



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, dihexylester, branched
and linear**

EC number: 271-093-5
CAS number: 68515-50-4

CLH-O-0000002695-67-03/A2

Adopted
7 June 2013

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 1,2-BENZENEDICARBOXYLIC ACID, DIHEXYLESTER, BRANCHED AND LINEAR

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

Substance name: 1,2-Benzenedicarboxylic acid, dihexylester, branched and linear

EC number: 271-093-5

CAS number: 68515-50-4

Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07/09/2012	Belgium		MSCA	1
Comment received				
<p>We thank the Dossier Submitter for the clear analysis in relation to DIHP. We agree with the proposed classification Repr. 1B - H360 according to CLP regulation and Repr. Cat. 2; R 60-61 according to Directive 67/548/EEC, respectively.</p> <p>We support the category defined in the dossier: The similarity of the severe reproductive effects of the <i>ortho</i>-phthalates, with side-chain lengths C4 to C6, in experimental animals has been well conducted and is supported by many scientific lectures. Besides, we also agree with the inclusion of DIBP (C3) in the category as a sentinel chemical regarding the clear evidence of its classification as Repr. 1B.</p> <p>The available data of the reference chemicals are clear and relevant and give a good overview of the reproductive toxicity of this category.</p> <p>We agree that this category spectrum of phthalates including DIHP presents the similar physicochemical, biological and toxicological properties and that reproductive toxicity is an intrinsic hazard.</p> <p>We support the proposed classification as Repr. 1B - H360 (CLP).</p> <p>We have only few remarks:</p> <ul style="list-style-type: none">- As the classification is based on category approach, we were wondering how relevant it is to have the same classification as DEHP, DIPP, DPP and DnHP, meaning H360FD?- DBP, DIPP and DPP are classified Aquatic Acute 1 H400, what about this endpoint regarding DIHP?				

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Dossier Submitter's Response				
Thank you for your support.				
Initially, we reasoned that the general hazard statement H360 (May damage fertility <u>or</u> the unborn child) was more prudent than H360FD (May damage fertility. May damage the unborn child.) considering that there is no available data on reproductive toxicity of DIHP itself and because there is no clear consensus among the reference chemicals in the category regarding hazard statement (H360Df or H350FD). However, since we strongly consider the chemical grouping valid for read across we agree that DIHP may also have the hazard statement H360FD indicating that the substance is classified in Repr. 1B on the basis of fertility <u>and</u> developmental toxicity similar to the reference chemicals DEHP, DIPP, DPP and DnHP in the category. Still, DIBP and DBP have the hazard statement H360Df, and this could also be justified for DIHP.				
We agree that the chemical grouping approach also may be used for classification for hazardous to the aquatic environment. However, since this endpoint is not an endpoint for harmonised classification it is not within the scope of this proposal.				
RAC's response				
The classification of DIHP as Repr. 1B with the hazard statement H360FD is more consistent with the proposal for Repr. Cat. 2; R60-61 under DSD. RAC supports this classification, as read-across data includes endpoints for both fertility and developmental toxicity. Classification for Aquatic Toxicity was not assessed by RAC, as the dossier submitter did not consider this endpoint to be within the scope of the proposal.				
Date	Country	Organisation	Type of Organisation	Comment number
17/09/2012	Netherlands		MSCA	2
Comment received				
We suggest checking whether the CAS registry provides information on the ratio between DIHP and DnHP in the substance with the CAS nr 68515-50-4. If this has already been done and no information appeared to be available, it may be useful to add to the CLH report that no information on the ratio of the isomers was available in the CAS registry.				
Dossier Submitter's Response				
Thank you for your comment.				
No information appears to be available on the ratio between branched and linear isomers of the substance with CAS nr 68515-50-4 in the CAS registry.				
RAC's response				
Noted.				
Date	Country	Organisation	Type of Organisation	Comment number
18/09/2012	Norway		MSCA	3
Comment received				
CLH report for Diisohexyl phthalate - Comments from Norway				
Norway would like to thank Sweden for the proposal for harmonised classification and labelling of Diisohexyl phthalate (DIHP), CAS No 68515-50-4.				
We support the proposal to classify DIHP for reproductive toxicity with Repr. 1B - H360 based on a chemical category approach.				
The available studies on the selected phthalates in the category demonstrate significant effects on the male reproductive organs and developmental effects. The reproductive toxicity is concluded to be an intrinsic hazard of the phthalates in the current chemical group, and consequently DIHP is anticipated to behave in a similar way as the reference chemicals. We therefore support that classification of DIHP as Repr. 1B is warranted.				
Dossier Submitter's Response				
Thank you for your support.				

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RAC's response				
Agrees with the comment and notes the support.				
Date	Country	Organisation	Type of Organisation	Comment number
20/09/2012	France		MSCA	4
Comment received				
France agrees with the classification proposal Repr. 1B - H360 of DIHP.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
The support is noted.				
Date	Country	Organisation	Type of Organisation	Comment number
20/09/2012	Germany		MSCA	5
Comment received				
The German CA supports to the proposed classification Repr. 1B – H360 according to CLP-regulation (CLP) and Repr. Cat. 2; R60-61 according to Directive 67/548/EEC (DSD), respectively.				
<p>There is clear evidence of reproductive toxicity as an intrinsic and hazardous property of the phthalates with 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.</p> <p>Nevertheless, the substance identity is unclear. The stated name of the CLH Dossier on the cover page and in part A of the report is Diisohexylphthalate. The chosen CAS and EC no. are for the for the substance</p> <ul style="list-style-type: none"> - 1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear - CAS no.: 68515-50-4 - EC no.: 271-093-5 <p>This CAS no. represents a reaction product containing linear isomers with CAS no. 84-75-3 and branched isomers (e.g. CAS no. 71850-09-4) with unknown concentrations.</p> <p>The mono constituent substance "Diisohexylphthalate" is covered of the CAS no.: 71850-09-4 and of the EC no.: 276-090-2. Therefore we would kindly ask you to revise the name or the CAS no to specify the substance identity.</p> <p>Furthermore in Part B (the test substance should be stated) also the substance name "Diisohexylphthalate" is given, but all further information like CAS-, EC-no and further description are for "1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear". So it is not clear which substance should be included in to Annex VI. It might be better to check if both substances will be accepted to Annex VI.</p>				
Dossier Submitter's Response				
Thank you for your support and your comments.				
<p>As we indicated in the remarks of table 6 (part B, page 12): "DIHP (68515-50-4) is composed of branched isomers with 5 carbon side chains and methyl branching, and linear isomers with 6 carbon side chains to a varying extent. The branched isomers with CAS number 71850-09-4 are referred to the current CAS number 68515-50-4. Commercial blends of DIHP may contain up to 25% the linear di-n-hexyl phthalate (DnHP; CAS no 84-72-3). However, there is no information available on the exact concentrations of the isomers that constitute DIHP".</p> <p>1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear with CAS-number 68515-50-4 and EC-number 271-093-5 is a substance with non-defined structure. According to the CAS registry this substance has a variable composition and was introduced into the registry file for regulatory agencies (e.g. TSCA Inventory and EINECS).</p>				

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1,2-Benzenedicarboxylic acid, diisohexyl ester with CAS-number 71850-09-4 and EC-number 276-090-2 may also be of variable composition but in contrast to 68515-50-4 there are no linear hexyl groups in this molecule.

Hence, we agree that the substance name on the front page should be revised to "1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear" to correctly specify the substance identity. Similarly, the substance name in Table 1 should also be revised.

Moreover, our intention is to cover also CAS number 71850-09-4 in the classification proposal and should be included in the same entry of Annex VI as CAS number 68515-50-4.

RAC's response

RAC has clarified that the chemical name 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS nr. 68515-50-4, EC nr. 271-093-5) was correctly indicated as the IUPAC name in the CLH dossier, and it is hence this substance that is covered by the original CLH proposal.

It has also been clarified that the substance name diisohexyl phthalate (DIHP), although not being a correct chemical name, can cover both the substance with EC number 271-093-5, and the substance with EC number 276-090-2. It has hence been agreed that DIHP can be used in the opinion and background document as a "common name", but the correct chemical name 1,2-Benzenedicarboxylic acid, dihexylester, branched and linear should be included in the Annex VI entry.

RAC noted that the substance with EC number 276-090-2, CAS number 71850-09-4 is not notified in the Classification and labelling inventory, and hence has not been placed on the EU market.

It is not possible to add another substance with a different EC and CAS number after public consultation and since the CLH dossier submitted and published for public consultation covered only the substance with EC number 271-093-5, CAS number 68515-50-4, the opinion and the future entry in Annex VI to CLP will only cover the substance 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS nr. 68515-50-4, EC nr. 271-093-5).

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
17/09/2012	Netherlands		MSCA	6

Comment received

NL CA agrees with the proposal to classify DIHP for Repr. 1B – H360.

Dossier Submitter's Response

Thank you for your support.

RAC's response

The support is noted.

Date	Country	Organisation	Type of Organisation	Comment number
20/09/2012	Germany		MSCA	7

Comment received

A classification as Repr. 1B (CLP Regulation) based on read-across is justified. Some further comments are added below:

Page 12: In addition, it should be reflected whether a classification of the remaining phthalate isomer/mixture characterized by CAS no 71850-09-4 (EC no 276-090-2) and mentioned on page 12 is indicated.

On page 22 and 23 of the CLH report, the REACH guidance on read across (Chapter R.6: QSARs and grouping of chemicals) is mentioned. To improve acceptance of your proposal it could be added that transitional phthalates are even mentioned as an example for read-across in the REACH Guidance (see page 109 of the guidance)

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Page 23 ff.: The Applicability domain (AD) of the category should be more clearly described according the REACH Guidance document on grouping of chemicals (Chapter R.6):

"Applicability domain (AD) of the category

Describe the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members. Clearly indicate the borders of the category and for which chemicals the category does not hold. For example, the range of log Kow values or carbon chain lengths over which the category is applicable. The justification for the inclusion and/or exclusion rules should be reported under Section 2) Category justification below."

The simple definition of ortho-phthalates with carbon side chains in the length interval 3-6 would also include di-n-propyl phthalate which is not classified for reproductive toxicity. Therefore differentiation needs to be made between carbon backbone of 3-6 carbon atoms and the total number of carbon atoms in the side chain already in the definition.

Note that the category formally includes diisooheptyl phthalate (DiHepP, abbreviation not explained in report p. 40, CAS no 71888-89-6) which consists of at least 80% of methylhexyl phthalate and therefore the linear backbone is predominantly C6.

On page 26 the following sentences can be found: "The phthalates for which most data is available are DEHP, DBP and DIBP. Less information is available for DnHP and DPP. "In contrast it reads on page 38: "The most well studied phthalates in the current chemical grouping are DEHP and DBP. Less information is available for DIBP, DnHP and DPP." Please harmonize your assessment on DIBP.

Page 27: It reads: "Therefore, classification of DIHP as Repr. 1B is warranted. The specific hazardous effect (fertility or developmental toxicity) of the reproductive toxicity is however not indicated. The anticipated effective dose level for reproductive toxicity is approx. 100-700 mg/kg bw/day."

Some more explanation would be helpful why a specific hazardous effect (fertility or developmental toxicity) of the reproductive toxicity is not indicated. In contrast such a specification is given in your proposal according to Directive 67/548/EEC (Repr. Cat. 2; R60/R61) on page 5 and on 41 because R 60 clearly refers to fertility impairment and R 61 refers to developmental toxicity.

Furthermore some more information would be helpful how you arrive at the assumption that the anticipated effective dose level for reproductive toxicity is approx. 100-700 mg/kg bw/day.

On page 38 f: Phthalates with backbones of < 3 or > 7 carbon atoms should be mentioned earlier in the report in order to define the borders of the category.

On page 39 of the CLP report the relevance of the liver effects in Beagle dogs is not clear. Liver and reproductive effects might occur independently from each other.

p 39, Developmental toxicity: Reference should be added following the second sentence: U. Bernauer, E. Rosenthal, B. Heinrich-Hirsch, A. Schulte, Toxicology Letters 205S (2011) S180-S300.

p 39, Developmental toxicity: Chain lengths for DMP (1C) and DEP (2C) are mixed up. Please correct.

Page 41: Relevance to humans might need to be elaborated further, see: Heger, N.E.; Hall, S.J.; Sandrof, M.A.; McDonnell, E.V.; Hensley, J.B.; McDowell, E.N.; Martin, K.A.; Gaido, K.W.; Johnson, K.J.; Boekelheide, K., Environmental Health Perspectives, Vol. 120, No 8, 2012.

Dossier Submitter's Response

Thank you for your support and your comments.

Page 12: Classification of CAS No 71850-09-4 – please refer to the response to comment above (No 5).

Page 22 and 23: OK, thank you for the suggestion. We agree that it could be added that transitional phthalates are mentioned as an example for read-across for reproductive toxicity in the REACH Guidance (Chapter R6, page 109).

Page 23 ff.: The description of Applicability domain could be developed for clarification: "Criterion for selection of the *ortho*-phthalates was primarily the length of the alkyl chain: 3-6 carbon atoms; and the total number of carbon atoms in the side chain: at least four carbons, and maximum eight carbons in total in the side chain."

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Page 23:

Di-n-propyl phthalate has linear side chains of 3 carbons in length, and also has 3 carbons in total in the side chains and therefore does not fit in to the category that is applicable to phthalates with $\geq 3C$ in side chain length and in $\geq 4C$ in total in the side chain (please refer to comment above where we have clarified the boundaries of the category in the Applicability domain).

1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich (CAS nr 71888-86-9) has a predominant length of 6C carbons in the backbone, a typical molecular weight of 362.51 (range: 334-391) and is included in CLP Annex VI and classified as Repr. 1B; H360. DiHepP could therefore fit in the chemical grouping of phthalates in the current dossier as the DE CA mention. However, since DiHepP also has isomers with 7 carbon atoms in length (of unknown concentration) we decided not to include this phthalate in the chemical grouping not to compromise the robustness of the definition.

Page 26 and 38: We agree, the sentences should be corrected: Less information is available for DIBP, DnHP and DPP.

Page 27: Regarding specific hazardous effect (fertility or developmental) – please refer to the response to the comment from BE CA above.

Page 27: The indicated anticipated effective dose level in the report is a roughly estimated dose range. It may be reasonable to assume that DIHP is not among the most potent phthalates in the chemical category regarding reproductive effects. The approximate order of potency among the six reference phthalates (no data for DIPP was available) was estimated to be:

- fertility: DBP > DEHP > DIBP = DnHP > DPP
- development: DBP > DEHP > DIBP = DnHP > DPP
- repeated dose toxicity – reproductive organs: DEHP > DBP > DIBP > DPP

Based on the average LOAELs for reproductive effects (fertility and development; values indicated in table 19) for the most potent reference chemical and the least potent reference phthalate respectively we arrived at the rough estimate 100-700 mg/kg bw/day.

Page 38: We agree that the borders of the category could be defined more clearly earlier in the report, e.g. in the applicability domain (see our response to comment on Applicability domain above).

Page 39: We agree that there is no correlation between liver effects and reproductive effects. This was never the intention for presenting this data from repeated dose toxicity studies. Nevertheless, the liver is one of most common target organs (excluding the reproductive organs) of the phthalates in the category and by presenting this data we wanted to point to the similarity in effects induced by the phthalates. In addition, effects on testis are typically induced by C4-6 phthalates, and were also indicated in the repeated dose toxicity studies of DIHP. The intention was to strengthen the justification for the category by pointing at similarities in effects induced by the category members.

Page 39: Reference – could be included.

Page 39: We agree, should be corrected according to: DMP (1C) and DEP (2C)

Page 41: At present, human data from epidemiological studies and case studies are insufficient to determine a causal association between reproductive effects and phthalate exposure. However, 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 based on studies with *in utero* exposure of rats. In an attempt to refine models for studying the human fetal testis response to phthalates Mitchell et al., 2012 and Heger et al., 2012 (mentioned in the comment by DE CA) 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

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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 result if there is a reduction in androgen production/action in this period. In the studies by Heger et al and Mitchell et al, the exposure of human grafts may not be in the most sensitive time (estimated to be between 8 and 14 weeks of gestation in humans) for phthalate influences on steroidogenesis. Hence, 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.

RAC's response

RAC agrees with the comment and with the reply. There is little doubt that phthalates may present a hazard for humans.

ATTACHMENTS RECEIVED: none