Committee for Risk Assessment

RAC

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

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4 December 2014

CLH-O-0000001412-86-24/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: diisobutyl phthalate

EC number: 201-553-2

CAS number: 84-69-5

The proposal was submitted by **Germany** and received by RAC on **10 March 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **25 March 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **9 May 2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Elodie Pasquier**

Co-Rapporteur, appointed by RAC: -

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was reached on **4 December 2014.** The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **diisobutyl phthalate** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Entry	607-623-00-2	diisobutyl phthalate	201-553-2	84-69-5	Repr. 1B	H360Df	GHS08 Dgr	H360Df		Repr. 1B; H360Df: C ≥ 25 % Repr. 2; H361f: 5 % ≤ C < 25 %	
Proposal for RAC	607-623-00-2	diisobutyl phthalate	201-553-2	84-69-5	Removal of SCL						
RAC opinion	607-623-00-2	diisobutyl phthalate	201-553-2	84-69-5	Removal of SCL						
Resulting Annex VI entry if agreed by COM	607-623-00-2	diisobutyl phthalate	201-553-2	84-69-5	Repr. 1B	H360Df	GHS08 Dgr	H360Df			

SCIENTIFIC GROUNDS FOR THE OPINION

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Diisobutyl phthalate (DIBP) has an existing entry in Annex VI to the CLP Regulation, as Repr. 1B; H360Df: C ≥ 25 % and Repr. 2; H361f: 5 % ≤ C < 25 %. However, the specific concentration limit (SCL) which is currently on Annex VI is based on an outdated method, whereas a new method has meanwhile been agreed in ECHA's Guidance on the Application of the CLP Criteria, (Version 4, November 2013). The dossier submitter's proposal is for removal of the SCL from Annex VI.

The dossier submitter (DS) referred to two studies in rats, one prenatal development and one post natal development study. The grounds for classification were not challenged by the DS. Adverse effects on development were seen in both studies, which were not deemed to be caused by secondary, non-specific toxic effects.

The DS calculated an ED_{10} value for the most sensitive adverse effects observed and found them to range from 125 mg/kg/day to 382 mg/kg/day. Thus the calculated ED_{10} values were between 4 and 400 mg/kg/day, i.e. in the range of medium potency substances.

The DS also evaluated possible modifying factors and concluded that there were no relevant modifying factors to be taken into account.

The DS concluded that an SCL for this substance is not warranted, but that instead the Generic concentration limit (GCL) of 0.3% should apply.

Comments received during public consultation

Four MSCAs were in support of the proposal, while some others raised specific comments.
Two MSCA requested consideration and justification of the removal of the SCL for fertility.
One MSCA questioned whether the presence of an increased number of thoracic areolae and nipples itself should be considered a sufficiently severe effect for ED_{10} calculation, but recognised that it is considered an important indicator of hormone disruption which results in adverse effects. Another MSCA proposed also considering the testicular findings, to which the DS agreed. The response and additional data provided by the DS in response to the comment can be found in the Background Document (BD).

The ED_{10} value calculated based on the additional data was also within the range of those presented in the CLH report.

Assessment and comparison with the classification criteria

Considerations about an SCL for developmental effects

Two key developmental toxicity studies performed in rats by the oral route were included by the DS in the analyses to support the removal of SCL (Saillenfait, 2006; Saillenfait, 2008). RAC agrees with the justification of the DS for the exclusion of three other developmental toxicity studies based on an insufficient number of animals (5-8 by treatment group) and/or use of a single treatment group that does not allow a robust calculation of the ED_{10}.
For each of the two key studies, the DS calculated the ED_{10} values for the most sensitive parameters by linear interpolation, in accordance with the ECHA guidance for setting SCL.
According to CLP Guidance, the ED_{10} value is the lowest dose which induces reproductive toxic effects fulfilling the criteria for classification for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence.

In the study by Saillenfait (2006), DIBP induced a decrease in fetal body weight and increased incidences of resorptions as well as external, visceral and skeletal malformations. ED_{10} values were not calculated in the CLH report for each effect. However, the analysis of the dose-response relationship (see table 1 below) for the different adverse effects as well as for the visceral variation undescended testes (consistent with impairment of the male reproductive development)

confirms the conclusion of the DS that the most sensitive effect in this study for ED_{10} calculation is induction of skeletal malformations on a litter basis.
The ED_{10} for skeletal malformations is **382 mg/kg** on a litter basis while ED_{10} values for other effects exceed the upper boundary of 400 mg/kg for medium potency.

Table 1 – dose response of developmental effects in Saillenfait (2006)

Dose (mg/kg)	0	250	500	750	1000	ED_{10}[a]
% post-implant. loss per litter	6.7±7.6%	11.0±23.6%	13.9±20.9%	28.2±18.9%*	59.6±21.5%*	$500<ED_{10}<750$
Fetal body weight (g)	5.71±0.28	5.69±0.33	5.31±0.40*	4.72±0.33*	4.32±0.35*	$500<ED_{10}<750$
% fetuses with external malf.	0	0	0	2.4%	5.4%	> 1000
% litters with external malf.	0	0	0	19%	22.2%	$500<ED_{10}<750$
% fetuses with visceral malf.	0	1.4%	1.7%	12.3%	17.9%	$500<ED_{10}<750$
% litters with visceral malf.	0	4.8%	9.5%	38.1%	44.4%	$500<ED_{10}<750$
% male fetuses with testis, ectopic	0	0	5.5%	54%	88%	$500<ED_{10}<750$
% litters with testis, ectopic	0	0	9%	76%	88%	$500<ED_{10}<750$
% fetuses with skeletal malf.	0	0	3.4%	17.0%	61.8%	621
% litters with skeletal malf.	0	0	19.0%	52.4%	83.3%	**382**

*statistically significant

[a] calculated by DS or estimated by RAC

In the study by Saillenfait (2008), in male pups DIBP induced a decrease in body weight, a decrease in absolute and relative anogenital distance (AGD) at PND 1, retention of thoracic areolae and/or nipples and a delay of the onset of puberty (preputial separation (PPS)). At postnatal week 11-12 or 16-17, mature males displayed severe malformations of the reproductive tract and underdeveloped reproductive organs, with hypospadias, unilateral undescended testes and decrease in prostate weight (post-natal week 11-12) being the most sensitive effets. Histological examination revealed oligo/azoospermia in the epididymides and tubular degeneration and necrosis in the testes.
The analysis of the dose-response (see table 2 below) for the most sensitive effects confirms the conclusion of the DS that the lowest ED_{10} in this study is **125 mg/kg** based on decreased prostate weights in mature males and corresponds to medium potency (i.e. boundaries: 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day).
This is further supported by ED_{10} values for decreased AGD, retention of areolas, azoospermia in epidydimides and tubular degeneration/atrophy, which are also in the range 4-400 mg/kg and therefore considered as medium potency.
For the decrease in AGD, RAC notes that a more appropriate assessment of potency should be based on a percentage of feminisation relative to an AGD in control females, representing 100% feminisation. This is however not considered to impact on the overall assessment of the developmental potency of DIBP.

Table 2 – dose response of developmental effects in Saillenfait (2008)

Dose (mg/kg)	0	125	250	500	625	ED_{10} [a]
Male pup body weight PND1 (g)	7.19±0.71	7.10±0.70	7.04±0.43	7.03±0.53	6.45±0.60*	$500<ED_{10}<625$
Male AGD at PND 1 (mm)	2.55±0.17	2.44±0.15	2.28±0.30*	2.02±0.13**	1.98±0.16**	**234**
Incidence of males with thoracic areolae and/or nipples at PNW 12-14.	0%	0%	8.3%	59.5%	73.7%	**258**
Mean litter age at PPS (days)	46.9±1.5	45.1±1.6*	46.3±1.8	51.5±3.1*	49.8±3.2*	Not appropriate
Incidence of hypospadias in adult males	0%	0%	0%	11%	56%	Approx. 500 mg/kg

*statistically significant

[a] calculated by DS or estimated by RAC
[b] Calculated by RAC by interpolation between 250 mg/kg (3.6%) and 500 mg/kg (13.7%):
(500-250) / (13.7-3.6) = 25 mg/kg / % (steepness)
Note: the difference between 3.6 and 10% is +6.4%. This equals to 6.4*25= 160 plus 250 as the starting point = 410 mg/kg.

Overall, the most sensitive ED_{10} values derived by the DS and agreed by RAC correspond to the medium potency group (i.e. boundaries: 4 mg/kg bw/day < ED_{10} value < 400 mg/kg bw/day) for DIBP.

Modifying Factors

According to the CLP Guidance (section 3.7.2.5.5), modifying factors should also be considered when deriving an SCL. The modifying factors include type and severity of the effect observed, data availability (e.g. limitations in the database), dose-response relationship, mode or mechanism of action, toxicokinetics and bioaccumulation of substances. These modifying factors are used to account for case-specific data situations which indicate that the potency group for a substance, as obtained by the preliminary assessment, should be changed. The modifying factors were assessed for DIBP as follows:

Dose-response relationship:
No adaptations of the potency group are considered necessary on this basis, as most calculated ED_{10} values were not borderline.

Type and severity of the effect:
The type of effects observed in reproductive toxicity studies following exposure to DIBP included malformations. These are considered as severe and do not change the potency group.

Data availability:
The available data for DIBP were considered as adequate and do not justify adaptation of the potency group.

Mode or mechanism of action:
The mechanism of action of DIBP (antiandrogen activity) is considered relevant for humans. Therefore adaptation of the potency group is not necessary.

Toxicokinetics:
No toxicokinetic data are presented in the CLH report. It is noted that RAC concluded in its opinion on a proposal to restrict four phthalates including DIBP[1] that the available data do not allow a

[1] Opinion of the Committee for Risk Assessment (RAC) on an Annex XV dossier proposing restrictions on four phthalates. Adopted on 15 June 2012. ECHA/RAC/RES-O-0000001412-86-07/F

conclusion to be drawn on whether humans are less, equally or more sensitive than rats. No adaption to the potency group is therefore justified.

Bio-accumulation of substance:
No evidence for bioaccumulation is presented in the dossier and adaptation of the potency group is not necessary.

Conclusion on modifying factors:
Based on the available data, RAC considers that the consideration of possible modifying factors does not affect the potency of DIBP.

Therefore, DIBP is considered to be a medium potency reproductive toxicant for developmental toxicity and RAC agrees that according to CLP Guidance table 3.7.2-e, the GCL of 0.3% should be applied for DIBP developmental toxicity and the current SCL of 25% should be removed.

Considerations about an SCL for fertility effects

No specific justification for the removal of the SCL for fertility was given in the CLH report. The DS concludes that the application of a GCL for developmental toxicity (Repr. 1B at concentration > 0.3%) would be inconsistent with an SCL of 5% for fertility. However, the CLP guidance states in section 3.7.2.5.6.1 that "*The potency and resulting concentration limits have to be determined separately for the two main types of reproductive toxic effects. [...] These concentration limits will in all cases trigger different specifications of the hazard statements for the two main types of effects, to be applied to mixtures containing the substance.*"

RAC therefore concludes that although classification as Repr. 1B will apply from 0.3%, as a consequence of the removal of the SCL for development, the existing SCL for fertility has implications for the labelling specifications and its removal needs to be justified.

RAC notes that only SCLs for developmental toxicity were agreed by TC C&L during the last discussions on DIBP and no SCL for fertility was introduced in the Dangerous Substance Directive (DSD). The current SCL for fertility corresponds to the previous GCL under the DSD. Their introduction in the 1st ATP of CLP most probably results from a translation mistake from DSD to CLP and therefore their removal is justified.

As a supportive element, RAC notes that although fertility has not been thoroughly evaluated in the present CLH report, the data presented demonstrate that the male reproductive tract is a target for DIBP, with medium potency, during its development. Several of the most sensitive calculated developmental ED_{10} values involve effects on the developing male reproductive tract. In particular, the ED_{10} for decreased prostate weight, azoospermia in epidydimides and tubular degeneration/atrophy (Saillenfait, 2008) are in the range of 4-400 mg/kg defining medium potency and do not support the existing SCL of 5% for fertility.

Therefore, RAC considers that the GCL of 3% should be applied for fertility classification of DIBP and the current SCL of 5% should be removed.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).