

Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of

diisohexyl phthalate

EC Number: 276-090-2
CAS Number: 71850-09-4

CLH-O-0000001412-86-158/F

Adopted
9 June 2017

9 June 2017

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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 Regulation (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: diisohexyl phthalate

EC Number: 276-090-2

CAS Number: 71850-09-4

The proposal was submitted by **Sweden** and received by RAC on **6 July 2016**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

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 **16 August 2016**. Concerned parties and Member State Competent Authorities (MSCAs) were invited to submit comments and contributions by **30 September 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Stine Husa**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **9 June 2017** by **consensus**.

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 statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	xxx-xxx-xx-x	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
RAC opinion	xxx-xxx-xx-x	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by COM	xxx-xxx-xx-x	diisohexyl phthalate	276-090-2	71850-09-4	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

GROUNDNS FOR ADOPTION OF THE OPINION

RAC general comment

RAC adopted an opinion for harmonised classification of 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS number 68515-50-4, DHP) on 7 June 2013. The substance was classified as Repr. 1B; H360FD. 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear is composed of branched and linear C6 isomers to a varying extent, and diisohexyl phthalate (DIHP) with CAS number 71850-09-4 is one of the branched constituents.

At the time, the intention of the dossier submitter for 1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (CAS number 68515-50-4, DHP) was to include CAS number 71850-09-4 in the same classification proposal, however due to procedural issues this was not possible. Hence, an additional proposal for a harmonised classification of 1,2-benzenedicarboxylic acid, dihexyl ester (CAS number 71850-09-4, DIHP) was submitted to ECHA.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

There are no mammalian reproductive toxicity studies available for DIHP and the proposal is therefore based on read-across, using a chemical category approach. DIHP has a branched structure and is one of the isomers in DHP, which consist of a mixture of branched and linear isomers.

The estrogenic activity of an isomeric mixture of DHP (including DIHP) has been examined using a series of short-term *in vitro* and *in vivo* assays. Results from some *in vitro* studies suggest that an isomeric mixture of DHP 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 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 (the full names and chemical structures for each of these are presented in the figure below).

DIPP was included in the group, but it should be noted that there are no data available for this substance and the classification of this substance was based on read-across using data from other phthalates.

DHP, which to a large extent consists of branched isomers including DIHP, was also included in the category. The harmonised classification for reproductive toxicity of DHP is largely based on read-across using data from other phthalates.

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 three MSCAs, all of which supported the classification proposal of the dossier submitter. One MSCA pointed out that not all C4-C6 phthalates in the group have a harmonised classification as Repr. 1B for fertility. The DS in their response indicated that H360FD would be appropriate, but noted that not all of the substances used in the category approach have this hazard statement (DEHP, DIPP, DPP, DHP and DnHP are classified as H360FD, while DIBP and DBP are classified as H360Df).

One MSCA briefly mentioned studies questioning the mode of action and human relevance of the anti-androgenic effects of phthalates, but no new references were included in the comment. The DS in their response referred to studies indicating that there might be some differences in the response to phthalates between humans and rats, and that humans might not be more sensitive to phthalates than rats. However, the results were not considered to be conclusive.

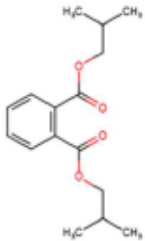
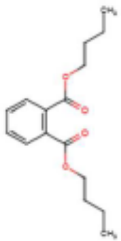
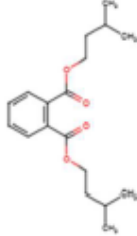
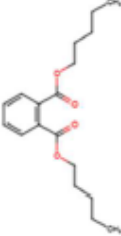
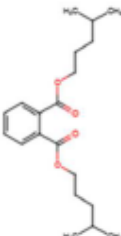
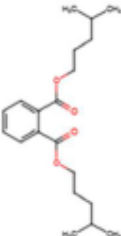
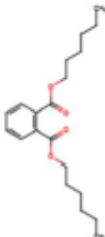
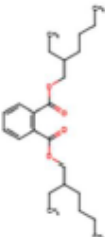
One commenting MSCA suggested removing DHP from the read-across justification, since the classification for this substance already is based on a read-across. The DS responded that DHP is included in the group as a supporting member since DIHP is only one of the branched constituents of DHP.

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 mode of action relevant to humans. There are no such data for DIHP, and the proposed classification is based on read-across from other phthalates with similar chemical structures, for which there are consistent data for adverse reproductive effects.

To enable such read-across, the CLP Regulation 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 eight structurally similar ortho-phthalates (DIBP, DBP, DIPP, DPP, DIHP, DHP, DnHP and DEHP) with increasing alkyl side-chain length (C3(C4), C4, C4(C5), C5, C5(C6), C5(C6), C6, C6(C8)), respectively (see figure below).

Figure: Category members are eight ortho-phthalates with carbon side chains in the interval of 3-6 carbon atoms.

<p>Diisobutyl phthalate (DIBP) CAS 84-69-5</p>  <p>3C (4C)</p>	<p>Di-n-butyl phthalate (DBP) CAS 84-74-2</p>  <p>4C</p>
<p>Diisopentyl phthalate (DIPP) CAS 605-50-5</p>  <p>4C (5C)</p>	<p>Di-n-pentyl phthalate (DPP) CAS 131-18-0</p>  <p>5C</p>
<p>Diisohexyl phthalate (DIHP) CAS 71850-09-4</p>  <p>5C (6C)</p>	<p>1,2-benzenedicarboxylic acid, dihexyl ester, branched and linear (DHP) CAS 68515-50-4</p>  <p>5C* (6C) (*predominant length, representative structure)</p>
<p>Di-n-hexyl phthalate (DnHP) CAS 84-75-3</p>  <p>6C</p>	<p>Diethylhexyl phthalate (DEHP) CAS 117-81-7</p>  <p>6C (8C)</p>

RAC considers the justification given for this chemical category by the dossier submitter well-explained and well-argued. RAC supports the conclusion of the dossier submitter that there is clear evidence of reproductive toxicity (both fertility and developmental toxicity) as an intrinsic and hazardous property of the transitional phthalates in the category, all of which are already classified (in Annex VI to CLP) as Repr. 1B.

There are no relevant toxicity data for DIHP. Reduced fertility and number of viable offspring and effects on male reproductive organs (testicular lesions) were seen following treatment with DPP, DnHP and DEHP (all of which have harmonised classifications as Repr. 1B for fertility). In addition, there are data from two 90-day (oral) repeated dose toxicity studies available for 1,2-

benzenedicarboxylic acid, dihexyl ester, branched and linear (including branched isomer CAS no. 71850-09-4), in which decreased testes weight and atrophy of the spermatogenic epithelium were seen in rats and testicular changes were seen in dogs. Developmental toxicity findings in those members of the category for which data were available (DIBP, DBP, DPP, DnHP and DEHP, all of which have harmonised classifications as Repr. 1B for development) included decreased anogenital distance, degeneration of seminiferous tubules and testicular damage.

It is noted that for fertility the classification for the various phthalates in the category varies between Repr. 2 and Repr. 1B. However, classification as Repr. 2 for fertility is considered inappropriate, as the read-across is based on data where reproductive effects relevant for classification as Repr. 1B have been seen in at least two species (rat and mouse) and the proposed mechanism of action is considered relevant to humans. Furthermore, the read-across data include endpoints for both fertility and developmental toxicity and the substances in the category include both phthalates with shorter and longer chain lengths compared to DIHP, which are classified as Repr. 1B H360FD (based on alkyl side-chain length; DIPP and DPP having shorter alkyl side-chains, and DnHP and DEHP having longer alkyl side chains). The proposed read-across from these phthalates to DIHP is therefore considered justified, and **RAC agrees with the DS that classification of DIHP as Repr. 1B; H360FD is warranted.**

ANNEXES:

- Annex 1 The 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 RAC (excluding confidential information).