Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

di-n-hexyl phthalate (DnHP)

ECHA/RAC/CLH-O-0000001541-83-03/F

Adopted

13 September 2011

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

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

Substance Name: ***di-n-hexyl phthalate (DnHP)***

EC Number: ***201-559-5***

CAS Number: ***84-75-3***

The proposal was submitted by ***France***
and received by RAC on ***17 January 2011***.

The proposed harmonised classification:

	CLP Regulation (EC) No 1272/2008	Directive 67/548/EEC
Current entry in Annex VI CLP Regulation	None	none
Current proposal for consideration by RAC	Repr. 1B – H 360FD	Repr. Cat. 2; R61 Repr. Cat. 2; R60
Resulting harmonised classification (future entry in Annex VI of CLP Regulation)	Repr. 1B – H 360FD	Repr. Cat. 2; R61 Repr. Cat. 2; R60

PROCESS FOR ADOPTION OF THE OPINION

France 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp*** on ***17 January 2011***. Parties concerned and MSCAs were invited to submit comments and contributions by ***03 March 2011***.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: ***Bert-Ove Lund***
Co-rapporteur, appointed by RAC: ***Eugenio Vilanova***

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

The RAC opinion on the proposed harmonised classification and labelling has been reached on ***13 September 2011,*** in accordance with Article 37(4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

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

OPINION OF RAC

The RAC adopted the opinion that di-n-hexyl phthalate (DnHP) should be classified and labelled as follows:

Classification & Labelling in accordance with the CLP Regulation

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)		
	di-n-hexyl phthalate (DnHP)	201-559-5	84-75-3	Repr. 1B	H 360FD	GHS08 Dgr	H 360FD			

Classification & Labelling in accordance with Directive 67/548/EEC:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	di-n-hexyl phthalate (DnHP)	201-559-5	84-75-3	Repr. Cat. 2; R61 Repr. Cat. 2; R60	T R: 60/61 S: S(1/2)-45-53		

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by ***France***.

Reproductive Toxicity

The dossier submitter has prepared a thorough analysis of the available data, and RAC supports that the data warrant classification for reproductive toxicity, including effects on sexual function and fertility as well as developmental toxicity.

Regarding effects of DnHP on fertility, a dose-related decrease in the proportion of pairs able to produce litter (100-74-5-0% fertility in the pairs exposed to 0 – (380-430) – (800-880) – (1670-1870) mg/kg/day for 7 days prior to and during the 98-day cohabituation period) together with a decreased number of live pups per litter and proportion of pups born alive have been observed in a continuous breeding study in mice (Lamb J.C. *et al.*, 1987). These effects were observed from the low dose 370-430 mg/kg onward in absence of parental toxicity. Only control and high dose animals were necropsied, no histological findings were observed in reproductive organs in females, whereas findings in the treated males (1670-1870 mg/kg/day) included severe effects on testis weight, epididymal sperm concentration and motility, and extensive atrophy of the seminiferous tubules, providing a plausible basis for the decreased mating index in the mouse study. There were no live pups at the high dose, one litter with four pups at middle dose, and at the low dose a significant reduction of number of litters per pair (3.4 vs 4.9) and the number of live pups per litter (3.4 vs 12.3). The mating index in crossover mating trials showed that treated females were cycling and could be receptive and that mating capability was reduced in the group of treated males. Some systemic effects (decreased mean body weight (6-10%), increased liver weight (32-34%), and decreased kidney weight (6-9%)) were described in both sexes at the high dose but the reproductive effects occurred also at the low and middle doses.

Testicular effects were also observed in adult rats exposed during gestation. At a dose of 250 mg/kg/day, intense degeneration or complete athrophy of the seminiferous tubules were noted in 25% of the males (Saillenfait *et al.*, 2009b), correlating with oligospermia and azoospermia in the corresponding epididymes. Some of these cases (6%) were explained by occurring in undescended testis. The testicular toxicity will result in a decreased fertility, but the potency in rats has not been assessed in a 2-generation study. Developmental toxicity of DnHP was shown in rats where marked embryo mortality was consistently observed at 750 mg/kg/day (exposure on GD 6-20) with high incidence of post implantation loss (Saillenfait *et al.*, 2009a) and at 625 mg/kg/day in the preliminary study of Saillenfait et al. (exposure on GD 12-20) (Saillenfait *et al.*, 2009b). DnHP also decreased the number of live pups per litter as from exposure levels of 370-430 mg/kg/day in a continuous breeding study in mice (Lamb et al, 1987).

Dose-related developmental effects were observed, such as delay of ossification and an increase in the incidence of skeletal variants (e.g. supernumerary lumbar ribs) that appeared at 250 mg/kg/day onward, as well as presence of malformations (cleft palates and eye defects) and significant decreases in foetal weight at 500 and 750 mg/kg/day (Saillenfait et al 2009a). These effects occurred in absence of maternal toxicity.

DnHP induced a significant and dose-related decrease in the anogenital distance and increased incidence of thoracic aerolas and/or nipples of male rat foetuses at all doses (Saillenfait et al, 2009a;Saillenfait et al 2009b), and there was a significant increase in the incidence of male

fetuses with undescended testis at 500 and 750 mg/kg/day of DnHP. Malformations of the male reproductive tract were still present at adult age and were accompanied by histological effects on epidydimes and testes. Prenatal exposure to DnHP therefore caused permanent and dose-related developmental toxicity on the male reproductive tract (Saillenfait et al, 2009a; Saillenfait et al, 2009b). This is in line with impairment of fertility in males as identified in the fertility studies considering that *in utero* development is a sensitive window for the reproductive system and that the toxicity seems to affect Sertoli cells in particular (Foster et al. 2001; Gray and Gangolli 1986).

The information from experimental studies on DnHP is sufficient in itself as supporting the proposal for classification for effects on sexual function and fertility and development. A read across analysis based on other C4-C6 phthalates is considered as supportive information, as the effects and dose-effect relationships for DnHP are compatible with those for the other phthalates. Effects of phthalates on fertility and development are dependent on their chemical structure. It is generally acknowledged that ortho-phthalic esters with a linear portion of four to six carbons in their alkyl side chains (e.g., DEHP, DBP, and BBP) will produce developmental and reproductive toxic effects in rodents. DnHP has a straight backbone chain of six carbons, and based on the similarity in structure and toxicity profile with those of DEHP, DBP, and BBP, the reproductive toxicity observed by DnHP is supported by read across arguments. The read across is particularly relevant for DEHP-DnHP, which have very similar chemical structures and similar toxicological profiles. The proposed classification for DnHP is thus identical to the current classification for DEHP.

Six member states have commented the proposal. They all support classification for developmental toxicity, and five support classification for effects on fertility. One member state has questioned whether the evidence for effects on sexual function and fertility is sufficient for classification. RAC is of the opinion that the severe testicular toxicity observed in rats at doses well below the limit dose is a sufficient basis for classification. The testicular toxicity, observed in developmental toxicity studies, will result in a decreased fertility, although this has not been studied in a 2-generation study. Classification for effects on sexual function and fertility is also supported by a decreased mating index in mice and read across from similar phthalates with C4-C6 carbon chains, which are presently classified for effects on sexual function and fertility.

Overall, based on animal studies:

- DnHP dose-dependently reduces the fertility of adult mice in a continuous breeding study;
- Teratogenicity has been described in rats with numerous malformations at higher doses. Specifically, DnHP impacts the male reproductive system with permanent alteration of testis, epididymis and seminal vesicle weight and histopathology in rats exposed *in utero*, likely leading to impairment of fertility after repeated exposure;
- DnHP induces embryo-mortality (decrease in litter and pups production) in absence of maternal body weight modification in mice and rats by oral route;
- Embryo-toxicity has been described in rats with reduced pup body weight, delayed ossification and increased incidence of skeletal variants.

It is concluded that the data provided in the report provide **clear evidence** of teratogenic and foeto-toxic effects of DnHP. They also provide **clear evidence** of an adverse effect on male

sexual function and fertility. Moreover, there is no mechanistic evidence that could lead to think that these effects are not relevant for human.

When comparing the data with the criteria, RAC is of the opinion that there is clear evidence of effects both on fertility and development supporting CLP classification in Repr. Cat. 1B. Repr Cat. 1A is not appropriate considering the lack of human data. Repr Cat. 2 is not appropriate as the database gives clear evidence and not only 'some evidence' as required for Cat. 2. The corresponding classification resulting according to Directive 67/548 (DSD) is Repr. Cat. 2; R 60-61.

Additional information

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[1]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information)

[1] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal. The BD is based on the CLH report prepared by a dossier submitter.