

## Butyl benzyl phthalate; CASRN 85-68-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR Butyl benzyl phthalate

**File First On-Line 08/22/1988**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	09/01/1989
<b>Inhalation RfC (I.B.)</b>	not evaluated	
<b>Carcinogenicity Assessment (II.)</b>	yes	08/22/1988

## I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

### I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Butyl benzyl phthalate

CASRN — 85-68-7

Last Revised — 09/01/1989

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

### I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
<b>Significantly increased liver-to-body weight and liver-to-brain weight ratios</b>	NOAEL: 2800 ppm (159 mg/kg/day)	1000	1	2E-1 mg/kg/day
	LOAEL: 8300 ppm (470 mg/kg/day)			
<b>6-Month Rat Study</b>				
<b>Oral Exposure (diet)</b>				
<b>NTP, 1985</b>				

\*Conversion Factors -- approximately 300 g bw and 17 g of food consumption/day from data presented in the report

### I.A.2. Principal and Supporting Studies (Oral RfD)

NTP (National Toxicology Program). 1985. Twenty-six week subchronic study and modified mating trial in F344 rats. Butyl benzyl phthalate. Final Report. Project No. 12307-02, -03. Hazelton Laboratories America, Inc. Unpublished study.

NTP (1985) conducted a toxicity study in F344 rats in which 15 males/group were administered concentrations of either 0, 0.03, 0.09, 0.28, 0.83, or 2.5% BBP in the diet for 26 weeks. Using body weight and food consumption data presented in the report these dietary levels correspond to 0, 17, 51, 159, 470, and 1417 mg/kg/day, respectively. In this study powdered rodent meal was provided in such a way that measured food consumption at the highest dose level could include significant waste and spillage rather than true food intake. For this reason a standard food consumption rate of 5% rat body weight was used in the 2.5% dose conversion. Throughout the study body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls. There were no deaths attributed to BBP toxicity. All the rats given 2.5% BBP had small testes upon gross necropsy; 5/11 had soft testes and 1/11 had a small prostate and seminal

vesicle. In the 0.03, 0.09, 0.28, and 0.83% dose groups there were no grossly observable effects on male reproductive organs. Terminal mean organ weight values were significantly decreased ( $p < 0.05$ ) for the heart, kidney, lungs, seminal vesicles and testes in the 2.5% group. Hematological effects at 2.5% BBP included decreased red cell mass (which the authors state is indicative of deficient hemoglobin synthesis), reduced values for hemoglobin, total RBC and hematocrit. The kidneys of six animals in the 2.5% group contained focal cortical areas of infarct-like atrophy. In addition, testicular lesions were also observed at the 2.5% dose level. Lesions were characterized by atrophy of seminiferous tubules and aspermia. At 0.83% the effects noted were significantly ( $p < 0.05$ ) increased absolute liver weight, increased liver-to-body weight and liver-to-brain weight ratios and increases in mean corpuscular hemoglobin. The 0.03, 0.09, 0.28, and 0.83% treatment groups showed no evidence of abnormal morphology in any organ. No adverse effects were observed at the 0.28% treatment level or below.

The only other information on subchronic effects is reported by Krauskopf (1973) from an unpublished study by Monsanto (1972). Rats fed diets containing 0.25% (125 mg/kg/day) and 0.5% (250 mg/kg/day) for 90 days showed no toxic effects. Liver weights were increased in animals fed diets containing 1.0, 1.5, or 2.0% (500, 750, or 1000 mg/kg/day, respectively) for 90 days, and a mild decrease in growth rate was reported for the 1.5 and 2.0% groups. No other hematologic, histopathologic or urinalysis effects were observed. When dogs were administered gelatin capsules containing doses equivalent to 1.0, 2.0, or 5.0% of the daily diet (10,000, 20,000 and 50,000 ppm) for 90 days, no effect on hematological parameters, urinalysis or liver and kidney functions were observed. No further details of this study were available for review.

Similar LOAELs of 470 and 500 mg/kg/day for increased liver weight were identified in both the NTP (1985) and Monsanto (1972) studies, respectively. NOAELs differ slightly: 159 (NTP, 1985) versus 250 mg/kg/day (Monsanto, 1972). It is recommended that the NOAEL of 159 mg/kg/day from the NTP (1985) study be used to derive the RfD for two reasons: 1) the NTP (1985) study is of longer duration, and 2) The Monsanto (1972) study provides an incomplete description of methods comparing study design and clinical analysis. Treatment-related effects across similar dose ranges including liver effects in both studies support the use of 159 mg/kg/day as a NOAEL.

### **I.A.3. Uncertainty and Modifying Factors (Oral RfD)**

UF — 10 for intraspecies sensitivity, 10 for interspecies variability and 10 for extrapolating from subchronic to chronic NOAELs.

MF — None

### **I.A.4. Additional Studies/Comments (Oral RfD)**

Two 14-day studies support the selection of the NTP (1985) bioassay for deriving the oral RfD. Agarwal et al. (1985) administered BBP to male F344 rats in the diet for 14 consecutive days at dose levels of 0.625, 1.25, 2.5, and 5.0%. Significant increases in liver and kidney weights and kidney pathology (proximal tubular regeneration) was observed at 0.625% (375 mg/kg/day), which represents a LOAEL.

In male Sprague-Dawley rats administered 160, 480, or 1600 mg/kg/day BBP for 14 days by gastric intubation, biochemical or morphological changes in the liver as well as effects on testes weights were not observed in the 160 mg/kg/day dose group (Lake et al., 1978). However, at 480 mg/kg/day activities of ethyl morphine N-demethylase and cytochrome oxidase were significantly increased and testicular atrophy was observed in one-third Sprague-Dawley rats in the first portion of this experiment. In the second position, the 480 mg/kg/day dose induced testicular atrophy in one-sixth Sprague-Dawley rats, whereas the Wistar albino strain revealed no such effects. A NOAEL for this study would be 160 mg/kg/day based on the absence of liver and testicular effects.

In an addendum to the NTP (1985) final report, evaluation of the data revealed a significantly reduced total marrow cell count in the 2.5% dose group (NTP, 1986). The change in total cell count was comprised primarily of significant decreases in neutrophil, metamyelocytes, bands, segmeters, lymphocytes and leasophilic rubricytes. The total marrow cell counts, metamyelocyte, and leasophilic rubricyte counts were also significantly decreased in the lowest dose group, 0.03%. No statistically significant differences were noted in the middle dose groups (0.09, 0.28, or 0.83%) when compared with controls. The addendum states that decreased total marrow cell count in the 0.03 and 2.5% dose group represent change of uncertain meaning in light of the systemic effects noted in the middle dose groups. Trend analysis by the Terpstra- Jonckheere test revealed significantly ( $p < 0.05\%$ ) decreasing trends in all of the previously mentioned parameters as well as an increasing trend for monocytes at 0.03 and 2.5%.

NTP (1985) also conducted a male mating trial study concomitantly with the toxicity study. Testicular atrophy was observed in male F344 rats after 10 weeks of exposure to 2.5% (2875 mg/kg/day) BBP. Throughout the study, body weight gain was significantly depressed at the 2.5% BBP level when compared with the controls.

### **I.A.5. Confidence in the Oral RfD**

Study — Medium

Database — Low

RfD — Low

The critical study is of adequate quality and is given a medium confidence rating. Since the critical study used only male rats and there are no adequate supporting studies of chronic duration, the database is given a low confidence rating. Low confidence in the RfD follows.

#### **I.A.6. EPA Documentation and Review of the Oral RfD**

Source Document — U.S. EPA, 1987a,b; 1988

U.S. EPA (1987a, 1988) have been both OHEA reviewed and Agency Reviewed. U.S. EPA (1987b) has been OHEA reviewed.

Other EPA Documentation — None

Agency Work Group Review — 06/15/1989

Verification Date — 06/15/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Butyl benzyl phthalate conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

#### **I.A.7. EPA Contacts (Oral RfD)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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#### **I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)**

Substance Name — Butyl benzyl phthalate  
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Not available at this time.

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## **II. Carcinogenicity Assessment for Lifetime Exposure**

Substance Name — Butyl benzyl phthalate

CASRN — 85-68-7

Last Revised — 08/22/1988

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

### **II.A. Evidence for Human Carcinogenicity**

#### **II.A.1. Weight-of-Evidence Characterization**

Classification — C; possible human carcinogen.

Basis — Based on statistically significant increase in mononuclear cell leukemia in female rats; the response in male rats was inconclusive and there was no such response in mice.

#### **II.A.2. Human Carcinogenicity Data**

None.

#### **II.A.3. Animal Carcinogenicity Data**

Limited. A bioassay was performed by the NTP (1982) to evaluate the carcinogenic potential of orally administered butyl benzyl phthalate (BBP) to both rats and mice. Dietary levels of 0, 6000, and 12,000 ppm BBP were fed to groups of 50 male and 50 female F344 rats and 50 male and 50 female B6C3F1 mice for 103 weeks. The male rats at both dose levels experienced high

mortality within the first 30 weeks of the study due to apparent internal hemorrhaging; all male rats were, thus, terminated at 30 weeks. No chronic toxicity or carcinogenic effects were observed in male or female mice. Among female rats a statistically significant increase in mononuclear cell leukemia (MCL) or lymphoma ( $p=0.007$ ) was observed at the high dose level compared with controls with an increasing trend at  $p=0.006$ . The time to first tumor was 83 weeks in control as well as in the high-dose group. NTP indicated that BBP was "probably" carcinogenic in female rats. The tumor incidence was 7/49 (14%) for controls, 7/49 (14%) in low dose and 19/50 (38%) in the high dose as compared with historical control incidence in the laboratory of 19% (12-24% range).

Given the similarity of the MCL pathology in the control and the dosed female rats as well as the absence of a reduction in time to first tumor, the response is judged to be an acceleration of an old age tumor in the F344 rats. This weakens somewhat the interpretive value of the MCL response. The NTP has initiated a retest in the rats.

BBP did not induce lung adenomas in strain A mice administered 24 intraperitoneal injections of 160, 400 or 800 mg/kg (Theiss et al., 1977).

#### **II.A.4. Supporting Data for Carcinogenicity**

Studies indicate that BBP is not a direct acting mutagen in the reverse mutation assay in *Salmonella typhimurium* (Rubin et al., 1979; Kozumbo et al., 1982; Zeiger et al., 1982) or in *E. coli* (NTP, 1982). Mammalian cytogenicity studies using chinese hamster ovary cells were also negative (NTP, 1982). NTP (1982) noted that additional studies on metabolites, benzyl alcohol and n-butanol was important.

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#### **II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure**

Not available. The qualitative weaknesses of the MCL response does not provide a compelling basis to model the dose-response data.

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#### **II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure**

Not available.

## **II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)**

### **II.D.1. EPA Documentation**

Source Document — U.S. EPA, 1987

The 1987 Draft Drinking Water Quality Criteria Document received Agency review.

### **II.D.2. EPA Review (Carcinogenicity Assessment)**

Agency Work Group Review — 08/26/1987

Verification Date — 08/26/1987

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Butyl benzyl phthalate conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) or 202-566-1676.

### **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (internet address).

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Butyl benzyl phthalate  
CASRN — 85-68-7



## VI.A. Oral RfD References

Agarwal, D.K., R.R. Maronpot, J.C. Lamb, IV and W.M. Kluwe. 1985. Adverse effects of butylbenzyl phthalate on the reproductive and hematopoietic systems of male rats. *Toxicology*. 35: 189-206.

Krauskopf, L.G. 1973. Studies on the toxicity of phthalates via ingestion. *Environ. Health Perspect.* 3: 61-72.

Lake, B.G., R.A. Harris, P. Grasso and S.D. Gangollia. 1978. Studies on the metabolism and biological effects of n-butyl benzyl phthalate in the rat. Prepared by British Industrial Biological Research Association for Monsanto, Report No. 232/78, June.

Monsanto Chemical Company. 1972. Unpublished work. (Cited in Krauskopf, 1973)

NTP (National Toxicology Program). 1985. Twenty-six week subchronic study and modified mating trial in F344 rats. Butyl benzyl phthalate. Final Report. Project No. 12307-02, -03. Hazelton Laboratories America, Inc. Unpublished study.

NTP (National Toxicology Program). 1986. Addendum to Final Report. Bone marrow differential results - 26 Week study. LBI/HLA Project No. 12307-02. Hazelton Laboratories America, Inc. Unpublished report.

U.S. EPA. 1987a. Health and Environmental Profile for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1987b. Health Effects Assessment for Selected Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1988. Drinking Water Criteria Document for Phthalic Acid Esters (PAEs). Prepared by the Office of Health and Environmental Assessment Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. Final Draft.

## **VI.B. Inhalation RfD References**

None

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## **VI.C. Carcinogenicity Assessment References**

Kozumbo, W.J., R. Kroll and R.J. Rubin. 1982. Assessment of the mutagenicity of phthalate esters. *Environ. Health Perspect.* 45: 103-109.

NTP (National Toxicology Program). 1982. Carcinogenesis Bioassay of Butyl Benzyl Phthalate (CAS No. 85-68-7) in F344 Rats and B6C3F1 Mice (Feed Study). NTP Tech. Rep. Ser. TR No. 213, NTP, Research Triangle Park, NC. p. 98

Rubin, R.J., W. Kozumbo and R. Kroll. 1979. Ames mutagenic assay of a series of phthalic acid esters: Positive response of the dimethyl and diethyl esters in TA100. *Soc. Toxicol. Ann. Meet.*, New Orleans, March 11-15. p. 11. (Abstract)

Theiss, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisburger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. *Cancer Res.* 37: 2717-2720.

U.S. EPA. 1987. Drinking Water Criteria Document for Phthalic Acid Esters. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

Zeiger, E., S. Haworth, W. Speck and V. Mortlemans. 1982. Phthalate ester testing in the National Toxicology Program's environmental mutagenesis test development program. *Environ. Health Perspect.* 45: 99-101.

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## VII. Revision History

Substance Name — Butyl benzyl phthalate

CASRN — 85-68-7

Date	Section	Description
08/22/1988	II.A.	Carcinogen summary on-line
09/01/1989	I.A.	Oral RfD summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

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## VIII. Synonyms

Substance Name — Butyl benzyl phthalate

CASRN — 85-68-7

Last Revised — 08/22/1988

- 85-68-7
- BBP
- 1,2-BENZENEDICARBOXYLIC ACID, BUTYL PHENYLMETHYL ESTER
- BENZYL-BUTYLESTER KYSELINY FTALOVE
- BENZYL BUTYL PHTHALATE
- BENZYL n-BUTYL PHTHALATE
- Butyl benzyl phthalate
- n-BUTYL BENZYL PHTHALATE
- BUTYL PHENYLMETHYL 1,2-BENZENEDICARBOXYLATE
- NCI-C54375
- PALATINOL BB
- PHTHALIC ACID, BENZYL BUTYL ESTER
- SANTICIZER 160
- SICOL 160
- UNIMOLL BB