Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Diisobutyl phthalate (DIBP)

EC number: 201-553-2
CAS number: 84-69-5

CLH-O-0000001412-86-24/F

Adopted

04 December 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON Diisobutyl phthalate

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 attachments including confidential documents received during the public consultation have been provided in full to the dossier submitter, to RAC members and to the Commission (after adoption of the RAC opinion). 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.

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Substance name: diisobutyl phthalate
CAS number: 84-69-5
EC number: 201-553-2
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.05.2014	Norway		MemberState	1
Comment received				
Norway would like to thank Germany for the proposal for harmonised classification and labelling of diisobutyl phthalate, CAS- no. 84-69-5. We support the proposal to remove the specific concentration limit (SCL) of 25 % for classification with Repr. 1B for diisobutyl phthalate, and to replace the SCL with the generic concentration limit (GCL) of 0,3 %. The calculated ED10 values shown are in the range of medium potency, and therefore, based on the calculations in accordance with the new method described in in the revised guidance on the application of the CLP criteria, a GCL of 0,3% is warranted.				
Dossier Submitter's Response				
The German CA acknowledges the Norwegian statement.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2014	Sweden		MemberState	2
Comment received				
The Swedish CA supports the removal of the specific concentration (SCL) limit for Repr. 1B of DIBP (CAS No 84-69-5) as specified in the proposal for adverse effects on the development of the offspring. We do not consider that the removal of SCL for adverse effects on sexual function and fertility has been justified in the current proposal, however we consider that re-evaluation of this SCL should also be addressed.				
Dossier Submitter's Response				
The German CA acknowledges the Swedish agreement to the removal of the SCL based on the adverse effects on the development. As a result of our evaluation the SCL has to be replaced by the generic concentration limit (GCL) of 0.3%. Based on a scientific argument for the GCL of 0.3% there is no room for other SCL values above the GCL. Therefore, we did not address the adverse effects on sexual function and fertility.				
RAC's response				
Noted. Discussion on the removal of SCL for fertility has been included in the RAC opinion.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
15.04.2014	Netherlands		MemberState	3
Comment received				
We agree with the proposal to remove the SCL of 25% for effects on development based on the provided data. However, DIBP also seems to have an SCL of 5% for effects on sexual function and fertility. No information is provided to justify that this SCL can also be removed. In our understanding this 5% SCL is a translation of the GCL of 5% for R62 and therefore not specific. As no SCL is required for effects on development, also no SCL is needed any more for effects on sexual function and fertility. Further, it can be questioned whether the presence of increased number of thoracic areolas and nipples itself should be considered a severe effect as all human males retain areolas and nipples and the adversity is doubtful. However, this effect is considered an important indicator of hormone disruption, which results in adverse effects.				
Dossier Submitter's Response				
The German CA acknowledges the agreement to the proposal to remove the SCL of 25% for effects on development. We have scientifically evaluated the SCL for effects on development and concluded that it has to be replaced by the generic concentration limit (GCL) of 0.3%. We agree with the Dutch position that there is no room for other SCL values above the GCL. The presence of increased number of thoracic areolas and nipples in male rat offspring is not the only argument in the CLH dossier and we considered it in agreement with the Netherlands as an important indicator of hormone disruption.				
RAC's response				
Noted. Discussion on the removal of SCL for fertility has been included in the RAC opinion. RAC agrees that retained thoracic areolas and nipples may not be considered as an adverse effect but considers it relevant to include this effect in the weight of evidence demonstrating medium potency, together with more severe adverse effects consistent with this indication of hormone disruption.				

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2014	Sweden		MemberState	4
Comment received				

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According to the CLH report (table 2, page 3), the current proposal for consideration by RAC is the removal of specific concentration limits (SCL) for 'Repr. 1B H360Df and Repr. 2 H361f'. However, it is unclear to us if the proposal intends to also remove the SCL for adverse effects on sexual function and fertility, since in the 'Conclusion on classification and labelling' (page 23) only conclusion on SCL for developmental toxicity is stated. In addition, only data supporting removal of SCL for developmental toxicity are presented in the CLH-proposal. According to the Guidance on the Application of the CLP Criteria (Version 4.0, November 2013) the effects on development and on sexual function and fertility are considered separately and thus the potency and resulting concentration limits have to be determined separately. It is not apparent that changing the SCL of developmental effects influences the SCL for sexual function and fertility. We consider that an evaluation of the SCL for adverse effects on sexual function and fertility should also be performed and the removal of the SCL should be justified and transparent as well. If removal of SCL for adverse effects on sexual function and fertility is warranted, and DIBP demonstrated to belong to the medium potency group, then the GCL of 3% is applicable. Or if DIBP is extremely potent, with an ED 10 below 4 mg/kg bw/day for adverse effects on sexual function and fertility, then a SCL of 0.3% is valid. For adverse effects on the development of the offspring we agree that DIBP is of medium potency resulting in a SCL of 0.3%, which corresponds to the generic concentration limit (GCL), and therefore the current SCL of ≥25% is not valid. The basis for arriving at the medium potency group was four ED 10 values in the range of 125 to 382 mg/kg bw/day with effects on total numbers of litters with skeletal malformations, male anogenital distance (PND 1), incidence of males with thoracic areolas and/or nipples at PND 12-14, and prostate weight at PNW 11-12. The histopathological effects in testis (degeneration of seminiferous tubules) and oligo-/azospermia in epididymes observed in male rats perinatally in the postnatal developmental study (Saillenfait et al., 2008) were not evaluated for ED 10 since the DS considered that there were sufficient endpoints for ED 10 calculations and that only a low numbers of testes were moderately effected. However, we consider that these effects could be used in determining the ED 10, both for developmental effects and effects on sexual function and fertility. (The total incidences for histological effects in testes were 8, 10, 25, 73 and 100% at 0, 125, 250, 500 and 625 mg/kg bw/d respectively. Incidences for histological effects graded 3-5 were 0, 5, 14, 55, 95% at 0, 125, 250, 500 and 625 mg/kg bw/d respectively. The LOAEL for these effects could be taken as 125 mg/kg bw/day, but no NOAEL could be set. To compensate for the lack of a NOAEL a modifying factor should be applied when calculating ED 10 according to the Guidance on the Application of the CLP Criteria (Version 4.0, November 2013)).
Dossier Submitter's Response

The DE CA acknowledges the agreement of Sweden with classification of DIBP as medium potency for developmental effects and the resulting SCL of 0.3%.

As pointed out in the answer to comment #2, we have developed a scientific argument for the GCL of 0.3% and therefore, there is no room for other SCL values above the GCL. In conclusion, we did not address the adverse effects on sexual function and fertility.

We acknowledge the Swedish suggestion to consider the histopathological effects in testes in male rats (Saillenfait et al., 2008) and propose additional rows in table 13 and 14 of the dossier as follows:

Table 13 (addition): Effects of prenatal DIBP treatment in rats (Saillenfait et al., 2008)

Dose (mg/kg bw/d)	0	125	250	500	625
Incidence of males with tubular degeneration-atrophy/hypoplasia of testes (Grade 3 to Grade 5)	0%	5%	17,9%	54,5%	95%

Calculation tubular degeneration-atrophy/hyperplasia of testes (grade 3 to 5)

Control incidence of males with tubular degeneration-atrophy/hyperplasia of testes (grade 3 to 5) is 0%, ED10 rate would be 10%.

Calculation: Interpolation between 125 mg/kg bw/d (5%) and 250 mg/kg bw/d (17,9%) leads to an ED10 of 173 mg/kg bw/d.

(250 - 125)/(17.9 -5.0) = 9.7 mg/kg per % (steepness).
Going from 5% to 10% requires addition of 5%. This equals 5% * 9.7 mg/kg per % = 48 plus 125 mg/kg bw/d as the starting point = **173 mg/kg bw/d**

Table 14 (addition: Compilation of sensitive endpoints for preliminary potency evaluation.

Endpoint	ED10 in mg/kg bw/d	Reference
Incidence of males with tubular degeneration-atrophy/hypoplasia of testes (Grade 3 to Grade 5)	173	Saillenfait et al., 2008

RAC's response

Noted. Discussion on the removal of SCL for fertility has been included in the RAC opinion.

RAC agrees that histopathological effects in the testes and epididymides are a relevant and sensitive effect for potency assessment of developmental effects. This element has been included in the opinion in support to the other effects demonstrating a medium potency for developmental toxicity of DIBP.

Date	Country	Organisation	Type of Organisation	Comment number
09.05.2014	Finland		MemberState	5
Comment received				

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The proposal is very clear and well written. The Finnish CA supports the proposed removal of SCL for Repr.1B; H360Df and Repr.2; H361f for Diisobutyl phthalate.
Dossier Submitter's Response
The DE CA acknowledges the Finnish statement.
RAC's response
Noted.