Substance Name: Dipentyl phthalate (DPP)

EC Number: 205-017-9

CAS Number: 131-18-0

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

DIPENTYL PHTHALATE (DPP)

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR[1] PROPERTIES

Adopted on 31 May 2013

[1] CMR means carcinogenic, mutagenic or toxic for reproduction.

CONTENTS

TABLES

ABBREVIATIONS

CAS	Chemical Abstracts Service
CLP	Classification, Labelling and Packaging
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
DPP	Dipentyl phthalate
EC	European Community
ECHA	European Chemicals Agency
EU	European Union
ERC	Environmental release category
HSDB	Hazardous Substances Data Bank
NOAEL	No Observed Adverse Effect Level
PBT	Persistent, Bioaccumulative and Toxic
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical substances
SVHC	Substance of Very High Concern
vPvB	Very Persistent and very Bioaccumulative

Substance Name(s): **Dipentyl phthalate**

EC Number(s): **205-017-9**

CAS number(s): **131-18-0**

The substance is identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1B[2] which corresponds to classification as toxic for reproduction category 2[3].

Summary of how the substance meets the criteria set out in Article 57 (c) of REACH

Dipentyl phthalate (DPP) is covered by Index number 607-426-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as toxic for reproduction, Repr. 1B (H360FD: "May damage fertility. May damage the unborn child."). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is toxic for reproduction, Repr. Cat. 2 (R60/61: "May impair fertility. May cause harm to the unborn child").

Therefore, this classification of DPP in Regulation (EC) No 1272/2008 shows that it meets the criterion for classification as toxic for reproduction in accordance with Article 57 (c) of REACH.

Registration dossier submitted for the substance: No

[2] Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances, OJ L 353, p.1, 31.12.2008.

[3] Classification in accordance with Regulation (EC) No 1272/2008, Annex VI, part 3, Table 3.2 List of harmonised classification and labelling of hazardous substances (from Annex I to Council Directive 67/548/EEC), OJ L 353, p.1, 31.12.2008.

JUSTIFICATION

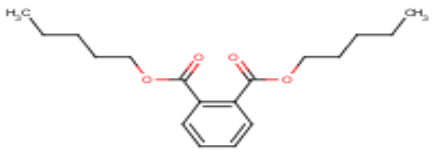
1. Identity of the substance and physical and chemical properties

1.1. Name and other identifiers of the substance

Table 1: Substance identity

EC number:	205-017-9
EC name:	dipentyl phthalate
CAS number (in the EC inventory):	131-18-0
CAS number:	131-18-0
CAS name:	1,2-Benzenedicarboxylic acid, 1,2-dipentyl ester
IUPAC name:	dipentyl phthalate
Index number in Annex VI of the CLP Regulation	607-426-00-1
Molecular formula:	$C_{18}H_{26}O_4$
Molecular weight range:	306,397 g/mol
Synonyms:	1,2-Benzenedicarboxylic acid, dipentyl ester Amoil Amyl phthalate Di-N-Pentyl Phthalate Di-n-pentylphthalatediamyl phthalate Dipentyl 1,2-benzenedicarboxylate Dipentyl phthalate Phthalic acid, diamyl ester Phthalic acid, dipentyl ester di-n-pentylphthalate Diamyl Phthalate Dipentyl phthalate

Structural formula:



1.2. Composition of the substance

Name: Dipentyl phthalate

Description: Colourless, oily liquid

Degree of purity: The substance has not been registered. Information on purities in the range between 95% and 99% is provided at supplier websites (http://www.chemicalbook.com/ProductChemicalPropertiesCB4197568_EN.htm#MSDSA)

Table 2: Constituents

This information is not relevant for identification of a mono constituent substance

Constituents	Typical concentration	Concentration range	Remarks
Name and EC number			

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Name and EC number			

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
Name and EC number			

1.3. Physico-chemical properties

Table 5: Overview of physicochemical properties

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	4.1	Colorless, oily liquid	Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 346
VII, 7.2	Melting/freezing point	4.2	-55°C	Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 346
VII, 7.3	Boiling point	4.3	342°C	Lewis, R.J. Sr.; Hawley's Condensed Chemical Dictionary 14th Edition. John Wiley & Sons, Inc. New York, NY 2001., p. 346
VII, 7.4	Density	4.4	1.03 g/cm^3	
VII, 7.5	Vapour pressure	4.6	1.96 x10^{-4} mmHg at 25°C	HSDB
VII, 7.7	Water solubility	4.8	0.8 mg/L at 25°C	Leyder Y, Boulanger P; Bull Environ Contam Tox 30: 152-7 (1983)
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7	log P_{ow} 5.62 at 20°C	Ellington JJ, Floyd TL; Octanol/water partition coefficients for eight phthalate esters. USEPA-600/S-96-006. Athens,GA: USEPA, Natl Exp Res Lab (1996)
IX, 7.9	Flashpoint	4.11	118-180^{0}C	HSDB

2. Harmonised classification and labelling

Dipentyl phthalate (DPP) is listed by Index number 607-426-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as follows:

Table 6: Classification according to Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling	
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)
607-426-00-1	di-n-pentyl phthalate	205-017-9	131-18-0	Repr. 1B Aquatic Acute 1	H360FD H400	GHS08 GHS09 Dgr	H360FD H400

DPP is covered by Index number 607-426-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Council Directive 67/548/EEC) as follows:

Table 7: Classification according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling
607-426-00-1	di-n-pentyl phthalate	205-017-9	131-18-0	Repr. Cat. 2; R60-61 N; R50	T; N R: 60-61-50 S: 53-45-61

3. Environmental fate properties

Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).

4. Human health hazard assessment

See section 2 Harmonised Classification and Labelling and Supplementary Information in Annex I.

5. Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).

6. Conclusions on the SVHC Properties

6.1. PBT, vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).

6.2. CMR assessment

Dipentyl phthalate (DPP) is covered by Index number 607-426-00-1 of Regulation (EC) No 1272/2008 and classified in Annex VI, part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as toxic for reproduction, Repr. 1B (H360FD: "May damage fertility. May damage the unborn child."). The corresponding classification in Annex VI, part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is toxic for reproduction, Repr. Cat. 2 (R60/61: "May impair fertility. May cause harm to the unborn child").

Therefore, this classification of DPP in Regulation (EC) No 1272/2008 shows that it meets the criterion for classification as toxic for reproduction in accordance with Article 57(c) of REACH.

6.3. Substances of equivalent level of concern assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57(c).

7. References

Creasy, D.M., J.R. Foster, and P.M. D. Foster. The morphological development of di-npentyl phthalate induced testicular atrophy in the rat. J Pathol 39 (3): 309-21, 1983

Foster PM, Thomas LV, Cook MW, Gangolli SD. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicol Appl Pharmacol. Jul; 54(3):392-8, 1980.

Foster, P.M., L.V. Thomas, M.W. Cook, and D.G. Walters. Effect of di-n-pentyl phthalate treatment on testicular steroidogenic enzymes and cytochrome P-450 in the rat. Toxicol Lett. 15(2-3):265-71, 1983.

Gangolli SD. Testicular effect of phthalate esters. Environmental Health Perspectives. Vol. 45, pp.77-84, 1982, 1983.

Gray, T.J. and S.D. Gangolli. Aspects of the testicular toxicity of phthalate esters. Environ Health Perspect. 65:229-35, 1986

Hazardous Substances Data Bank (HSDB) Entry for diamyl phthalate, 2011

Heindel, J.J., D.K. Gulati, R.C. Mounce, S.R. Russell, and J.C. Lamb. Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. Fund Appl Toxicol 12(3): 508-518, 1989.

Howdeshell K.L., Wilson V.S., Furr J., Lambright C.R. , Rider C., Blystone C.R., Hotchkiss A.K. and Gray L.E. A mixture of five phthalate esters inhibits fetal testicular testosterone production in the Sprague-Dawley rat in a cumulative, dose-additive manner. Toxicological Sciences 105(1): 153-165, 2008.

Liu, K., K.P. Lehmann, M. Sar, S.S.Young, and K.W. GaidoGene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology oftesticular dysgenesis. Biol Reprod. 73: 180–192, 2005.

National Toxicology Program (NTP). Di-N-Pentylphthalate (CASRN 131-18-0). Reproduction and fertility assessment in CD-1 mice when administered in feed. NTP Report RACB84048, 1985.

ANNEX I

SUPPLEMENTARY INFORMATION ON THE LEADING HEALTH EFFECTS AND TOXICOKINETICS

1. Toxicokinetics (absorption, metabolism, distribution and elimination)

No data were identified specific to the absorption of DPP. Dermal absorption of phthalate diesters depends on several competing factors, such as lipophilicity, molecular size, and metabolism. Dermal uptake decreases with increasing side chain length beyond four carbons, and uptake decreases progressively with side chain length beyond four carbons, despite the fact that the lipophilicity increases.

Histological data from acute toxicity studies suggest that DPP is distributed quickly.
Following oral exposure, DPP is rapidly metabolized in vivo to its corresponding monoester by nonspecific esterases in the intestinal mucosa and other tissues.

For phthalate esters in general, after formation of the monoester, there can be further hydrolysis in vivo to phthalic acid or the corresponding alcohol, which can be excreted or further oxidized to an aldehyde, ketone, or carboxylic acid. The monoester can also undergo glucuronidation.

The monoester and oxidative metabolites and conjugants of phthalate diesters are excreted in the urine and feces (HSDB 2010).

2. Reproductive and Developmental Toxicity

DPP demonstrates testicular atrophy and a fertility impairing effect in dose ranges of relevance for classification (Gangolli 1982; Creasy et al., 1983; Granholm et al. 1992; Jones et al. 1993; Gray and Gangoli 1986; Foster at al., 1980).

In a study of the reproductive toxicity of eight phthalate esters to rats (2100 mg/kg bw/day for four days), DPP caused the most severe testicular atrophy (Foster et al. 1980).
Treatment of rats via gavage with 7.2 mmol/kg bw DPP (~2200 mg/kg bw) was shown to decrease testicular cytochrome P-450, cytochrome P-450 dependent microsomal steroidogenic enzymes (17 alpha-hydroxylase, 17-20 lyase) and the maximal binding of a natural substrate (progesterone) to microsomes of the testes. The study authors concluded that DPP has a direct effect on cytochrome P-450-dependent steroid production, which may be directly responsible for the toxic effects on testicular structure and function (Foster et al. 1983).

Lindstrom et al. (1988) described the effect of DPP on fertility. Fischer 344 rats received single gavage doses of 0, 250, 1000, or 2000 mg/kg bw DPP. Treated males were mated with untreated females at 3, 6, and 10 weeks post-exposure. The percentage of high-dose rats successfully impregnating at least one female was 65 percent of controls at week 3; 15 percent at week 6; and 35 percent at week 10. The number of live fetuses per pregnant female crossed with a high-dose male was 35 percent, 43 percent, and 72 percent of controls at weeks 3, 6, and 10, respectively. Preimplantation loss in cross-matings was three times that of controls. There was no significant difference in the number of resorptions or dead fetuses (i.e., post-implantation loss) at any time. All males showed typical phthalate ester-induced testicular lesions, which did not recover within the 30-week monitoring period. There were no effects on fertility at the mid- or low- doses.

The National Toxicology Program (NTP) tested the reproductive toxicity of DPP in mice. Male and female mice received DPP in the diet at concentrations of 0.5, 1.25, or 2.5% (approximately equivalent to 760, 2160, and 4800 mg/kg/day, respectively) for 7 days prior

to and during a 98-day cohabitation. The reproductive NOAEL was determined to be less than 760 mg/kg/day, based on significant decreases in the proportion of fertile pair groups, number of litters per pair, number of live pups per litter, and the proportion of live births. At the two high doses, there was a complete inhibition of fertility (Heindel et al. 1989; NTP 1985).

More recent study revealed changes in reduction of anogenital distance of male foetuses exposed in utero to 500 mg/kg/day DPP on gestation days 12-19 (Liu et al. 2005).
Howdeshell et al. (2008) compared the reproductive toxicity of a number of individual phthalates. Doses of 0, 25, 50, 100, 200, 300, 600, or 900 mg/kg/day DPP were administered by gavage on gestation days (GD) 8-18 to Sprague-Dawley rats.

The NOAEL for reproductive and maternal effects was 200 mg/kg/day based on significant changes in maternal body weight gain, number of live fetuses, total resorptions, and fetal mortality. Testicular testosterone production was measured on gestation day 18. The effective dose which inhibited fetal testosterone production by 50% (ED50) was calculated to be 130 mg/kg/day.