Committee for Risk Assessment

RAC

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/F

Adopted

7 June 2013

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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:

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

EC number: 271-093-5

CAS number: 68515-50-4

The proposal was submitted by **Sweden** and received by the RAC on **7 August2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Sweden 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 **7 August 2012**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **21/09/2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Benjamin Piña**

Co-rapporteur, appointed by RAC: **Marja Pronk**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **7 June 2013** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that 1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear should be classified and labelled as follows:

Classification and labelling in accordance with the CLP

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard state-ment Code	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard stateme nt Code(s)		
Current Annex VI entry		–									
Dossier submitter's proposal		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. 1B	H360	GHS08 Dgr	H360			
RAC opinion		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

Classification and labelling in accordance with the DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry		–						
Dossier submitter's proposal		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. Cat. 2; R60-61	T R: 60-61 S: not included		
RAC opinion		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. Cat. 2; R60-61	T R: 60-61 S: 45-53		
Resulting Annex VI entry if agreed by COM		1,2-Benzenedicarboxylic acid, dihexyl ester, branched and linear	271-093-5	68515-50-4	Repr. Cat. 2; R60-61	T R: 60-61 S: 45-53		

SCIENTIFIC GROUNDS FOR THE OPINION

General comment

During the public consultation, one MSCA commented that the identity of the substance to be covered by the CLH dossier was unclear, referring to the EC number and CAS number on the front page of the CLH report, which is for 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear, and not for diisohexyl phthalate (DIHP). The dossier submitter in their response indicated that the CLH proposal is intended to cover 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (EC nr. 271-093-5, CAS nr. 68515-50-4) and, in the same entry, diisohexyl phthalate (DIHP; EC nr. 276-090-2, CAS nr. 71850-09-4). It was further clarified that 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear, is a reaction product containing branched isomers with 5 carbon side chains and methyl branching (DIHP), and linear isomers with 6 carbon side chains (di-n-hexyl phthalate (DnHP)) to a varying extent. Commercial blends may contain up to 25% of DnHP. The branched part of the reaction product is DIHP (synonym: 1,2-benzenedicarboxylic acid, diisohexyl ester), which may also be of variable composition but does not contain linear groups.

RAC has clarified that the chemical name 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (EC nr. 271-093-5, CAS nr. 68515-50-4) 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)' may be ambiguous as it is used both as a common name for 1,2-Benzenedicarboxylic acid, dihexylester, branched and liner, and as the chemical name for the substance with the EC number 276-090-2. It has hence been agreed that while 'DIHP' can still be used for practical reasons in the opinion and background document, as a common name representing the substance with EC number 271-093-5, the correct chemical name '1,2-Benzenedicarboxylic acid, dihexylester, branched and linear' should be included in the Annex VI entry.

It should be 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, this opinion and the future entry in Annex VI to CLP will only cover the substance 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear.

Evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The data on the toxicity of DIHP or the total reaction product are very limited and there are no mammalian reproductive or developmental toxicity studies available for this substance (or the total reaction product).

The estrogenic activity of DIHP has been examined using a series of short-term *in vitro* and *in vivo* assays. Some *in vitro* studies suggest that DIHP (or an isomeric mixture of DIHP) was able to induce human estrogen receptor α-agonistic activity as well as androgen receptor-antagonistic activities, but did not induce a vaginal cornification response or an increase in uterine weight *in vivo*.

The dossier submitter performed an extensive and in the view of the Committee, well-conducted read-across analysis based on the existing data on reproductive and developmental toxicity of the transitional phthalates with high structural similarity to DIHP, which includes DIBP, DBP, DIPP, DPP, DnHP and DEHP. These phthalates constitute a clear structural category that allows for read-across to fill data gaps for DIHP and supports the conclusion that DIHP is a reproductive

toxicant. Adverse effects in the developing male pup, including malformations of the male reproductive system and feminisation of male sexual differentiation, appear to be the most sensitive developmental endpoints. Other relevant effects are decreased testes weight, decreased sperm production, and decreased testosterone levels.

Comments received during public consultation

Comments were received from five MSCAs, all of which supported the classification proposal of the dossier submitter. One MSCA queried whether a more specific hazard statement (i.e., H360FD) would be more appropriate. As the proposed classification relates to both fertility and developmental toxicity, the dossier submitter in their response indicated that H360FD could indeed be appropriate, but noted that not all of the substances used in the category approach have this hazard statement (DEHP, DIPP, DPP and DnHP are classified as H360FD, but the DIBP and DBP classification is H360Df).

Assessment and comparison with the classification criteria

The CLP criteria for classification as Repr. 1B requires data from animal studies, with evidence of effects on the reproductive system in the absence of major general toxic effects, and with a MoA relevant to humans. While there are no such data for DIHP or the total reaction product, the proposed classification is based on read-across from other phthalates with similar chemical structure, for which consistent data exist for adverse reproductive effects.

To allow for such read-across, CLP requires that a group of substances are identified which have similar physicochemical, toxicological and ecotoxicological properties, based on their structural similarities, common functional group(s), common precursors and/or a consistent pattern of variation of the relevant biological potency across the category. These conditions are met in the case of DIHP, where a category was built consisting of seven structurally similar *ortho*-phthalates (DIBP, DBP, DIPP, DPP, DIHP, DnHP and DEHP) with increasing alkyl side-chain length (C3(C4), C4, C4(C5), C5, C5(C6), C6, C6(C8), respectively).

RAC considered the justification given for this chemical category by the dossier submitter well-explained and well-argued. RAC supported the conclusion of the dossier submitter that there was clear evidence of reproductive toxicity (both fertility and developmental toxicity) as an intrinsic and hazardous property of the transitional phthalates (supported with data on DIBP) in the category, all of which are already classified as Repr. 1B (DIBP, DBP, DIPP, DPP, and DEHP) or about to be classified in this hazard class and category (DnHP; RAC has adopted the opinion as Repr. 1B, but DnHP is not yet included in the list of substances with a harmonised classification in Annex VI to CLP).

The proposed read-across from these phthalates to DIHP and the total reaction product was therefore considered justified, and the proposed classification of these compounds as Repr. 1B – H360 was supported. Repr. 2 is considered inappropriate, as the read-across is based on data where reproductive effects have been seen in at least two species (rat and mouse) and the proposed mechanism of action is considered relevant to humans. In the absence of relevant toxicity data on the compounds themselves, it is difficult to decide on a specific hazard statement under CLP and on the most appropriate category under DSD (in particular for fertility, since that classification is not the same for the various phthalates in the category). In the response to the comments received during public consultation, the dossier submitter expressed a preference for H360FD, which is consistent with the proposal for Repr. Cat. 2; R60-61 under DSD. RAC supported this classification, as the read-across data includes endpoints for both fertility and developmental toxicity. Moreover, the substances on both sides of DIHP in the category (based on alkyl side-chain length; DIPP and DPP having shorter alkyl side-chains, and DnHP and DEHP having longer alkyl side chains) have H360FD, and one of these (DnHP) is even part of the total reaction product.

Evaluation of environmental hazards

Summary of the Dossier submitter's proposal

Not evaluated in this dossier.

Comments received during public consultation

One MSCA pointed out that DBP, DIPP and DPP are classified as Aquatic Acute 1 – H400, and wondered whether this classification should be applied to DIHP. The dossier submitter responded that they agree that the chemical grouping approach could also be used for environmental hazards, but since this hazard class is not among the hazard classes to be harmonized it was not within the scope of the proposal.

Assessment and comparison with the classification criteria

Since the dossier submitter did not take this endpoint on board in the CLH proposal, RAC did not assess the endpoint.

ANNEXES:

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

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and the RAC (excl. confidential information).