BUTYL BENZYL PHTHALATE

This substance was considered by previous working groups, in 1981 (IARC, 1982) and 1987 (IARC, 1987). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

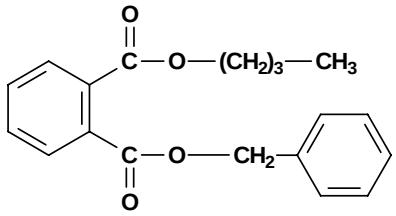
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 85-68-7
Deleted CAS Reg. No.: 58128-78-2
Chem. Abstr. Name: 1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester
IUPAC Systematic Name: Phthalic acid, benzyl butyl ester
Synonyms: BBP; benzyl butyl phthalate; benzyl *n*-butyl phthalate

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_{19}H_{20}O_4$ Relative molecular mass: 312.4

1.1.3 *Chemical and physical properties of the pure substance* (from Verschueren, 1996, except where noted)

(*a*) *Description*: Clear, oily liquid
(*b*) *Boiling-point*: 370°C
(*c*) *Melting-point*: < –35°C
(*d*) *Density*: 1.1 g/cm^3 at 25°C
(*e*) *Solubility*: Slightly soluble in water
(*f*) *Volatility*: Vapour pressure, 1.14 mPa at 20°C; relative vapour density (air = 1), 10.8 (National Toxicology Program, 1991)
(*g*) *Octanol/water partition coefficient (P)*: log P, 4.91
(*h*) *Conversion factor*: mg/m^3 = 12.78 × ppm

1.2 Production and use

Information available in 1995 indicated that butyl benzyl phthalate was produced in 12 countries worldwide (Chemical Information Services, 1995).

Butyl benzyl phthalate is used as a plasticizer for polyvinyl chloride in vinyl floor tiles, vinyl foam and carpet backing, in cellulosic resins, and as an organic intermediate. It has also been used as a solvent and fixative in perfume (National Toxicology Program, 1991; Lewis, 1993).

1.3 Occurrence

1.3.1 *Natural occurrence*

Butyl benzyl phthalate is not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 330 000 workers in the United States were potentially exposed to butyl benzyl phthalate. Occupational exposure may occur during its production and in its use as a plasticizer in polyvinyl chloride products such as vinyl floor tiles.

1.3.3 *Environmental occurrence*

According to the United States Environmental Protection Agency Toxic Chemical Release Inventory for 1987, 147 000 kg butyl benzyl phthalate were released into the air, 860 kg were discharged into water, and 3900 kg were released onto the land from manufacturing and processing facilities in the United States. By 1993, 170 000 kg were released into air, 620 kg were discharged into water, 38 kg were disposed of by underground injection, and 1200 kg were released onto the land (National Library of Medicine, 1998a).

Butyl benzyl phthalate has been detected in surface water, groundwater and drinking-water in many locations at levels generally well below 10 μg/L. Concentrations lower than 0.1 μg/m^3 have been found in indoor air due to release from products such as vinyl flooring, caulks and adhesives and carpets. It also has been detected at parts per million in a few foods (Solutia, 1998; National Library of Medicine, 1998b).

1.4 Regulations and guidelines

The time-weighted average exposure limits for exposure to butyl benzyl phthalate in workplace air are 3 mg/m^3 in Sweden and 5 mg/m^3 in Ireland and the United Kingdom (International Labour Office, 1991; National Library of Medicine, 1998c).

No international guidelines for butyl benzyl phthalate in drinking-water have been established (WHO, 1993).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Butyl benzyl phthalate was tested in mice and in female rats by oral administration and in male mice by intraperitoneal injection. A somewhat increased incidence of monocytic leukaemias was reported in female rats. In mice, no increased incidence of tumours was observed (IARC, 1982).

New studies

3.1 Oral administration

Rat: Groups of 60 male and 60 female Fischer 344/N rats, six weeks of age, were fed diets containing 0, 3000, 6000 or 12 000 mg/kg (ppm) (males) and 0, 6000, 12 000 or 24 000 mg/kg (females) butyl benzyl phthalate (purity, > 99.5%) for 105 weeks. Ten rats per group were killed at 15 months. A decrease in body-weight gain was dose-related, especially in females at the high dose. There was no effect on survival. Male rats had an increased incidence of pancreatic acinar-cell adenomas (control, 3/50; low dose, 2/49; intermediate dose, 3/50; high dose, 10/50; $p < 0.016$); one pancreatic acinar-cell carcinoma was seen in a male at the high dose. The prevalence of focal hyperplasia of the pancreas was also increased in males in a dose-related manner (4/50, 7/49, 9/50, 12/50). Urinary bladder transitional-cell hyperplasia [type not specified] was seen in 4/50, 0/50, 1/50 and 10/50 females in the four groups, respectively (National Toxicology Program, 1997a). [The Working Group noted that no bladder lesions were seen in a 90-day study.]

A further study was conducted with animals on restricted diets in an effort to evaluate the effect of weight-matched control groups on the sensitivity of the bioassay. The aim was to achieve a body weight reduction of about 15% in comparison with rats fed *ad libitum.* Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were fed diets containing concentrations of 0, 12 000 (males) or 24 000 (females) mg/kg (ppm) butyl benzyl phthalate for either 24 or 30–32 months and killed at those times. Body-weight depression was observed in females but not males; the rate of survival of male rats was slightly decreased. There was no increase in the incidence of pancreatic tumours at either 24 or 30–32 months. The incidence of urinary bladder papillomas or carcinomas was marginally increased in female rats (6/50 versus 1/49; $p = 0.077$) at 32 months; four of these females had bladder carcinomas, with none in controls ($p > 0.079$ by the Kaplan-Meier test after adjustment for intercurrent mortality). The incidence of bladder hyperplasia was also increased in females at 24 months (14/50 versus 0/50 in controls) and at 32 months (16/50 versus 0/49) (National Toxicology Program, 1997b).

3.2 Administration with known carcinogens or modifying agents

Groups of 27 female Sprague-Dawley rats, 43 days of age, were given butyl benzyl phthalate [purity unspecified] at doses of 250 or 500 mg/kg bw intragastrically in corn oil, daily for seven days before intragastric administration of 31 mg/kg bw dimethylbenz-[*a*]anthracene (DMBA) in corn oil at 50 days of age. After 15 weeks, the rats were killed and the mammary tumour incidences determined. Administration of butyl benzyl phthalate did not affect body-weight gain. The incidence of palpable mammary tumours was significantly inhibited by pretreatment with butyl benzyl phthalate, by 58 and 71% at 250 and 500 mg/kg bw, respectively ($p < 0.05$). The number of adenocarcinomas per rat was also significantly reduced, being 4.0 with DMBA alone, 1.6 with 250 mg/kg bw butyl benzyl phthalate and 1.2 with 500 mg/kg bw ($p < 0.05$) (Singletary *et al*., 1997).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

A few studies on the absorption, distribution, metabolism and excretion of butyl benzyl phthalate have been conducted in rats, and one study has been performed in beagle dogs. Initial metabolism involves cleavage of one ester, as shown by the studies described below. After dosing by gavage of male Fischer 344 rats with 2, 20 or 200 mg/kg bw [ring-^{14}C]butyl benzyl phthalate, 62–72 and 13–15% of the dose was excreted in urine and faeces, respectively, within 24 h. By 96 h, 92–98% of the dose had been eliminated, 71–80 and 18–23% being eliminated in urine and faeces, respectively. The radiolabel found in urine was associated with monophthalates (22–42% of the dose), monophthalate glucuronide conjugates (14–21% of the dose) and unknown metabolites. At a dose of 2000 mg/kg bw, 22 and 72% were eliminated after 96 h in urine and faeces, respectively. The increased faecal elimination at this high dose relative to excretion in urine may represent incomplete absorption of butyl benzyl phthalate. After intravenous administration of a 20-mg/kg bw dose, [ring-^{14}C]butyl benzyl phthalate was rapidly distributed to the tissues, and the radiolabel was eliminated with a half-life of around 6 h in all tissues. Some 55% of an intravenous 20-mg/kg bw dose was excreted in the bile after 4 h. Analysis of the bile revealed the presence of mono-*n*-butyl phthalate and monobenzyl phthalate glucuronides, representing 26 and 13% of the dose, respectively; trace amounts of the free monoesters, representing 1.1 and 0.9% of the dose, respectively; and unknown metabolites (14% of the dose), but no parent butyl benzyl phthalate. This study demonstrates that butyl benzyl phthalate is rapidly metabolized in rats; the metabolites are excreted in the bile and, after enterohepatic circulation, are eliminated in the urine. Mono-*n*-butyl phthalate is formed in

large amounts, mono-*n*-butyl and monobenzyl phthalates accounting for 44 and 16% of a 20-mg/kg bw intravenous dose, respectively (Eigenberg *et al*., 1986).

Similarly, when male Wistar-Imamichi rats were given 3.6 mmol/kg bw (about 1100 mg/kg bw) of butyl benzyl phthalate orally for three days, both free and glucuronide conjugated (ratio, about 7:3) butyl benzyl phthalate monoester metabolites were excreted in the urine. The ratio of mono-*n*-butyl phthalate to monobenzyl phthalate was about 5:3 (Mikuriya *et al*., 1988).

After dermal application of 157 µmol/kg bw (about 49 mg/kg bw) [ring-^{14}C]butyl benzyl phthalate to the shaved skin of male Fischer 344 rats, some 30% of the dose was excreted in the urine and faeces within seven days; 45% of the dose was found in the skin at the application site, 6.3% in the plastic cap used to occlude the skin and 4.6% in muscle and < 1% in other tissues (Elsisi *et al*., 1989).

Beagle dogs were given a 5-g/kg bw oral dose of butyl benzyl phthalate divided over a 4-h period. Unchanged butyl benzyl phthalate in the faeces comprised 88–91% of the dose. While butyl benzyl phthalate was not present in the urine, some 4.2% of the dose was present as phthalic acid (Erickson, 1965).

4.2 Toxic effects

4.2.1 *Humans*

Butyl benzyl phthalate has been reported to be slightly irritating to the skin, eye and mucous membranes and to depress the central nervous system (Gosselin *et al*., 1984). In a patch test with 200 volunteers, which involved 15 daily applications over a three-week period, Hammond *et al.* (1987) observed neither primary irritation nor sensitization reactions.

4.2.2 *Experimental systems*

The oral LD_{50} of butyl benzyl phthalate administered in corn oil to male and female Fischer 344 rats was reported to be 2.3 g/kg bw and that in male and female B6C3F_1 mice to be 6.2 and 4.2 g/kg bw, respectively (National Toxicology Program, 1982). In male Sprague-Dawley rats, the oral LD_{50} of butyl benzyl phthalate administered in undiluted form was 20 g/kg (Hammond *et al*., 1987). In Swiss Webster mice, the intraperitoneal LD_{50} of butyl benzyl phthalate was 3.2 g/kg (Calley *et al*., 1966). The dermal LD_{50} in rabbits was reported to be > 10 g/kg (Hammond *et al*., 1987).

Like other phthalate diesters, butyl benzyl phthalate increases the weight of the liver in rats. When administered at dietary levels of 0.6, 1.2 or 2.5% for 21 days to male and female Fischer 344 rats, butyl benzyl phthalate produced hepatic peroxisome proliferation, with weak induction of peroxisomal activity (palmitoyl-coenzyme A oxidation) in both males and females. Microsomal activites (lauric acid 12-hydroxylase) were strongly induced in males but hardly at all in females. Ultrastructural examination of liver sections revealed an increase in the numbers of peroxisomes (Barber *et al*., 1987).

Many chemicals are known to produce hepatic peroxisome proliferation in rats and/or mice, and the characteristics of rodent peroxisome proliferators have been described

elsewhere (Bentley *et al.,* 1993; Ashby *et al*., 1994; Lake, 1995a,b; IARC, 1995; Cattley *et al*., 1998). Butyl benzyl phthalate was less potent than di(2-ethylhexyl)phthalate and some branched-chain phthalate diesters in producing hepatic peroxisome proliferation in rats (Barber *et al.,* 1987; Lin, 1987). In comparison with rodent peroxisome proliferators in general, butyl benzyl phthalate is only a weak agent (Barber *et al*., 1987; Ashby *et al*., 1994; IARC, 1995). While an association between peroxisome proliferation and liver tumour formation in rodents has been reported (Ashby *et al*., 1994), weak peroxisome proliferators do not necessarily produce liver tumours in rats or mice after chronic administration (Bentley *et al*., 1993; Lake, 1995a).

Butyl benzyl phthalate was one of several phthalates tested for oestrogenic activity in a recombinant yeast cell line containing the human oestrogen receptor gene, which was expressed in such a way that it controlled expression of the reporter gene *lacZ*. The maximum induction of *lacZ* via the human oestrogen receptor was 50% that caused by oestradiol-17β, while the relative potency was 0.000001. Comparable results were obtained in a similar test for proliferation of the oestrogen-responsive human breast cancer cell lines MCF-7 and ZR-75 (Harris *et al*., 1997).

The oestrogenic activity of phthalates was further investigated *in vitro* in competitive ligand-binding assays, in assays for yeast and mammalian gene expression and *in vivo* in a uterotrophic assay. Butyl benzyl phthalate competed weakly for oestrogen receptor binding (the concentration causing 50% inhibition being 36 μmol/L in comparison with 1.3 nmol/L for oestradiol), induced luciferase activity in transfected MCF-7 cells and stably transfected HeLa cells at a concentration of 10 μmol/L and weakly supported oestrogen-inducible growth in yeast cells (also at 10 μmol/L), but did not demonstrate any oestrogenic activity in mammals *in vivo* (Zacharewski *et al*., 1998).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Butyl benzyl phthalate was tested for developmental toxicity by dietary administration in rats and mice (Schwetz & Harris, 1993). In Sprague-Dawley rats exposed on days 6–15 of gestation to concentrations of 0.5–2%, maternal and developmental toxicity were observed at ≥ 1.25%. The developmental effects reported included an increased incidence of malformations and variations at 1.25% and embryonic death, reduced fetal body weights and an increased incidence of malformations and variations at 2%. In CD-1 mice exposed on days 6–15 of gestation to concentrations of 0.1–1.25%, maternal and developmental toxicity were reported at 1.25%. The developmental effects included embryonic death, reduced fetal weight and an increased incidence of malformations and variations. [The Working Group noted that only summary data of these studies of the National Toxicology Program studies were reported in the published literature.]

Groups of 10 adult male Fischer 344 rats were fed diets containing 0, 0.625, 1.25, 2.5 or 5% butyl benzyl phthalate (purity, > 98%) for 14 days. Rats exposed to the two higher doses were weak and lethargic and showed reduced body-weight gain and reduced weights of the testes, epididymides, prostate and seminal vesicle. The changes in organ weights persisted after correction for differences in body weight, except for that of the prostate, and were accompanied by dose-related atrophy of the testes and epididymides. Isolated sperm granulomas were found at the two highest doses (Agarwal *at al*., 1985).

Groups of 15–18 Wistar rats received diets containing 0, 0.25, 0.5, 1 or 2% butyl benzyl phthalate on days 0–20 of gestation, providing daily intakes estimated to be 0, 180, 380, 650 and 970 mg/kg bw, respectively. Maternal food consumption and body-weight gain were reduced at the two higher doses, and the litters of dams at the highest dose were resorbed. The body weights of pups at all but the lowest dose were reduced. No increase in the incidence of anomalies or malformations in the fetuses was observed (Ema *et al*., 1990). To determine whether the embryolethality was the result of reduced food consumption, a pair-feeding study was conducted in which pregnant rats received the same amount of diet consumed by the rats given 2% butyl benzyl phthalate. Although effects of the dietary reduction were observed, complete resorption was not seen in any of the pair-fed rats (Ema *et al*., 1991). When exposure to 2% was limited to days 0–11 or 11–20 of pregnancy, complete resorptions were seen only in the former group, while reduced fetal body weights, cleft palate and fused sternebrae were observed in the group exposed during days 11–20 (Ema *et al*., 1992a). When exposure was restricted to days 0–7, 7–16 or 16–20, increased resorptions in comparison with pair-fed rats were present only in groups exposed to 2.0% butyl benzyl phthalate on days 0–7 or 7–16, while reduced fetal body weights were present in all treated groups; malformations (cleft palate and fused sternebrae) were present only in the group exposed on days 7–16 of gestation (Ema *et al*., 1992b). In rats exposed to butyl benzyl phthalate by gavage at a dose of 0, 0.5, 0.75 or 1 g/kg bw daily on days 7–15, maternal lethality was seen at the highest dose and reduced body-weight gain and an increased incidence of resorptions at the two higher doses; complete resorption was observed at 1 g/kg bw. Reduced fetal weight and an increased incidence of cleft palate, fused ribs and dilated renal pelves were found at 0.75 mg/kg bw (Ema *et al*., 1992c). In an effort to define further the critical period for induction of teratogenicity by butyl benzyl phthalate, groups of rats were gavaged with 0.6, 0.75 or 1 g/kg bw daily on days 7–9, 10–12 or 13–15 of gestation. Exposure during any period resulted in dose-related increases in the rate of resorptions. Decreases in fetal body weight were observed only in groups exposed on days 7–9 or 10–12 of gestation, while malformations were present in fetuses exposed on days 7–9 or 13–15 (Ema *et al*., 1993). Post-implantation loss after dietary exposure to 2% butyl benzyl phthalate was seen as early as gestation day 11 and appeared to be related to reduced maternal plasma progesterone concentrations and impaired luteal function (Ema *et al*., 1994). The spectra of phase-specific effects on fetal development induced by metabolites of butyl benzyl phthalate (mono-*n*-benzyl phthalate and mono-*n*-butyl phthalate) and a related phthalate

(di-*n*-butyl phthalate) were similar to that of butyl benzyl phthalate itself (Ema *et al*., 1995, 1996a,b,c).

Butyl benzyl phthalate was given to female Wistar rats [number not specified] in the drinking-water at a concentration of 0 or 1000 μg/L two weeks before mating, during gestation and throughout three weeks of lactation. Treatment had no effect on litter size at birth, but male offspring were significantly larger on day 22. By days 90–95, the body weights were similar to those of controls, but the relative weight of the testes was reduced. There were no effects on testicular tissue, but butyl benzyl phthalate-treated males had a significantly reduced daily rate of sperm production (Sharpe *et al.*, 1995). A recent note from the authors, however, reported an unexplained temporal decrease in absolute testicular weight in control animals in their breeding colony. This decrease appeared to be at least as large as the effects seen with diethylstilboestrol, which had been used as a positive control in the studies of developmental toxicity (Sharpe *et al*., 1998).

Butyl benzyl phthalate was administered in the drinking-water to AP rats at a concentration of 0 or 1000 μg/L, the latter resulting in an estimated exposure to 180 μg/kg bw per day, during gestation and lactation. The weight of male pups at birth was significantly increased, as was the anogenital distance in males on day 2; female pups showed slightly earlier vaginal opening. Butyl benzyl phthalate had no significant effect on male body weights at day 90 or 137, however, nor were there effects on testicular weight, caudal or testicular sperm counts or the degree of positivity of pituitary cells for follicular-stimulating hormone (Ashby *et al*., 1997).

Butyl benzyl phthalate (purity, 98%) was evaluated for reproductive toxicity in the OECD 421 screening protocol. Groups of 10 WU rats, 10–11 weeks of age, were exposed for 29 days (males) or from 14 days before mating to six days *post partum* (females) to 0, 250, 500 or 1000 mg/kg bw per day by oral gavage. Mating, fertility and the viability and growth of the offspring were examined, and the reproductive tracts of the parental animals were assessed histologically. The body-weight gain of males at the high dose was reduced during treatment, while that of females was reduced during gestation. The numbers of animals that became pregnant were nine, eight, seven and four, with increasing dose. The litter size of dams at the high dose was significantly reduced at parturition, while the average pup weight at birth was reduced at the two higher doses. No dose-related anomalies were observed. At the high dose, the offspring had reduced testicular weights, while the parental males showed degeneration and Leydig-cell hyperplasia (Piersma *et al*., 1995).

Groups of 10–14 Wistar rats received 0, 250, 500, 750 or 1000 mg/kg bw per day butyl benzyl phthalate (purity, 98.2%) by oral gavage on days 0–8 of gestation or pseudogestation. The high dose was lethal to 2/14 pregnant females, and the body-weight gain was lower in all treated groups during exposure. A dose-related increase was seen in the percentage of females that did not become pregnant, and the numbers of implantation sites and fetal body weights at term were decreased. Similar overt toxicity was seen in pseudopregnant females exposed to butyl benzyl phthalate, which also had dose-related reductions in ovarian and uterine weights. The authors concluded that altered ovarian

and/or uterine function may contribute to the embryotoxicity of butyl benzyl phthalate (Ema *et al*., 1998).

Butyl benzyl phthalate did not affect uterine vascular permeability in ovarectomized Swiss mice 4 h after subcutaneous administration of 10^{-4} mol [31 mg/mouse], nor did it inhibit oestradiol-stimulated increases in uterine vascular permeability (Milligan *et al.*, 1998).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Butyl benzyl phthalate did not induce gene mutation in *Salmonella typhimurium* strains TA100, TA1535, TA1537 or TA98 with or without addition of an exogenous metabolic activation system. In single studies, it did not induce sex-linked recessive lethal mutation in *Drosophila,* gene mutation at the *tk* locus in mouse lymphoma L5178Y cells or sister chromatid exchange or chromosomal aberrations in Chinese hamster ovary cells *in vitro*. In one study, butyl benzyl phthalate given as a single intraperitoneal injection did not induce sister chromatid exchange in the bone marrow of male B6C3F1 mice. After a standard harvest time of 17 h, chromosomal aberrations were induced in the bone marrow of these mice; there was no increase in in the incidence of aberrations when a delayed harvest time of 36 h was used.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to butyl benzyl phthalate occurs during its production and use as a plasticizer, mainly in polyvinyl chloride products. It has been detected at low levels in indoor air, water and a few foods.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Butyl benzyl phthalate was tested for carcinogenicity by oral administration in one experiment in mice and three experiments in rats, including two studies with dietary restriction. No increase in the incidence of tumours was observed in mice. A marginal increase in the incidence of bladder tumours was observed in female rats after 32 months of dietary restriction. An increased incidence of benign pancreatic tumours was seen in one conventional study in male rats, but not after dietary restriction, despite extension of the period of dosing to 32 months.

Table 1. Genetic and related effects of butyl benzyl phthalate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Salmonella typhimurium TA100, TA98, reverse mutation	–	–	1000 µg/plate	Kozumbo *et al*. (1982)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, reverse mutation	–	–	11 550 µg/plate	Zeiger *et al*. (1985)
Drosophila melanogaster, sex-linked recessive lethal mutation	–		50 000 ppm feed	Valencia *et al*. (1985)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	67	Myhr & Caspary (1991)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	1250	Galloway *et al*. (1987)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	1250	Galloway *et al*. (1987)
Sister chromatid exchange, male B6C3F_1 mouse bone-marrow cells *in vivo*	–		2500 ip × 1	National Toxicology Program (1997a)
Chromosomal aberrations, male B6C3F_1 mouse bone-marrow cells *in vivo*	(+)		5000 ip × 1	National Toxicology Program (1997a)

[a] (+), weakly positive; –, negative

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro tests, µg/mL; in-vivo tests, mg/kg bw per day; ip, intraperitoneal

In one study in rats, butyl benzyl phthalate inhibited mammary carcinogenesis produced by prior administration of 7,12-dimethylbenz[*a*]anthracene.

5.4 Other relevant data

Butyl benzyl phthalate is hydrolysed in the gastrointestinal tract to mono-*n*-butyl phthalate and monobenzyl phthalate, which are absorbed, further metabolized, glucuronidated and excreted in the urine. Butyl benzyl phthalate weakly stimulated hepatic peroxisome proliferation. Although the compound binds weakly to oestrogen receptors *in vitro*, it had no oestrogenic activity *in vivo* in tests which included uterotropic effects and vaginal cornification.

Butyl benzyl phthalate has been tested for developmental toxicity in mice by administration in the diet and in rats by administration in the diet, by gavage and in drinking-water. Malformations and embryonic deaths were observed in both species, generally at maternally toxic doses. In rats, alterations in ovarian and/or uterine function appeared to be involved in the decreased embryonic viability. Testicular toxicity has been observed in male rats exposed to butyl benzyl phthalate.

No data were available on the genetic and related effects of butyl benzyl phthalate in humans. Butyl benzyl phthalate was not genotoxic in experimental systems, except for weak clastogenicity in bone-marrow cells of mice treated *in vivo* in one study.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of butyl benzyl phthalate.

There is *limited evidence* in experimental animals for the carcinogenicity of butyl benzyl phthalate.

Overall evaluation

Butyl benzyl phthalate is *not classifiable as to its carcinogenicity to humans (Group 3)*.

6. References

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