Industry of Trade Association	Comment on the Annex XV Dossier for DnHP Page 20, Section 4.11.1.2 Human Information, line 2 states the following: "Numerous studies linking phthalate exposure and various impacts on human fertility are published". This is not an accurate statement. ECPI recommends that this statement is corrected as follows: "Some studies have suggested a possible association between exposure to low molecular weight classified phthalates and effects on human fertility. In particular these studies have looked at DEHP which is used in medical device applications. In reviewing these studies the Scientific Committee for Emerging and Newly-Identified Health Risks concluded as follows: "Sofar, there is no conclusive scientific evidence that DEHP exposure via medical treatments has harmful effects in humans (SCENIHR - Opinion of February 6, 2008).	The sentence has been modified. Part of the text proposed has been included in the proposal.	The text has been modified, focusing on that none of the studies have dealt with DnHP.

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		No comments received		

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	Response	Rapporteur's comments
		No comments received		

Toxicity to reproduction

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
16/02/2011	Netherlands / RIVM / National Authority	Effects on sexual function and fertility Direct evidence of effects on fertility is limited to effects at high dose levels in mice at 1800 mg/kg bw/day. Effects on sexual function were observed in the mice study at 1800 mg/kg bw/day and rats at 2400 mg/kg bw/day. These dose levels are clearly above the limit dose for DSD and could also be considered as not relevant for CLP. At dose levels below 1000 mg/kg bw/day, a reduction in production of litters, litters per pair and live pups per litter was observed in the RACB study in mice. Without further knowledge it is not possible to judge whether this is an effect on fertility or on development. It is argued in the proposal that it is an effect on fertility because no effect on embryolethality was observed in the rat developmental study at the dose of 400 mg/kg bw/day. However, this is a rat study. A justification that the effect at this dose level in rats is also relevant for mice is missing. The evidence for an effect on sexual function and fertility is therefore limited. Read-across from other phthalates could be considered but this should focus specifically on the effects on sexual function and fertility. Based on the currently available data, classification for effects on sexual function and fertility may be more appropriate. Alternatively,	We agree that available studies for DnHP regarding fertility are using high dosage. It has to be noted that decrease of litter/ pair is observed in the Lamb study since low dose (without data on embryolethality, we agree that it is difficult to judge if the effect is due to impact on fertility or development). However, the effects observed at high doses together with mode of	RAC acknowledge that some of the studies have been conducted using very high exposure levels. Still, in the opinion of RAC, there is sufficient evidence on effects on fertility to warrant classification; decreased mating index at 430 mg/kg/day in mice, read across to similar phthalates known to affect the fertility, and extensive testicular toxicity observed in rats exposed to 250 mg/kg/day. The testicular

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		CLP classification without specification of the effect could be considered as effects on sexual function and fertility cannot be excluded. Further, inclusion of SCLs could be considered as most effects occurred at relatively high dose levels close to the limit dose of 1000 mg/kg bw/day. Further, we do not agree with the statement that effects on the reproductive development should be considered for the fertility endpoint. In our opinion effects on the development of the reproductive organs is only relevant for the endpoint developmental effects. Determinative is the exposure period (development) and not the type of effect. Developmental effects We agree with the proposed classification for developmental toxicity. Has setting of SCLs been considered?	action (*in vitro* data compared to *vivo* ones) , data available from substances of the same category and effects observed on male reproductive system after *in utero* exposure gives enough weight of evidence for fertility classification. Text has been modified to clarify our position. Setting of SCLs for fertility or development has not been considered as guidance is under preparation for the time being.	toxicity noted in the developmental studies would affect fertility. Therefore, in the case of DnHP there is an intrinsic mutual link/interaction between developmental testicular toxicity and male fertility effects. The support for dev tox is noted. It is correct that no agreed guidance for setting SCLs is available. We believe the default SCL suffices in this case.
01/03/2011	Germany / Franziska Wittmann / MSCA	p. 15, table 11, results, crossover mating trial: please check for uterine weight decrease of 31% for DnHP in the reference given Effects on fertility: p. 17, section 4.11.1.1.1, first paragraph: during the continuous breeding phase males and females are exposed, "For females, "should be deleted There were 4 litters for one pair with 6.5 pups in the middle dose (table 12). The sentence "There were no live pups at the high dose and one litter of four pups at the middle dose" should be corrected accordingly. p. 18, section 4.11.1.1.1, second paragraph: order of sentences should be changed to keep relationship of referring phrases like "these organs" from original article	Modified Modified Modified Modified	The text is revised

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		p. 19, section 4.11.1.1.1, table 14: please specify unit for weigth determination: are kidneys and adrenals weight given in grams? Developmental toxicity: p. 22 3rd sentence of paragraph starting with "DnHP produced...": This sentence is hardly understandable, suggest rewording. Human information: Section 4.11.1.2 (page 20), section 4.11.2.2 (p. 33) and section 4.11.5 (p.40) The relevance of animal data for humans should be further substantiated by scientific data, references or argumentations, otherwise human relevance might be questioned: there are statements such as "A testicular dysgenesis syndrome (i.e., a failure of normal in utero development of the testis) has been proposed to explain the secular increases in a number of human male reproductive deficits, including decreased semen parameters, increased incidence of cryptorchidism and hypospadias (two of the most common human birth defects), and increased incidence of testicular (germ-cell-derived) cancer. Thus far, no cause-and-effect relationship has been established between any environmental agent and these human deficits. However, the rodent data lend support to the hypothesis" (Foster, P.M.D. (2005): Mode of action: Impaired Fetal Leydig Cell Function – Effects on Male Reproductive Development Produced by Certain Phthalate Esters" Crit. Rev. Toxicol. 35, 713- 719. We recommend to built up an argumentation based on the Human Relevance Framework. Endocrine disruptor property: p. 33, section 4.11.3.2: It should be mentioned that some of the tests were conducted with mixtures (e.g. DnHP with di-iso-hexyl phthalate, with a DnHP content of 25% only)	Modified Modified This information is interesting but as mentioned, it has not been link neither to environmental agent exposure nor to phthalates exposure. We do not think it is appropriate to report this information when we have clear animal data on DnHP: the level of evidence is not the same. No such details are given in this paragraph. Either I describe in details the protocols, or I don't. We choose the latest as those data are	As sufficient animal data exist for DnHP, and no human study concerns DnHP, RAC supports not discussing human data further in the BD. Human relevance of the animal data is assumed for other phthalates, and has to be assumed also for DnHP. As no firm conclusions can be drawn from these studies, we support not going into detail with respect to reporting technical details.

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			only given as supportive information.	
		p. 37, first paragraph, last sentence: please check for uterine weight decrease in given reference.	Modified	
		QSAR, Category Approach: Section 4.11.3.3, pp 33 – 36: We strongly support the integration of QSAR considerations into the C&L proposal. However, the section should be substantiated by taking into account more recent publications on this area (e.g. Fabjan, E., Hulzebos, E., Mennes, W. and Piersma, A.H. (2006): A Category Approach for Reproductive Effects of Phthalates" Crit. Rev. Toxicol.36, 695 – 726) p. 34, second paragraph: reference should be given for DCHP	Information from this reference and reference have been added.	Noted
02/03/2011	Sweden / Ing-Marie Olsson / MSCA	Page 15-17. Section 4.11 Toxicity for reproduction There is a good and thorough presentation of data in this section, but the usability of Summary Table 11 could be improved by adding some more quantitative information (e.g., by quantifying the 'decrease' or 'increase'). Alternatively, it could be useful to add the LOAELs from the studies to this table.	Quantitative information has been added. LOAEL were not added because it is not useful for CLP purpose.	Noted
02/03/2011	UK / Helen McGarry / MSCA	Overall, we agree with the classification proposal The document makes several references to the reproductive toxicity of other phthalates, perhaps to support the classification position adopted. We consider that the effects reported on DnHP are sufficient to support the proposed classification without reference to other phthalates, and this information could be deleted	Thanks for your support. We tried to be exhaustive within the proposal and consider the "read-across" data as supportive evidences.	The support is noted. RAC agrees that the animal data on DnHP by itself are sufficient to support the proposed classification. The data for DnHP is also compatible with the observed effects and dose-effect relationships

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				for other short-chain phthalates, supporting that DnHP belong to this group of reproductive toxicants. As the grouping supports the proposed classification, this information should also be included.
03/03/2011	Ireland / Health & Safety Authority	The Irish CA is in agreement with the proposed classification of Repr.1B-H360FD (Repr. Cat.2; R60/61).	Thanks for your support	The support is noted.
03/03/2011	Denmark / Peter Hammer Sørensen	Denmark agrees with the proposed classification regarding developmental toxicity and fertility.	Thanks for your support	The support is noted

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
		No comments received		

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
01/03/2011	Germany / Franziska Wittmann /	Identity of the substance: Table 8, p. 9: replace 'impurities' by 'additives'	Modified	

Date	Country / Person / Organisation / MSCA	Comment	Response	Rapporteur's comments
	MSCA	Toxicokinetics: p. 11, section 4.1.1.1: description should focus on/start with the classified phthalate. Use "14C-labelled phthalate" instead of "14C-phthalate". p. 11, section 4.1.2: the toxicological significance of n-hexanol should be discussed p. 12, section 4.1.3: the possibility of further oxidation of the side chain should be discussed Repeated dose toxicity p. 14, section 4.7.1.7: the term "this endpoint" should be specified p. 15, section 4.8: entry is missing Other information: p. 41, section 6, last paragraph: This paragraph is hardly understandable, please reword.	Modified Added Not known Modified Added Modified: this paragraph is of great importance in our point of view because it reflects the procedure we followed.	