European Chemicals Agency

Substance name: Benzyl butyl phthalate
EC number: 201-622-7
CAS number: 85-68-7

MEMBER STATE COMMITTEE SUPPORT DOCUMENT FOR IDENTIFICATION OF Benzyl butyl phthalate (BBP) AS A SUBSTANCE OF VERY HIGH CONCERN

Adopted on 1 October 2008

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TABLES

Substance Name: Benzyl butyl phthalate

EC Number: 201-622-7

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The substance is identified as a CMR according to Article 57 (c) of Regulation (EC) 1907/2006 (REACH).

Summary of the evaluation:

According to Annex I to Directive 67/548/EEC, Benzyl butyl phthalate (BBP) is classified as a substance toxic to reproduction Repr. Cat. 2; R 61 (May cause harm to the unborn child).

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

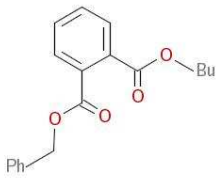
1.1 Name and other identifiers of the substance

Chemical Name:	Benzyl butyl phthalate
EC Number:	201-622-7
CAS Number:	85-68-7
IUPAC Name:	Benzyl butyl phthalate

1.2 Composition of the substance

From EU RAR (2007)

Chemical Name:	Benzyl butyl phthalate
EC Number:	201-622-7
CAS Number:	85-68-7
IUPAC Name:	Benzyl butyl phthalate
Molecular Formula:	$C_{19}H_{20}O_4$
Structural Formula:	



Molecular Weight:	312,35 g/mol
Typical concentration (% w/w):	Degree of purity > 98.5 % (w/w)
Concentration range (% w/w):	-
Identity and percentage (w/w) of impurities:	< 1.0% dibenzyl phthalate (CAS No. 523-31-9) < 0.5% benzyl benzoate (CAS No. 120-51-4) < 0.5% dibutyl phthalate (CAS No. 84-74-2) < 2 ppm α-clorotoluen (CAS No. 100-44-7) < 2 ppm α-α-diclorotoluen (CAS No. 98-87-3)
Additives	< 0.5 ppm pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydoxyphenyl)propionate. (CAS No. 6683-19-8)

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties, from EU RAR 2007

REACH ref Annex	Property	IUCLID section	Value	Reference
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	liquid	
VII, 7.2	Melting/freezing point	3.2	<-35°C	Monsanto internal data
VII, 7.3	Boiling point	3.3	370°C at 10.10 hPa	Bayer AG MSDS
VII, 7.5	Vapour pressure	3.6	0.00112 Pa at 20°C	Hoyer and Peperle (1957)
VII, 7.7	Water solubility	3.8	2.8 mg/l	
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	Log K_{ow} 4.84	
IX, 7.16	Dissociation constant	3.21		

2 CLASSIFICATION AND LABELLING

2.1 Classification in Annex I of Directive 67/548/EEC

Benzyl butyl phthalate (BBP) was inserted into Annex I of Directive 67/548/EEC with the 29. ATP (2004/73/EC) and is classified as follows:

Index: Number: 607-430-00-3

Repr. Cat. 2; R 61 (May cause harm to the unborn child)
Repr. Cat. 3; R 62 (Possible risk of impaired fertility)
N; R 50-53 (Dangerous for the environment; Very toxic to aquatic organisms, may cause long term effects in the aquatic environment)

Specific concentration limits: none

Labelling:

Symbols: T; N
R-Phrases: 61-62-50/53
S-Phrases: 53-45-60-61

2.2 Self classification(s)

Not relevant.

3 HUMAN HEALTH HAZARD ASSESSMENT

3.1 Toxicity for reproduction

3.1.1 Effects on fertility

3.1.2 Developmental toxicity

3.1.3 Human data

3.1.4 Other relevant information

Endocrine effects of BBP

Endocrine activity has been assessed in various *in vitro* and *in vivo* studies on BBP and its most important metabolites MBeP (mono-benzyl-phthalate) and MBuP (mono-n-butyl-phthalate) as described in the EU RAR, 2007:

Estrogenicity

A potential estrogen activity of BBP and the major BBP metabolites MBuP and MBeP has been investigated in both *in vitro* and *in vivo* studies. The *in vitro* studies include a recombinant yeast screen assay, an estrogen-receptor (ER) competitive ligand binding assay, mammalian- and yeast-based gene expression assays and an estrogen-dependent cell proliferation assay. In these assays only a weak estrogen activity at high concentrations of BBP (10-100 µM) was reported. In the same assays the positive control E2 (17ß-estradiol) was approximately 10^4 to 10^6 more potent than BBP. The metabolites MBuP and MBeP did not exhibit estrogenic activity in a recombinant yeast screen assay. The estrogenic activity of BBP and its major metabolites were studied in standard *in vivo* uterotrophic assays. In these studies BBP and MBuP did not possess the potential to promote uterine growth in immature female rats exposed orally to BBP (up to 2,240 mg/kg bw/day) or subcutaneous to BBP (up to 5,000 mg/kg bw/day), whereas, MBeP caused a significant reduction in absolute and relative uterine weight at 500 and 1,000 mg/kg bw/day, which was most probably due to systemic toxicity. Furthermore only weak estrogenic activity of BBP was concluded in a study that investigated the expression of estrogen regulated mRNAs in the hypothalamus, preoptic area and pituitary.

Anti-androgenicity

BBP was shown in one *in vitro* study to be a potent anti-androgen in yeast cells expressing the androgen receptor. Nine *in vivo* studies are available which indicate an anti-androgen-like activity of BBP or its major metabolites MBuP and MBeP in rats (Piersma et al., 2000; Gray et al., 2000; Parks et al., 1999; Imajima et al., 1997; Shono et al., 2000; Nagao et al., 2000; Tyl et al., 2004; Ema et al., 2002; Ema et al., 2003, all cited in EU RAR). Effects reported in the Piersma et al. (2000) study included a reduction in testicular weight in offspring, and effects on testicular migration from 270 mg/kg bw/day and 580 mg/kg bw/day after *in utero* exposure to BBP from gestation day 6 to 20. In the Gray et al. (2000) study malformations in the reproductive organs in 84% of male offspring (approximately 90 days of age) exposed to 750 mg/kg bw/day BBP from gestation day 14

through postnatal day 2 were reported. Furthermore in the Gray et al. (2000) and Parks et al. (1999) studies a reduced AGD and testis weight in males at day 2 of age, and males with areolas at day 13 of age were reported. In the Imajima et al. (1997) study and the Shono et al. (2000) study testicular descendent was studied, which is under androgenic control. In this study the testis were located significantly higher in the abdominal cavity on gd 20 offspring compared to control rats exposed *in utero* to MBuP from gd 15-18. Furthermore, in the Imajima et al. (1997) study, on pnd 30-40 cryptorchidism was reported in 84.6% of the exposed offspring, compared to 0% in the control group. In the study by Ema et al. (2002) *in utero* exposure to 500 and 1,000 mg/kg BBP on gd 15-17 induced a significant decrease in the AGD and a significant increase in the incidence of undescended testis. In the study by Ema et al. (2003) *in utero* exposure to MBeP on gd 15-17 was shown to induce a significant decrease in AGD and a significant increase in the incidence of undescended testis. In the study by Nagao et al. (2000) a decrease in the weight of the testis, epididymis, and seminal vesicle, and tubular atrophy and decreased germinal epithelium was reported in F1 male offspring exposed to 500 mg/kg bw/day BBP during gestation and lactation and evaluated at weaning or after puberty. Furthermore, a decrease in AGD was reported in male offspring in the 500 mg/kg bw/day dose group, which is a sensitive indicator of anti-androgen activity. In the Tyl et al. (2004) study a dose-related decrease in absolute and adjusted AGD was reported in F1 and F2 male pups from 250 mg/kg bw/day. Furthermore, at 750 mg/kg bw/day in F1 and F2 offspring a significant decrease in reproductive organ weights, and a significant increase in the percentage of males with reproductive tract malformations were reported.

An association between prenatal and postnatal exposure to phthalates and whether the exposure had any influence on reproductive organ development in newborn boys was studied in two epidemiological studies. In the study by Swan et al. (2005, cited in EU RAR) an association between maternal exposures to BBP as well as other phthalates and AGI in boys was reported. When comparing boys with prenatal MBeP (monobenzyl phthalate, reflecting exposure to BBP) exposure the odds ratio for a shorter AGI was 3.8. For the other monoester phthalates the odds ratio were 10.2 for MBuP (reflecting exposure to DBP), 4.7 for MEP (reflecting exposure to DEP), and 9.1 for MiBP (reflecting exposure to DINP) (all p-values < 0.05).

In the study by Main et al. (2005, cited in EU RAR) no association was found between phthalate monoester levels (MEP, MMP, MBuP, MBeP, MINP and MEHP) in breast milk and cryptorchidism in newborn boys. However, a significant association was found between intake of milk contaminated with phthalates (MEP, MBuP, MMP and MINP) and postnatal surge of reproductive hormones (SHBG, LH, testosterone and inhibin B) in newborn boys. As regards the monoester metabolite of BBP, MBeP the tendencies were similar, however, they were not statistically significant. These data support the hypothesis that prenatal phthalate exposure at environmental levels may affect male reproductive development in humans. However, due to the small sample size, (85 boys in Swan et al., 2005 and 130 boys in Main et al., 2005) further studies with larger sample size have to be performed before clear conclusions can be drawn from these studies.

The following study was published after publication of the EU RAR:

Hauser et al. (2006) reported altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites in humans. Semen from 463 male partners of subfertile couples was investigated and dichotomized according WHO reference values for sperm concentration and motility as well as the Tygberg Kruger Strict criteria for morphology. Results

were adjusted for age, abstinence time and smoking status. MBeP (mono-benzyl-phthalate) was found in 94% of the samples. There was suggestive evidence of an association between the highest MBeP quartile with low sperm concentration (Hauser et al., 2006).

3.1.5 Summary and discussion of reproductive toxicity

BBP has been assessed for potential toxic effects on fertility, reproductive organs, development, and endocrine activity. It is found to adversely affect the reproductive organs in experimental animal studies which may affect fertility. Furthermore, the substance is found to be a developmental toxicant. This is reflected in the classification as **Repr.Cat. 3; R 62** and **Repr.Cat. 2; R 61**, according to Directive 67/548/EEC.

BBP impairs the foetal development and causes malformations in rats and mice. A dose-related significant reduction in absolute and adjusted anogenital distance index (AGI) in both F1 and F2 offspring from 250 mg/kg bw/day was observed in rats. At 750 mg/kg bw/day a significant increase in F1 and F2 male pups with one or more nipples and/or areolae was reported. The NOAEL for maternal toxicity was 750 mg/kg bw/day (Tyl et al., 2004, cited in EU RAR).

The results of several *in vivo* studies indicate an anti-androgen-like activity of BBP or its major metabolites in rats following *in utero* exposure. Effects reported in the studies included a decreased AGI, increases in male offspring with reproductive tract malformations, as well as effects on testicular migration (EU RAR, 2007).

In studies commissioned by DG Environment of the European Commission a list of 146 substances with endocrine disruption properties have been established (http://ec.europa.eu/environment/docum/pdf/bkh_annex_13.pdf). BBP has been classified as Cat. 3 for wildlife, Cat. 1 for Humans and Combined as Cat. 1 (Cat.1: Evidence for endocrine disruption in living organisms; Cat. 2: Evidence of potential to cause endocrine disruption; Cat.3: No evident scientific basis). BBP is also listed in a list of 66 potentially endocrine substances with classification of high exposure concern (http://ec.europa.eu/ environment/docum/pdf/bkh_annex_15.pdf) (EUROPEAN COMMISSION DG ENV, 2000).

It is stated in the draft risk reduction strategy (April 2007) that BBP may be subjected to the authorisation system. In the OSPAR convention BBP is put on the list of substances for priority action. In the OSPAR Convention it is stated that BBP is a potential endocrine substance.

4 ENVIRONMENTAL HAZARD ASSESSMENT

There have been suggestions of estrogenic and anti-androgenic effects caused by BBP in fish. Following recent development of draft testing protocols for endocrine disruption in fish, more data has become available.

Estrogenicity

In an early study BBP was found to be weakly estrogenic (Jobling et al., 1995, cited in EU RAR). BBP at a concentration of approximately 0.01 – 10 mg/l reduced *in vitro* binding of natural estrogen, 17β−estradiol, to the rainbow trout estrogen receptor by about 40-60%. Furthermore, the EU RAR (2007) refers to a study performed by Christiansen et al. (2000) who injected rainbow trout intraperitoneally with different compounds. BBP was found to cause significant induction of vitellogenin *in vivo*, but was a weaker inducer than e.g. bisphenol A. In further injection studies with juvenile rainbow trout, no induction of the estrogen receptor was observed at an exposure concentration of 50 mg/kg BBP, but both 5 and 50 mg/kg significantly lowered plasma levels of eggshell proteins (Knudsen et al., 1998 cited in EU RAR), indicating an inhibition of synthesis of these proteins. Similarly, Knudsen and Pottinger (1998, cited in EU RAR) found that BBP would bind to the estrogen receptor, but only at high concentrations. There was no apparent binding of BBP to corticosteroid or testosterone receptors in that study. Work performed by Gimeno (at this time at TNO, The Netherlands) on the possible estrogenic effects of BBP on sexual differentiation in all-male carp did not indicate any effects of BBP (Gimeno, pers.comm. cited in EU RAR). Results for estrogenicity indicate that BBP may be estrogenic at high concentrations.

Harries et al. (2000, cited in EU RAR) exposed fish to BBP (100 µg/l) and nonylphenol (1, 10 and 100 µg/l). Breeding pairs were exposed for 3 weeks during which reproductive performance was monitored. Endpoints were number of spawnings, number of eggs and size of eggs. At the end of the exposure period plasma vitellogenin and gonadosomatic index was determined. In addition, secondary sexual characteristics in male were quantified (growth of tubercles and thickness of dorsal fat pad). While nonylphenol caused dose-dependent estrogenic effects down to 10 µg/l, no effects were seen following BBP exposure.

Anti-androgenicity

The EU RAR (2007) furthermore refers to studies suggesting that BBP may be anti-androgenic. These observations have been derived from mammalian studies (e.g. Zacharewski et al., 1998) as well as an *in vitro* study conducted by Sohoni and Sumpter (1998). BBP has been found to be an as potent anti-androgen as the model substance used for that purpose, flutamide. Unfortunately there is no established model to ascertain anti-androgenicity in fish. The Harries et al. (2000) study was not specifically designed to detect anti-androgenicity (e.g. through concomitant exposure to anti-androgens). Therefore, the lack of response following BBP exposure in this study does not disprove earlier suggestions that this phthalate may be anti-androgenic to wildlife. Recently, Ankley et al. (2004) provided *in vitro* support for using fathead minnow to identify anti-androgenic effects, but it is still necessary to establish such effects *in vivo*.

There is work ongoing within the OECD to establish appropriate test systems for endocrine disrupting effects. The test systems are expected to include a study in fish that will include endpoints relevant to estrogenic, androgenic, anti-estrogenic and anti-androgenic effects. The tests performed with BBP referred to above have not incorporated the aspect of transfer from parent to offspring included in the current test requirements for BBP. An agreement was reached with Industry to perform a partial life cycle study that was a combination of the two OECD recommended “tier 2 tests” for assessing possible endocrine disruption effects of chemicals in fish.

The test is a combination of the so-called pair-breeding test in which egg production and hatchability of eggs from a breeding pair of Fathead minnow is assessed and an enhanced early life stage test in which exposure of the eggs from the pair breeding test is continued for sufficient time to enable sexual differentiation of the offspring. Exposure concentrations should be 25 and 100 µg/l. After some pre-dosing trials a definite study with the pair breeding phase was attempted in March 2002. This study was aborted on day 47 because measured BBP concentrations in the exposure vessels were always below the nominal concentrations and appeared to decline throughout the study. In the nominal 25 µg/l exposure tanks mean concentration on day 32 was 20 µg/l and by day 47 the mean concentration had declined to 14 µg/l (56% of nominal). In the nominal 100 µg/l exposure tanks mean concentration on day 32 was 72 µg/l and by day 47 the mean concentration had declined to 59 µg/l (59% of nominal). Industry has performed a number of additional trials in order to investigate the optimal conditions for performing a chronic fish test. The trials included variable use of solvent, variable delivery systems and variable flow rates. These trials have indicated that it will not be possible to obtain a stable test concentration > 80% of the nominal BBP concentration as required according to the test guidelines. Apparently a plateau level could not be obtained either. Very high flow rates were also tested (residence time 1-1.15 hour) without attaining the required concentration level, although it seemed that a fairly stable level was achieved at about 50% of nominal. The industry report concluded that the reason for these problems was the biodegradation of BBP to its primary biodegradation products (monobutyl-phthalate and monobenzyl-phtalate) and that these metabolites were also rapidly degraded within this test system. It should however be pointed out that other factors cannot be excluded like adsorption to the test system and that some solubility problems as reported may also be part of the problem. The technical difficulties described above have been reported to the Technical Meeting. However, the TM (cf. minutes of TM II `03) “generally supported the request to industry to perform the endocrine effect test. The TM realised that the results would not meet the ideal test requirements, but would accept that in this particular case.

In the risk assessment report (EU-RAR, 2007) BBP is considered as a suspected endocrine disruptor. It was concluded that further information is needed concerning reproductive toxicity and endocrine effects in fish. A long term fish study on reproductive and endocrine effects has to be performed and therefore the PNECaquatic (7.5 µg/l wwt) has to be seen provisional. From informal contacts with the rapporteur (Norway) information was received that the long term fish study has been conducted, but still needs to be reviewed in detail.

OTHER INFORMATION

Benzyl butyl phthalate (BBP) is on the 3rd priority list under Council Regulation (EEC) No 793/93 on the Control and Evaluation of the Risks of Existing Substances with Norway as Rapporteur. The final risk assessment report was published in 2007. The risk reduction strategy was endorsed at the 13th RRS Meeting, publication in the Official Journal is foreseen for 2008.

Note that no re-evaluation was conducted of those references which are cited in this Annex XV dossier and which were taken from the Risk Assessment Report for benzyl butyl phthalate (EU RAR, 2007). The last full literature survey for the RAR was carried out in 2003 with subsequently conducted targeted searches. For the present dossier no comprehensive literature survey was carried out, but focus was given to exposure related data (especially monitoring data) and endocrine effects.

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