BUTYL BENZYL PHTHALATE

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Concise International Chemical Assessment Document 17

BUTYL BENZYL PHTHALATE

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World Health Organization
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The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide

technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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TABLE OF CONTENTS

FOREWORD

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) -- a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose-response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

[1] International Programme on Chemical Safety (1994)
    *Assessing human health risks of chemicals: deriviation of
    guidance values for health-based exposure limits:* Geneva,
   World Health Organization (Environmental Health Criteria 170).

Procedures

       The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world -- expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

       The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

       The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

       The CICAD Final Review Board has several important functions:

-     to ensure that each CICAD has been subjected to an appropriate
      and thorough peer review;
-     to verify that the peer reviewers' comments have been addressed
      appropriately;
-     to provide guidance to those responsible for the preparation of
      CICADs on how to resolve any remaining issues if, in the opinion
      of the Board, the author has not adequately addressed all
      comments of the reviewers; and
-     to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and

the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

CICAD PREPARATION FLOW CHART

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1   Taking into account the comments from reviewers.
2   The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3   Includes any revisions requested by the Final Review Board.

1. EXECUTIVE SUMMARY

This CICAD on butyl benzyl phthalate was prepared jointly by the Environmental Health Directorate of Health Canada and the Commercial Chemicals Evaluation Division of Environment Canada based on documentation prepared concurrently as part of the Priority Substances Program under the *Canadian Environmental Protection Act* (CEPA). The objective of assessments on Priority Substances under CEPA is

to assess potential effects of indirect exposure in the general environment on human health as well as environmental effects. Data identified as of the end of April 1998 were considered in these reviews. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Tokyo, Japan, on 30 June – 2 July 1998. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0834) for butyl benzyl phthalate, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Butyl benzyl phthalate (CAS No. 85-68-7), or BBP, is a clear, oily liquid that is used as a plasticizer mainly in polyvinyl chloride (PVC) for vinyl floor tile, vinyl foams, and carpet backing and to a minor extent also in cellulose plastics and polyurethane. Most environmental release is to the air. Once in the environment, BBP partitions to the atmosphere, soil, surface water, sediments, and biota and has been detected in each of these compartments.

BBP is removed from the atmosphere by photooxidation and by rainwater, with a half-life of a few hours to a few days. BBP is not persistent in water, sediments, or soil under aerobic conditions, with a half-life of a few days. Under anaerobic conditions, BBP is more persistent, with a half-life of a few months. BBP is readily metabolized by vertebrates and invertebrates. Reported bioconcentration factors (BCFs) are less than 1000 based on total residues and well under 100 based on intact BBP residues.

Available data in humans are inadequate to serve as a basis for assessment of the effects of long-term exposure to BBP in human populations.

The acute toxicity of BBP is relatively low, with oral LD_{50} values in rats being greater than 2 g/kg body weight. Target organs following acute exposure include the haematological and central nervous systems.

Available data are inadequate to assess the irritant and sensitizing effects of BBP in animal species.

The repeated-dose toxicity of BBP has been well investigated in recent studies, primarily in the rat, in which dose-response was well characterized. Effects observed consistently have been decreases in body weight gain (often accompanied by decreases in food consumption) and increases in organ to body weight ratios, particularly for the kidney and liver. Histopathological effects on the pancreas and kidney and haematological effects have also been observed. At higher doses, degenerative effects on the testes and, occasionally, histopathological effects on the liver have been reported. In specialized investigations, peroxisomal proliferation in the liver has been observed, although potency in this regard was less than that for other phthalates, such as bis(2-ethylhexyl) phthalate (DEHP).

The chronic toxicity and carcinogenicity of BBP have been investigated in US National Toxicology Program (NTP) bioassays in rats

(including standard and feed-restricted protocols) and mice. It was concluded that there was "some evidence" of carcinogenicity in male rats, based on an increased incidence of pancreatic tumours, and equivocal evidence in female rats, based on marginal increases in pancreatic and bladder tumours. Dietary restriction prevented full expression of the pancreatic tumours and delayed appearance of the bladder tumours. There was no evidence of carcinogenicity in mice.

The weight of evidence of the genotoxicity of BBP is clearly negative. However, available data are inadequate to conclude unequivocally that BBP is not clastogenic, although in identified studies it has induced, at most, weak activity of a magnitude consistent with secondary effects on DNA.

Therefore, BBP has induced an increase in pancreatic tumours primarily in one sex of one species, the full expression of which was prevented in a dietary restriction protocol, and a marginal increase in bladder tumours in the other sex, which was delayed upon dietary restriction. The weight of evidence of genotoxicity is negative, and, although weak clastogenic potential cannot be ruled out, available data are consistent with the compound not interacting directly with DNA. On this basis, BBP can be considered, at most, possibly carcinogenic to humans, likely inducing tumours through a non-genotoxic (although unknown) mechanism.

In a range of studies, including those designed to investigate the reproductive effects of BBP on the testes and endocrine hormones of male rats, a modified mating protocol conducted by the NTP, and a one-generation study, adverse effects on the testes and, consequently, fertility have generally been observed only at doses higher than those that induce effects on other organs (such as the kidney and liver), although decreases in sperm counts have been observed at doses similar to those that induce effects in the kidney and liver. This is consistent with the results of repeated-dose toxicity studies.

Reductions in testes weight and daily sperm production in offspring were reported at a relatively low level in rats exposed *in utero* and during lactation in a study in which dose-response was not investigated. However, such effects were not observed in a recent study of similar, but not identical, design in another strain of rats in which only increases in absolute and relative liver weights were observed at postnatal day 90. Additional investigation of potential effects on the reproductive systems of male and female animals exposed *in utero* and during lactation in studies designed to address dose-response is desirable and is under way.

Although BBP has been estrogenic in human breast cell cancer lines *in vitro*, results in yeast cells have been mixed. Neither BBP nor its principal metabolites have been uterotrophic *in vivo* in rats or mice. Although available data do not support the conclusion that BBP is estrogenic, other potential endocrine-mediated effects such as anti-androgenic activity associated with dibutyl phthalate (DBP) are not precluded.

There is considerable emphasis currently on development of more sensitive frameworks for testing and assessment of endocrine-disrupting substances; compounds such as phthalates are

likely early candidates for additional testing.

In several well-conducted studies in rats and mice, BBP has induced marked developmental effects, but only at dose levels that induce significant maternal toxicity.

Although the potential neurotoxicity of BBP has not been well investigated, histopathological effects on the central and peripheral nervous systems have not been observed following short-term exposure to relatively high dietary concentrations. Available data are inadequate to assess the potential immunotoxicity of BBP.

A sample tolerable daily intake (TDI) of 1300 µg/kg body weight per day has been derived for BBP. It is based upon the lower 95% confidence limit for the benchmark dose associated with a 5% increase in the incidence of pancreatic lesions in male rats in an oral subchronic bioassay divided by an uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation). Based upon concentrations in various environmental media, it appears (from sample estimates) that food contributes all of the estimated intake, which is considered, for the general population, to range from 2 to 6 µg/kg body weight per day. These estimates are 200-650 times less than the TDI. Data were inadequate to estimate exposure in the occupational environment or from consumer products.

A range of toxicity tests with aquatic organisms has indicated that adverse effects occur at exposure concentrations equal to or greater than 100 µg/litre. As concentrations in surface waters are generally less than 1 µg/litre, it is likely that BBP poses low risk to aquatic organisms.

No information about the effects of BBP on sediment-dwelling organisms, soil invertebrates, terrestrial plants, or birds has been identified on which to base an estimate of risk to these organisms.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

The physical and chemical properties of BBP have been summarized by Skinner (1992). BBP (CAS No. 85-68-7) is an aromatic ester that conforms to the formula $C_{19}H_{20}O_4$. Synonyms include 1,2-benzenedicarboxylic acid, butyl phenylmethyl ester, and benzyl *n*-butyl phthalate. BBP is a clear, oily liquid at room temperature with a molecular weight of 312.4 g/mol. Reported log octanol/water partition coefficients (log K_{ow}) range from 3.6 to 5.8; 4.91 is a measured value, whereas the 4.77 provided in the International Chemical Safety Card is an estimated value. Additional physical/ chemical properties are presented in the International Chemical Safety Card reproduced in this document.

3. ANALYTICAL METHODS

Analytical methods have been reviewed by Skinner (1992). BBP may be analysed by gas chromatography/mass spectrometry and by high-performance liquid chromatography. It is determined in water by an enrichment procedure using sequential reverse osmosis, followed by

extraction and analysis by gas chromatography/mass spectrometry, or after adsorption onto Tenax material and thermal desorption to a fused silica capillary gas chromatography column under whole-column cryotrapping conditions (Pankow et al., 1988). In air, BBP has been determined by liquid chromatographic separation using a florisil adsorbent and 10% 2-propanol in hexane as the eluent followed by gas chromatographic analysis with detection by ^{63}Ni electron capture (Stein et al., 1987). BBP can be determined in mixtures of semivolatile organic pollutants using gas chromatography/Fourier transform infrared spectroscopy with wall-coated open tubular capillary columns. Combining this technique with gas chromatography/mass spectrometry allows for better and faster identification of the components of complex mixtures of environmental pollutants.

In reports of analyses of environmental media for BBP, detection limits were 1 µg/litre for samples of drinking-water (G. Halina, personal communication, 1994; method not specified) and 0.2 mg/kg dry weight for soil (gas chromatography/mass spectrometry; Webber & Wang, 1995). Detection limits for analyses (by gas chromatography/flame ionization detection) of table-ready foods were 0.5 µg/g (butter), 0.2 µg/g (vegetables and fruits), and 0.1 µg/g (meat and fish) (Page & Lacroix, 1995). The detection limits varied with the fat content of the food and food matrix interferences.

4.   SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

BBP is manufactured by the reaction of the monobutyl ester of phthalic acid with benzyl chloride (Skinner, 1992). In the USA, Monsanto Company is the sole manufacturer of BBP (Anon., 1996). BBP is used mainly as a plasticizer in PVC for vinyl floor tile, vinyl foams, and carpet backing. Other polymers plasticized with BBP include cellulose plastics, polyvinyl acetate, polysulfides, and polyurethane. Consumption of BBP in Europe is approximately 18 000-45 000 tonnes per year (Harris et al., 1997).

BBP is released from facilities that manufacture the substance or blend it with PVC (Howard, 1990). Releases may also occur through diffusion of BBP from PVC products.

Total on-site environmental releases of BBP reported to the Canadian National Pollutant Release Inventory by 11 facilities using BBP amounted to 3.7 tonnes in 1994, all to the atmosphere. Total transfers of BBP for off-site disposal were much higher, amounting to 33.3 tonnes in 1994, with 25.1 tonnes going to incinerators and the remainder, 8.2 tonnes, to landfill. A reported total of 3.7 tonnes of BBP was sent for recovery in 1994, 2.3 tonnes for energy recovery and 1.4 tonnes for recovery, reuse, or recycling (NPRI, 1996).

In the USA, it was estimated that manufacturing facilities released approximately 176 tonnes to the environment in 1993, with about 99% released to the atmosphere (TRI93, 1995).

BBP may be released to air through automobile emissions and from combustion of refuse (Graedel et al., 1986). It has also been detected in stack emissions from hazardous waste combustion facilities and from

coal-fired power plants in the USA (Oppelt, 1987). Reasonable worst-case emissions of BBP from incinerators, boilers, and industrial furnaces burning such wastes were predicted to be 3 µg/m³ waste gas (Dempsey & Oppelt, 1993). In a study of four US coal-fired utility boiler plants, the emission rates for BBP in flue gases ranged from 210 to 3400 mg/h (Haile et al., 1984). BBP was identified, but not quantified, in extracts of municipal incinerator fly ash from the Netherlands, but it was not detected in extracts from Japan or Ontario (Eiceman et al., 1979).

In leachate from municipal landfills in the USA, BBP was detected, but not quantified (Brown & Donnelly, 1988). BBP has also been detected (detection limits not reported) in groundwater at disposal sites in the USA (Plumb, 1991). BBP was also detected in 2 of 44 groundwater samples at a Superfund site in Michigan, USA, at estimated concentrations of 0.6 and 1.0 µg/litre (US EPA, 1996).

In Canada, BBP has been detected in storm sewer effluents at concentrations up to 50 µg/litre (Hargesheimer & Lewis, 1987) and in effluents from municipal sewage treatment plants and industrial plants at concentrations up to 25 µg/litre (Munro et al., 1985; SIGMA, 1985; OMOE, 1988, 1990, 1991).[1] BBP has also been detected in sludges from Canadian sewage treatment plants at concentrations up to 914 498 ng/g dry weight (OMOE, 1988).

BBP can be emitted from products containing the substance. For example, BBP has been detected in emissions from carpets (Bayer & Papanicolopoulos, 1990), PVC floorings (Bremer et al., 1993), and vinyl wall coverings (Etkin, 1995), although quantitative data were not identified. It is also a component of some consumer products, such as nail polish (Martin, 1996). The possibility that toys made of plastic might contain BBP is currently being investigated, although quantitative data are not yet available.

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[1] Additional data from ENVIRODAT, Surveys and Information Systems Branch, Environment Canada, 1993.

5.   ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Fugacity modelling was based upon the assumption of continuous emissions of 1000 kg/h to air, water, or soil (DMER & AEL, 1996). Most environmental releases of BBP are to the atmosphere. The Level III calculations of the EQC fugacity model predict that when BBP is emitted into air, approximately 72% is found in soil, 22% in air, 4% in water, and 2% in sediment. When BBP is emitted into water, 65% is found in water, while about 35% partitions to sediment and a very small fraction to soil. When BBP is released to soil, more than 99% is found in the soil. Values for input parameters were as follows: molecular weight, 312.4 g/mol; vapour pressure, 0.001 15 Pa; water solubility, 2.69 mg/litre; melting point, -35°C; and log K_{ow}, 4.9. Average degrading reaction half-lives were assumed to be 55 h in air, 170 h in water, 550 h in soil, and 1700 h in sediment (Mackay et al., 1995). The calculated organic carbon/water partition coefficient (log K_{oc}) is 4.51 (based on the correlation $K_{oc} = 0.41$ K_{ow}), and the Henry's law constant is 0.133 Pa·m³/mol at 25°C.

Photooxidation is the most important process for the breakdown of BBP in the atmosphere (Atkinson, 1987). Howard et al. (1991) estimated a half-life in air of 6-60 h for BBP based on photooxidation rates. BBP is also readily removed from air by rain (Ligocki et al., 1985a).

BBP is readily biodegraded in aerobic surface water, with a half-life of about 1-7 days (Saeger & Tucker, 1976; Gledhill et al., 1980; Howard et al., 1991; Adams & Saeger, 1993). Biodegradation is considerably slower in cold water, as BBP was almost completely biodegraded after 7 days in Rhine River water at 20°C but was not biodegraded in the same water after 10 days at 4°C (Ritsema et al., 1989). BBP is expected to adsorb to suspended matter, sediments, and biota.

Biodegradation is the most important degradation pathway in sediments (Gledhill et al., 1980; Adams & Saeger, 1993). In a river water/sediment microcosm, the degradation pathway appeared to be BBP -> monobutyl/monobenzyl phthalate -> phthalic acid -> 4,5-dihydroxyphthalic acid -> oxalic acid -> formic acid -> carbon dioxide (Adams et al., 1986, 1989; Adams & Saeger, 1993). The half-life for complete mineralization of BBP in this study was 13 days (Adams & Saeger, 1993). BBP can also be biodegraded in sediment under anaerobic conditions (Shelton & Tiedje, 1984; Painter & Jones, 1990; Ejlertsson et al., 1996), with an estimated half-life of about 1 day to 6 months (Howard et al., 1991).

Biodegradation of BBP occurs readily in aerobic soils, with a half-life of about 1-7 days at room temperature (Howard et al., 1991). It is also biodegraded in anaerobic soils. For the removal of BBP in a silt loam, Kincannon & Lin (1985) determined a half-life of 59.2 days. BBP sorbs to soil, so soil leaching should not be significant (Zurmhhl et al., 1991).

With reported log K_{ow} values ranging from 3.6 to 5.8, BBP would appear to have a high potential for bioaccumulation. However, reported BCFs in oysters, microorganisms, and several species of fish are less than 1000, because BBP is readily metabolized, with a depuration half-life of less than 2 days (Barrows et al., 1980; Veith et al., 1980). The highest reported BCF was 776 for bluegill (*Lepomis macrochirus*) (Veith et al., 1980).

Based on physical/chemical properties of BBP, Wild & Jones (1992) predicted that retention of the substance by root surfaces of plants would be high, but that subsequent uptake by plants would be low. This prediction was confirmed by Müller and Kördel (1993), who demonstrated that plants grown on phthalate-enriched soil did not take up BBP from the soil through the roots. However, plants exposed to phthalate-treated dust did take up BBP through leaf cuticles (quantitative data not available).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

In air samples from Greater Vancouver, British Columbia, Canada,

BBP was detected at concentrations ranging from 0.38 to 1.78 ng/m^3 (W. Belzer, personal communication, 1997). Concentrations of BBP in air up to 9.6 ng/m^3 (in the aerosol phase at Portland, Oregon, USA) have been reported (Ligocki et al., 1985a,b). BBP has been identified in ambient air in Barcelona, Spain; concentrations of 1.0 and 8.0 ng/m^3 in winter and 0.25 and 2.0 ng/m^3 in summer, associated with coarse (>7.2 μm) and fine (<0.5 μm) aerosol fractions, respectively, have been reported (Aceves & Grimalt, 1993).

In Canadian surface waters, BBP was detected at concentrations up to 1 μg/litre.[1] Gledhill et al. (1980) reported a concentration of 2.4 μg/litre in the Mississippi River south of St. Louis, Missouri, USA. In central Italy, BBP was detected at concentrations up to 6.6 μg/litre in Lake Scandarello (Vitali et al., 1997). In water samples collected from the Rhine River and its tributaries, levels ranged up to 5.2 μg/litre (ECPI, 1996). In samples of inflow and outflow from sewage treatment plants in Sweden and Norway, concentrations of BBP up to 2.4 μg/litre and 0.58 μg/litre, respectively, were reported (ECPI, 1996; NIWR, 1996).

BBP has been reported in marine sediments from British Columbia, Canada, at concentrations up to 370 ng/g dry weight (Axys Analytical Services Limited, 1992; D. Goyette, personal communication, 1993). Outside Canada, the highest reported concentration of BBP in sediments was 3800 ng/g dry weight, in sediments from the Lower Passaic River, Newark, New Jersey, USA, adjacent to combined sewer overflow outfalls (Iannuzzi et al., 1997).

In limited surveys of soils from agricultural and typical urban residential and parkland locations in Canada, concentrations of BBP were less than 0.3 μg/g (Golder Associates, 1987; Webber & Wang, 1995).

At a lime disposal area of a refinery in Regina, BBP concentrations in soil of 0.15 and 0.55 μg/g were reported.[2] In soil in the neighbourhood of three phthalate-emitting plants in Germany from 1986 to 1989, the highest concentration in an individual sample was 100 μg/kg; the highest mean value for a single site was 30 μg/kg (Müller & Kördel, 1993).

[1] Data from ENVIRODAT, Surveys and Information Systems Branch, Environment Canada, 1993.

[2] Letter from D. Fast, Saskatchewan Department of Environment and Public Safety, to Senes Consultants Limited, Richmond Hill, Ontario, 1989.

In Canadian biota, BBP has been detected at concentrations up to 1470 ng/g wet weight (in butter sole, *Isopsetta* [*Pleuronectes*] *isolepis*, from Boundary Bay, British Columbia; Swain & Walton, 1990). BBP was detected in US biota at 3% of 182 STORET stations, with a median concentration of <2500 ng/g (Staples et al., 1985).

6.2 Human exposure

In 125 homes in California, USA, two 12-h indoor air samples were

collected during daytime and overnight periods. In indoor air, median daytime and nighttime concentrations were 34 and 35 ng/m^3, respectively. In a subset of 65 homes, outdoor air samples were also collected. In outdoor air, the median (for both daytime and nighttime sampling) was below the method quantifiable limit of 5.1 ng/m^3; the 90th percentiles were 5.3 and 6.7 ng/m^3 for daytime and nighttime sampling, respectively (California Environmental Protection Agency, 1992). In an early study, BBP concentrations of 1 and 20 ng/m^3 were reported in office air at two locations in the USA, although the compound was not detected (detection limit not reported) in ambient air (Weschler, 1984).

In surveys of drinking-water primarily from surface water supplies conducted at over 300 sites in two provinces in Canada between 1985 and 1994, BBP was detected in only one sample in 1991 (2.8 µg/litre; limits of detection 1–3 µg/litre) (D. Spink, personal communication, 1986; G. Halina, personal communication, 1994; A. Riopel, unpublished data, 1994, 1996).

Of approximately 100 foodstuffs (generally single composite samples from four supermarkets) purchased in Ontario, Canada, in 1985 and 1988 in a total diet study, BBP was detected only in yoghurt (0.6 µg/g), cheddar cheese (1.6 µg/g), butter (0.64 µg/g), and crackers (0.48 µg/g) (detection limits ranged from 0.005 to 0.5 µg/g; Page & Lacroix, 1995).

In foods purchased at retail stores in the United Kingdom and stored in their packaging until their "best before" date, BBP was not detected in chocolate or sugar confectioneries, although it was detected in baked savouries (1.5 mg/kg), meat pies (4.8 mg/kg), and sandwiches (14 mg/kg) (MAFF, 1987). In stored samples of composite fatty foods in a total diet study in the United Kingdom, BBP was detected in carcass meat (0.09 mg/kg), poultry (0.03 mg/kg), eggs (0.09 mg/kg), and milk (0.002 mg/kg) (MAFF, 1996a). Concentrations in 59 individual samples of 15 different brands of infant formula from retail outlets in five towns across the United Kingdom ranged from <0.004 to 0.25 mg/kg (MAFF, 1996b).

An example of indirect exposure in the general environment is presented here. Exposure of the general population to BBP in environmental media may be estimated based upon concentrations determined in various media and reference values for body weight and

consumption patterns. Owing to the availability of relevant data, exposure has been estimated based primarily upon data from Canada. However, countries are encouraged to estimate total exposure on the basis of national data, possibly in a manner similar to that outlined here. Indeed, estimates based on the data on concentrations in foodstuffs determined in the United Kingdom presented above would be higher than those provided as examples here.

Although concentrations of BBP in air (both ambient and indoor), drinking-water, and soil have been reported, they are so low that intakes from these routes are essentially negligible. Estimates of exposure for the general population are based almost entirely upon the estimates for intake from food. The estimates presented here are based upon identified concentrations for foodstuffs in Canada, as well as

assumed concentrations of zero or method detection limits for foods in which BBP was not identified (minimum and maximum estimates, respectively). Adults are assumed to breathe 15.8 m^3 of air per day (Allan, 1995), weigh 70 kg, drink 1.4 litres of water per day, ingest 20 mg soil per day, and consume, on a daily basis, 13.61 g butter, 3.81 g processed cheddar cheese, 1.54 g yoghurt, 22.73 g fresh pork, and 3.45 g crackers (Health Canada, 1994). Estimated intake for adults is 2 µg/kg body weight per day; intake values for infants and children are up to threefold higher. Data are inadequate to estimate intake in breast-fed infants.

Identified data on concentrations of BBP in the occupational environment are inadequate as a basis for estimation of exposure. Similarly, data are inadequate for estimation of exposure from consumer products, although it should be noted that inclusion of information on levels in indoor air in the estimates of exposure for the general population presented here should account at least partially for exposure from consumer products.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

No data were identified concerning the absorption, metabolism, or elimination of BBP in humans.

Based upon a limited number of studies (Erickson, 1965; Kluwe, 1984; Eigenberg et al., 1986; Mikuriya et al., 1988; Elsisi et al., 1989) conducted principally in rats following oral administration, BBP is readily hydrolysed in the gastrointestinal tract and the liver to the corresponding monobutyl or benzyl ester. These phthalate monoesters are then rapidly eliminated (90% in 24 h) in the excreta in ratios of approximately 80% in urine and 20% in faeces, although results of one study indicate that the fraction eliminated in faeces increases at higher doses (of approximately 2 g/kg body weight) (Eigenberg et al., 1986). The monobutyl ester is generally present in highest amounts; for example, the ratio of monobutyl to monobenzyl phthalate in rats in one study was 5:3 (Mikuriya et al., 1988).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

The acute toxicity of BBP is relatively low. Reported oral LD$_{50}$ values for rats range from 2 to 20 g/kg body weight (NTP, 1982; Hammond et al., 1987); a dermal LD$_{50}$ of 6.7 g/kg in both rats and mice has been reported (Statsek, 1974). Clinical signs at or near lethal doses following oral exposure of rats included weight loss, apathy, and leukocytosis. Histological examination revealed toxic splenitis and degenerative lesions of the central nervous system with congestive encephalopathy, myelin degeneration, and glial proliferation.

8.2 Irritation and sensitization

No tests have been conducted according to validated international

protocols.

Exposure to BBP did not cause immediate or delayed hypersensitivity in mice in a series of studies following administration of an initiating dose either intraperitoneally or by application to the abdomen or footpad and a challenging dose to the dorsal side of the ear up to 15 days later. Similarly, there was no immediate or delayed hypersensitivity in guinea-pigs initiated on the footpad and receiving a challenge dose on shaved abdominal skin. BBP did not form a detectable amount of hapten-protein complex when assayed with bovine serum albumin, although results were equivocal following intradermal initiation and challenge (24 h later) of mice with serum from BBP-exposed (intraperitoneally) mice (Little & Little, 1983).

Data reported in accounts of early studies on the irritancy of BBP, the results of which were inconsistent, are inadequate for evaluation (Dueva & Aldyreva, 1969; Hammond et al., 1987). Calley et al. (1966) injected BBP intradermally into the backs of rabbits, followed by trypan blue into the ear vein. Moderate irritation was indicated by extravasated trypan blue at the site of administration.

8.3 Short-term exposure

In short-term investigations by the oral route (excluding those addressing specifically reproductive effects or peroxisomal proliferation, which are addressed elsewhere) for which the range of end-points examined was often limited, consistent effects on body weight gain in rats were observed at doses of approximately 1000 mg/kg body weight per day and above, sometimes accompanied by a decrease in food consumption (NTP, 1982; Hammond et al., 1987). Although some effects on body weight gain were observed at lower doses, the pattern was inconsistent. In one study, minimal testicular changes were

observed in one of six male rats at 480 mg/kg body weight per day (Bibra, 1978; Hammond et al., 1987[1]). In general, though, testicular effects were observed only at much higher doses (i.e., atrophy at 1600 mg/kg body weight per day; Hammond et al., 1987). In a 6-week investigation, there were no adverse histopathological effects on the nervous system of rats exposed to 3000 mg/kg body weight per day, although reversible clinical signs were observed (Robinson, 1991).

In an inhalation study in rats, there were no effects upon haematology, urinalysis, blood chemistry, or histopathology following exposure for 4 weeks to 144 mg/m^3 (Hammond et al., 1987). At 526 mg/m^3, effects included reduced body weight gain and reduced serum glucose. In a similar study, exposure to 2100 mg/m^3 resulted in death of some animals; effects after 4 weeks included reduced body weight gain and atrophy of the spleen and testes (Hammond et al., 1987).

8.4 Long-term exposure

Detailed descriptions of the protocol and effect levels are presented here for critical studies only. Experimental details and effect levels for all key subchronic and chronic studies via ingestion are provided in Table 1.

8.4.1 Subchronic exposure

       The protocol of an early study in Charles River rats included
examination of body weight, clinical signs, organ weight, and limited
histopathology of liver, spleen, kidney, adrenal, stomach, and small
and large intestine (Hazleton Laboratories, 1958). The only effect
observed was a decrease in body weight gain in males at the highest
dose (1253 mg/kg body weight per day).

       In a range-finding NTP subchronic (13-week) dietary bioassay in
F344 rats, the only adverse effects observed upon examination of body
weight and clinical signs and histopathological examination of control
and high-dose animals were depressed weight gain and testicular
degeneration (nature of degeneration not specified) at the highest
dose (1250 mg/kg body weight per day) (NTP, 1982).

       Sprague-Dawley rats were administered BBP in the diet for 3
months at dose levels of 0, 188, 375, 750, 1125, or 1500 mg/kg body
weight per day in males and females (Hammond et al., 1987). End-points
examined included body weight gain, haematology, urinalysis, and
histopathology (control and high-dose groups only). No
compound-related lesions were observed at necropsy or upon
histopathological examination. In females, the increase in liver to
body weight ratio was significant at 750 mg/kg body weight per day and
higher; in males, the increase was significant at 1125 mg/kg body

[1] Full study reports for several of the investigations described
   therein were available to the authors.

weight per day and higher. No change occurred in kidney to body weight
ratio in females, but there was a significant increase in males at 750
mg/kg body weight per day and higher.

       A subchronic dietary study was also conducted in Wistar rats
(Monsanto Company, 1980a; Hammond et al., 1987) at dose levels of 0,
151, 381, or 960 mg/kg body weight per day in males and 0, 171, 422,
or 1069 mg/kg body weight per day in females for 3 months. Intake of
BBP, based on body weight and food consumption, was calculated at
4-day intervals throughout the study. Observations included slight
anaemia in males at the highest dose and decreased urinary pH in males
at the mid and high doses. At the highest dose, no reduction in food
consumption was apparent, suggesting that the reduced body weight gain
in those groups may have been compound related. Liver to body weight
ratio was significantly increased at all dose levels in females and at
the highest dose in males. A significant increase in kidney to body
weight ratio occurred in a dose-related manner in both sexes at the
mid and high doses. The caecum to body weight ratio was unaffected in
males but increased at all dose levels in females in a dose-related
manner. Gross pathological lesions were limited to increased incidence
of red spots on the liver of mid- and high-dose males.
Histopathological lesions of the pancreas were observed in males at
the mid and high doses and included islet enlargement with cell
vacuolization and peri-islet congestion. The liver of high-dose males
had small areas of cellular necrosis. No histopathological lesions
were described for females. The lowest-observed-adverse-effect level
(LOAEL) is 381 mg/kg body weight per day, based upon histopathological

effects in the pancreas in males. The lowest-observed-effect level (LOEL) in females is 171 mg/kg body weight per day, based upon increases in organ to body weight ratio at all doses for the liver and caecum (the no-observed-effect level, or NOEL, in males is 151 mg/kg body weight per day).

In a 6-month dietary study in male F344 rats (NTP, 1997a), effects on haematological parameters were reported at 550 mg/kg body weight per day. Only transitory changes in haematological parameters were reported at 180 mg/kg body weight per day.

In a 3-month dietary study in dogs (Hammond et al., 1987), decreases in body weight gain were associated with decreases in food consumption at the highest dose (1852 and 1973 mg/kg body weight per day for males and females, respectively).

In a 90-day study in mice, there were decreases in body weight gain at 208 mg/kg body weight per day and greater in males, although no histopathological effects were observed and food consumption was not reported (NTP, 1982). End-points included clinical observations, body weight, and histopathology (control and high dose).

One subchronic inhalation bioassay was identified, in which groups of 25 male or 25 female Sprague-Dawley rats were exposed to concentrations of 0, 51, 218, or 789 mg/m^3 for 6 h/day, 5 days/week, for a total of 59 exposures. End-points examined were limited to organ weight changes and histopathological examination of control and high-dose groups (Monsanto Company, 1982a; Hammond et al., 1987). A LOEL of 218 mg/m^3 was reported for male rats, based upon increases in kidney weight, measured at interim sacrifice only, although no dose-related histopathological changes were observed in any group. The NOEL was 51 mg/m^3.

8.4.2 Chronic exposure and carcinogenicity

A carcinogenicity bioassay was conducted by the NTP (1982) in F344 rats. Fifty rats per sex per group were administered BBP via the diet, at levels of 0, 6000, or 12 000 ppm (0, 300, and 600 mg/kg body weight per day,[1] respectively). Females were exposed for 103 weeks. Because of poor survival, all males were sacrificed at weeks 29-30; this part of the study was later repeated (NTP, 1997a).

Only females were examined histopathologically. The incidence of mononuclear cell leukaemias was increased in the high-dose group (P = 0.011); the trend was significant (P = 0.006). (Incidences for the control, low-dose, and high-dose groups were 7/49, 7/49, and 18/50, respectively.) The incidence in the high-dose group and the overall trend remained significant (P = 0.008 and P = 0.019, respectively) when compared with historical control data. The NTP concluded that BBP was "probably carcinogenic for female F344/N rats, causing an increased incidence of mononuclear cell leukemias" (NTP, 1982).

However, these results were not repeated in the 2-year dietary study in F344/N rats recently completed by the NTP (1997a). The average daily doses (reported by the authors) were 0, 120, 240, or 500 mg/kg body weight per day for males and 0, 300, 600, or 1200 mg/kg

body weight per day for females. The protocol included periodic
haematological evaluation and hormonal assays and a 15-month interim
sacrifice.

There were no differences in survival between exposed groups and
their controls. A mild decrease in triiodothyronine concentration in
the high-dose females at 6 and 15 months and at termination was
considered to be related to a non-thyroidal disorder. Changes in
haematological parameters were sporadic and minor. In this bioassay,
there was no increase in the incidence of mononuclear cell leukaemia
in female rats, as was reported in the earlier bioassay (NTP, 1982),
although the level of exposure (600 mg/kg body weight per day) at
which the incidence was observed in the early bioassay was common to
both studies.

[1] Conversion factor; 1 ppm in food = 0.05 mg/kg body weight per day
    (Health Canada, 1994).

Table 1: Effect levels in subchronic, chronic, reproductive, and
developmental studies by the ingestion route.

Study protocol   Effect level[a]
Critical end-point/comments   Reference

Subchronic exposure

Charles River rats   LOAEL (males) = 1253 mg/kg
Limited range of end-points,   Hazleton
   (10/sex/group)   body weight per day
including body weight, food   Laboratories, 1958
   90 days   NOEL (females) = 1270 mg/kg
consumption, organ weight, and
   median intake   body weight per day
histopathological examination of
   in diet: (highest doses administered)   only
seven organs/tissues,
   males: 0, 447, or
excluding the testes.
   1253 mg/kg body weight
   females: 0, 462, or
   1270 mg/kg body weight

   F344/N rats   LOAEL (males) = 1250 mg/kg body
Histopathological degeneration of   NTP, 1982
   (10/sex/group)   weight per day   the
testes and depressed weight
   13 weeks   NOEL = 625 mg/kg body weight
gain. End-points examined were
   approximate intake in   per day
restricted to clinical
   diet: 0, 80, 155, 315,
observations, body weight gain,
   625, or 1250 mg/kg body   and
histopathological observation

Study protocol	Effect level[a]	Critical end-point/comments	Reference
		weight per day of control and high-dose animals.	
Sprague-Dawley rats (10/sex/group) 3 months approximate intake in diet: 0, 188, 375, 750, 1125, or 1500 mg/kg body weight per day	LOEL (females) = 750 mg/kg body weight per day NOEL = 375 mg/kg body weight per day	Significant increases in liver to body weight ratio (females) and kidney to body weight ratio (males). No histopathological changes.	Hammond et al., 1987
Wistar rats (27-45/sex/group) (15-27 exposed for entire period) 3 months	LOAEL (males) (pancreas) = 381 mg/kg body weight per day LOEL (females) = 171 mg/kg body weight per day (lowest dose administered)	Histopathological changes in pancreas in males from two highest dose groups. Increases in organ to body weight ratio at all doses	Monsanto Company, 1980a; Hammond et al., 1987

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference
approximate intake in diet: males: 0, 151, 381, or 960 mg/kg body weight per day females: 0, 171, 422, or 1069 mg/kg body weight per day		for the liver (females) and caecum (females). No histopathological effects in either of these organs at higher doses in the same sex.	
Male F344 rats (15/group) 26 weeks approximate intake in diet for four lowest doses: 0, 30,	LOEL = 550 mg/kg body weight per day NOAEL = 180 mg/kg body weight per day	Effects on haematological parameters (significant increase in mean cell haemoglobin and mean cell haemoglobin concentration) and increased relative liver weight.	NTP, 1997a

Study protocol	Effect level[a]	Critical end-point/comments	Reference
60, 180, or 550 mg/kg body weight per day		Transitory changes only in haematological parameters at the lower dose (NOAEL).	
Beagle dogs (3 males and 3 females) 3 months approximate intake in diet or by capsule (high-dose group): males: 0, 400, 1000, or 1852 mg/kg body weight per day females: 0, 700, 1270, or 1973 mg/kg body weight per day	NOAEL (males) = 1852 mg/kg body weight per day NOAEL (females) = 1973 mg/kg body weight per day (highest doses administered)	Decreases in body weight gain at the highest doses associated with decreases in food consumption. (Body weight increased but remained depressed in relation to controls during 2 months of administration by capsule.)	Hammond et al., 1987

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference
B6C3F$_1$ mice (10/sex/group) 13 weeks approximate intake in diet: 0, 208, 403, 819, 1625, or 3250 mg/kg body weight per day	LOEL (males) = 208 mg/kg body weight per day LOEL (females) = 1625 mg/kg body weight per day	Decreases in body weight (of unspecified statistical significance), but no histopathological effects; food consumption was not reported. End-points examined restricted to body weight gain, clinical observations, and histopathology in control and high-dose groups.	NTP, 1982

Chronic exposure

Study protocol	Effect level[a]	Critical end-point/comments	Reference
F344/N rats (60/sex/group) 2 years approximate intake in diet: males: 0, 120, 240, or 500 mg/kg body weight per day females: 0, 300, 600, or 1200 mg/kg body weight per day	LOEL (females) = 300 mg/kg body weight per day LOEL (males) = 120 mg/kg body weight per day	Increased nephropathy (the latter observed at all dose levels in females). Relative kidney weight increased at all doses in males at interim sacrifice (not determined at terminal sacrifice). At high dose, increase in severity of renal tubular pigmentation in both sexes.	NTP, 1997a
B6C3F$_1$ mice (50/sex/group) 103 weeks approximate intake in diet: 0, 780, or 1560 mg/kg body weight per day	LOEL = 780 mg/kg body weight per day	Decrease in body weight gain (unspecified statistical significance). End-points examined restricted to clinical signs, body weight, and histopathology.	NTP, 1982

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference

Reproductive/developmental studies

Study protocol	Effect level[a]	Critical end-point/comments	Reference
RIVM-bred WU rats (10/sex/group) 14 days prior to and throughout mating (OECD 421 - combined reproductive/developmental	LOAEL = 1000 mg/kg body weight per day NOAEL = 500 mg/kg body weight per day	At top dose, reduction in body weight gain, fluctuation in food consumption, reduction in weight of testis and epididymis, and increase in testicular degeneration (males). At top dose, decrease in body weight gain and	Piersma et al., 1995

Study protocol	Effect level[a]	Critical end-point/comments	Reference
toxicity screening protocol) gavage in corn oil: 0, 250, 500, or 1000 mg/kg body weight per day		effects on food consumption; adverse effects on reproductive indices (females). The only effect observed at 500 mg/kg body weight per day was a transient decrease (day 1) in pup weight.	
Male F344 rats (10/group) 14 days approximate intake in diet: 0, 312.5, 625, 1250, or 2500 mg/kg body weight per day	LOAEL = 312.5 mg/kg body weight per day	Dose-related increases in relative weights of kidney and liver at all doses; increase in absolute kidney weight at two lowest doses, and decrease in absolute kidney weight at two highest doses. Proximal tubular regeneration and histopathological changes in the thymus were also observed at all dose levels; however, latter was minimal and not considered dose related. Histopathological effects on the liver, testes, epididymis, seminal vesicles, and prostate were observed only at higher concentrations.	Kluwe et al., 1984; Agarwal et al., 1985

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference
Male F344/N rats (15/group) 10 weeks prior to mating	NOEL = 20 mg/kg body weight per day LOAEL = 200 mg/kg body weight	Significant dose-related decrease in epididymal spermatozoal concentration at the two highest dose levels.	NTP, 1997a

Study protocol	Effect level[a]	Critical end-point/comments	Reference
(modified mating protocol) approximate intake in diet: 0, 20, 200, or 2200 mg/kg body weight per day	per day (it should be noted that dose spacing was poor in the study) only	Histopathological evidence of hypospermia and a decrease in fertility index were observed at the highest dose (2200 mg/kg body weight per day).	
Wistar rats (12 males, 24 females per group) one-generation reproductive study approximate intake in diet: males: 0, 108, 206, or 418 mg/kg body weight per day females: 0, 106, 217, or 446 mg/kg body weight per day	Reproductive effects: NOAEL (males) = 418 mg/kg body weight per day NOAEL (females) = 446 mg/kg body weight per day (highest doses administered) Parental effects: NOEL (males) = 418 mg/kg body weight per day NOAEL (females) = 217 mg/kg body weight per day LOEL (females) = 446 mg/kg body weight per day	No effects on reproductive performance and development of offspring. At top dose, significant increase in relative weight of livers and decrease in food consumption and body weight (females).	TNO Biotechnology and Chemistry Institute, 1993
Examination of effects on the testes of offspring of female Wistar rats (number unspecified) administered 0 or 1000 µg BBP/litre in drinking-water (estimated to be approximately 126–366 µg/kg body weight per day) for 2 weeks prior to mating, throughout mating and gestation, and until 22 days after giving birth	Dose-response was not investigated.	Reduction in testes weight and daily sperm production; effects were not replicated in the study of similar design in another strain of rats by Ashby et al. (1997a)	Sharpe et al., 1995

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference
Examination of effects on reproductive systems of	Dose-response was not investigated.	Reversible increase in absolute and relative liver weight at postnatal	Ashby et al., 1997a

Study protocol	Effect level[a]	Critical end-point/comments	Reference
male and female offspring of female Alpk:AP$_f$SD rats (n = 19) exposed during gestation and lactation to 0 or 1000 µg BBP/litre in drinking-water (estimated to be 183 µg/kg body weight per day)	day 90 in male offspring		
Sprague-Dawley rats (30 females/group) gestational days 6–15 approximate intake in diet: 0, 420, 1100, or 1640 mg/kg body weight per day	NOAEL (maternal and offspring) = 420 mg/kg body weight per day LOAEL (significant maternal and minimal developmental effects) = 1100 mg/kg body weight per day	An increase in the percentage of fetuses with variations per litter. Maternal toxicity was evident at the mid and high dose levels (decreased maternal weight gain, increased relative liver weight, increased food and water consumption).	NTP, 1989; Price et al., 1990
Swiss albino mice (30 females/group) gestational days 6–15 approximate intake in diet: 0, 182, 910, or 2330 mg/kg body weight per day	NOAEL (maternal and developmental) = 182 mg/kg body weight per day LOAEL (maternal and developmental) = 910 mg/kg body weight per day	Increased percentage of late fetal deaths per litter and non-live implants per litter, decreased number of live fetuses per litter, increased percentage of litters with malformed fetuses, and an increased percentage of malformed fetuses per litter. Decreased maternal weight gain at two highest doses; increased relative kidney and liver weight in mothers at top dose.	NTP, 1990; Price et al., 1990

Table 1 (continued)

Study protocol	Effect level[a]	Critical end-point/comments	Reference
Wistar rats (15–19	LOAEL (maternal) = 654 mg/kg	Significant dose-related reduction	Ema et al., 1990

Study protocol	Effect level[a]	Critical end-point/comments	Reference
females/group) gestational days 0–20 approximate intake in diet: 180, 375, 654, or 974 mg/kg body weight per day	body weight per day NOEL (embryo/fetal toxicity) = 654 mg/kg body weight per day Significant reduction in the number of live fetuses per litter at 375 and 654 mg/kg body weight per day (administration on days 0–20 in study of unconventional design) (maternal LOEL) NOEL (reproduction) = 185 mg/kg body weight per day	maternal body weight gain and reduced food consumption at three highest doses (significant only at highest doses when adjusted for gravid uterus). Additional studies conducted by these investigators in which effects in offspring were examined following administration of doses greater than 500 mg/kg weight per day either in the diet or by gavage during various periods of gestation are not additionally informative with respect to effect levels.	

Peroxisomal proliferation

| F344 rats (5/sex/group) 21 days approximate intake in diet: males: 0, 639, 1277, or 2450 mg/kg body weight per day females: 0, 679, 1346, or 2628 mg/kg body weight per day | LOEL (males) = 639 mg/kg body weight per day LOEL (females) = 679 mg/kg body weight per day (lowest doses administered) | Increase in relative liver and kidney weights in males and females; increase in cyanide-insensitive palmitoyl-CoA oxidation; increase in lauric acid 11- and 12-hydroxylase activity in males. | BIBRA, 1985 |

Table 1 (continued)

| Study protocol | Effect level[a] | Critical end-point/comments | Reference |

female F344/N rats (5 or 10)   LOEL = 300 mg/kg body weight
Increase in peroxisomal   NTP, 1997a
   1 or 12 months in the diet   per day
proliferation (carnitine
   approximate intake in diet: (lowest dose administered)
acetyl transferase activity).
   300, 600, or 1200 mg/kg body
   weight per day

       [a] NOEL = no-observed-effect level; NOAEL = no-observed-adverse-effect
level; LOEL = lowest-observed-effect level;
     LOAEL = lowest-observed-adverse-effect level.

       At the 15-month interim sacrifice, the absolute weight of the
right kidney in the females at 600 mg/kg body weight per day and the
relative weight in all exposed males were significantly greater than
in controls. The severity of renal tubule pigmentation in high-dose
males and females was greater than in controls, both at 15 months and
at 2 years. The incidence of mineralization in kidney was
significantly less than in controls in low- and high-dose females at 2
years; severity decreased in all groups of exposed females. The
incidence of nephropathy was significantly increased in all groups of
exposed females (34/50, 47/50, 43/50, and 45/50 in control, 300, 600,
and 1200 mg/kg body weight per day groups, respectively) (see Table 3
in section 11.1.2). The incidence of transitional cell hyperplasia
(0/50, 3/50, 7/50, and 4/50 in control, 300, 600, and 1200 mg/kg body
weight per day groups, respectively) was significantly increased at
600 mg/kg body weight per day.

       At final necropsy, the incidences of pancreatic acinar cell
adenoma (3/50, 2/49, 3/50, and 10/50 in control, 120, 240, and 500
mg/kg body weight per day groups, respectively) and pancreatic acinar
cell adenoma or carcinoma (combined) (3/50, 2/49, 3/50, and 11/50 in
control, 120, 240, and 500 mg/kg body weight per day groups,
respectively) in the high-dose males were significantly greater than
in the controls and exceeded those in the ranges of historical
controls from NTP 2-year feeding studies. One carcinoma was observed
in a high-dose male; this neoplasm had never been observed in the
historical controls. The incidence of focal hyperplasia of the
pancreatic acinar cell in the high-dose males was also significantly
greater than in the controls (4/50, 0/49, 9/50, and 12/50 in control,
120, 240, and 500 mg/kg body weight per day groups, respectively). Two
pancreatic acinar cell adenomas were observed in the high-dose
females.

       The incidences of transitional cell papilloma of the urinary
bladder in female rats at 2 years were 1/50, 0/50, 0/50, and 2/50 in
control, 300, 600, and 1200 mg/kg body weight per day groups,
respectively.

       The authors concluded that there was "some evidence of
carcinogenic activity" in male rats, based upon the increased

incidences of pancreatic acinar cell adenoma and of acinar cell adenoma or carcinoma (combined). There was "equivocal evidence of carcinogenic activity" in female rats, based upon the marginally increased incidences of pancreatic acinar cell adenoma and of transitional cell papilloma of the urinary bladder.

The NTP (1997b) has released a technical report of a study that compared outcomes when chemicals were evaluated under typical NTP bioassay conditions as well as under protocols employing dietary restriction. The experiments were designed to evaluate the effect of dietary restriction on the sensitivity of bioassays towards

chemical-induced chronic toxicity and carcinogenicity and to evaluate the effect of weight-matched control groups on the sensitivity of the bioassays. BBP was included in the protocol; the results were summarized as follows:

"Butyl benzyl phthalate caused an increased incidence of pancreatic acinar cell neoplasms in *ad libitum*-fed male rats relative to *ad libitum*-fed and weight-matched controls. This change did not occur in rats in the restricted feed protocol after 2 years ... Butyl benzyl phthalate also caused an increased incidence of urinary bladder neoplasms in female rats in the 32-month restricted feed protocol. The incidences of urinary bladder neoplasms were not significantly increased in female rats in any of the 2-year protocols, suggesting that the length of the study, and not body weight, was the primary factor in the detection of this carcinogenic response."

Fifty B6C3F$_1$ mice per sex per group were exposed to 0, 6000, or 12 000 ppm BBP (0, 780, or 1560 mg/kg body weight per day[1]) via the diet for 103 weeks (NTP, 1982). Approximately 35 tissues were examined histopathologically. The only compound-related sign of exposure was a dose-related decrease (statistical significance not specified) in body weight in both sexes. Survival was not affected, and there was no increased incidence of any neoplasm that was compound related. As well, non-neoplastic changes were all within the normal limits of incidence for B6C3F$_1$ mice. The NTP concluded that, under the conditions of the bioassay, BBP "was not carcinogenic for B6C3F$_1$ mice of either sex."

8.5 Genotoxicity and related end-points

In the (few) published reports of Ames assays with BBP, results have been negative (Litton Bionetics Inc., 1976; Rubin et al., 1979; Kozumbo et al., 1982; Zeiger et al., 1982, 1985). Negative results have also been reported for mouse lymphoma assays (Litton Bionetics Inc., 1977; Hazleton Biotechnologies Company, 1986), although equivocal findings have also been published (Myhr et al., 1986; Myhr & Caspary, 1991). In an assay for *in vitro* transformation of Balb/c-3T3 cells (Litton Bionetics Inc., 1985), results were negative. In an assay for chromosomal aberrations and sister chromatid exchanges in Chinese hamster ovary cells (Galloway et al., 1987), there was slight evidence for a trend in one sister chromatid exchange test without activation, but no convincing evidence for positive results for sister chromatid exchanges or aberrations.

The results from the mouse lymphoma (Myhr et al., 1986; Myhr & Caspary, 1991) and chromosomal aberration (Galloway et al., 1987) assays are equivocal. For the mouse lymphoma assay, the NTP concluded that "Increases in mutant colonies were observed in the absence of S9 in cultures treated with concentrations that produced precipitation, but such responses were not considered valid by experimental quality control parameters." However, it is difficult to dismiss the observed dose-response in several studies as spurious, although the repeat tests were negative, particularly in view of inconsistencies of results of the latter. In repeat studies (n = 5) in the absence of S9, there was limited evidence of activity in only one case; however, although BBP was positive at 80 nl/ml in the second trial, it was toxic at concentrations above 30 nl/ml in the third. The inconsistently observed increase in small colony mutants and percent damaged Chinese hamster ovary cells may be indicative of weak clastogenic activity, which warrants proper confirmation in well-conducted assays.

A negative response was reported for an assay for the induction of sex-linked recessive lethals in *Drosophila melanogaster* (Valencia et al., 1985). Recently, the NTP (1997a) published summary results of mouse bone marrow tests for sister chromatid exchanges and induction of chromosomal aberrations; responses were weak, and the sister chromatid exchange test was not repeated. Both of these responses, although statistically significant, were small and indicative of only weak clastogenic activity. Ashby et al. (1997a) reported negative results in a micronucleus assay in rats.

8.6 Reproductive and developmental toxicity

Detailed descriptions of the protocol and effect levels are presented here for critical studies only. Experimental details and effect levels for all key reproductive and developmental studies via ingestion are provided in Table 1.

With respect to reproductive effects, in repeated-dose toxicity studies by the oral route, decreases in the weight of the testes and histopathological effects in the testes have been observed, although only at doses greater than those that induce other effects, such as variations in organ to body weight ratios for the kidney and liver or histopathological effects in the pancreas or kidney. With the exception of a short-term gavage study in which minimal histopathological effects in the testes of rats were observed at 480 mg/kg body weight per day in one of six animals (control data not presented, and no statistical analysis) (Hammond et al., 1987), testicular atrophy or degeneration has been observed only in rats only at doses exceeding 1250 mg/kg body weight per day (NTP, 1982, 1997a; Hammond et al., 1987).

In a combined reproductive/developmental screening protocol, at 1000 mg/kg body weight per day there was a decrease in body weight gain, fluctuation in food consumption, reduction in the weight of testis and epididymis, and increase in testicular degeneration in males. In females at this dose, there was a decrease in body weight

gain, effects on food consumption, and adverse effects on reproductive indices. With the exception of a transient decrease in pup weight, there were no effects on the parental generation or offspring at 500 mg/kg body weight per day (Piersma et al., 1995).

Reproductive effects of BBP in male Fischer 344 rats have been investigated by the NTP (Kluwe et al., 1984; Agarwal et al., 1985). Groups of 10 males were administered 0, 0.625, 1.25, 2.5, or 5.0% (0, 312.5, 625, 1250, or 2500 mg/kg body weight per day[1]) in the diet for 14 days. The protocol included measurement of endocrine hormones and histopathological examination of brain, liver, kidney, spleen, thyroid, thymus, pituitary, testes, epididymis, prostate, seminal vesicles, and mesenteric lymph nodes. Bone marrow was also examined.

No deaths occurred during the study. Body weight was reduced in the two highest dose groups. Food consumption was consistently reduced in the highest dose group throughout the experiment. Absolute weights of testis, epididymis, prostate, and seminal vesicles were significantly reduced at the two highest dose levels in a dose-related manner and were accompanied by "generalized histological atrophy." Statistical analyses were presented for histopathological changes in testis (aspermatogenesis/seminiferous tubular atrophy), seminal vesicles (atrophy), and prostate (atrophy); significant changes were consistently observed at the two highest doses. The authors noted a "clear relationship" between dose and severity of morphological changes in testis, seminal vesicles, and prostate; the changes occurred only at the two highest dose levels. Similarly, effects on the epididymis were observed in only the two highest dose groups.

Absolute weight of liver was increased at the two lowest doses and decreased at the highest dose. The relative weight was increased at all levels of exposure, in a dose-related manner. Histopathological changes (mild multifocal chronic hepatitis) were described only for the highest dose. Absolute weight of kidney was also increased at the two lowest doses and decreased at the two highest. The relative weight was increased at all levels of exposure, in a dose-related manner. Proximal tubular regeneration was observed at all dose levels. Thymic weight was reduced at the two highest doses in a dose-related manner. Although histopathological changes were described for all dose groups, atrophy was observed only in the highest dose group. There were no effects upon absolute or relative pituitary weight, nor were morphological changes observed in thyroid, pituitary, spleen, or lymph nodes. Statistical analyses were not presented for histopathological observation of these organs.

[1] Conversion factor: 1 ppm in food = 0.05 mg/kg body weight per day (Health Canada, 1994).

Plasma testosterone was decreased at the highest dose. Follicle-stimulating hormone was increased at the two highest doses in a dose-related manner. Luteinizing hormone was increased at the lowest dose and at the two highest doses; there was a limited number of samples at the high dose. No effects were observed upon such haematological parameters as red blood cell count, packed cell volume, haemoglobin, mean corpuscular volume, or white blood cell count. There was no significant effect upon blood clotting ability, as measured by

prothrombin time. Bone marrow cell count was reduced at the two highest doses.

At the lowest dose (312.5 mg/kg body weight per day), there was a significant increase in both the absolute and relative weights of both liver and kidney. There was proximal tubular regeneration at all levels of exposure. Focal thymic medullary haemorrhage (minimal severity) was observed in a small number of animals in all BBP-exposed groups, but the incidences were not dose related. Based upon these observations, the LOAEL is 312.5 mg/kg body weight per day for effects on the liver and kidney.

Male F344/N rats (15 per group) were administered BBP via the diet for 10 weeks, then each mated to 2 unexposed females (NTP, 1997a). Dietary concentrations were relatively widely spaced at 0, 300, 2800, or 25 000 ppm, which were reported by the authors to be equivalent to 0, 20, 200, or 2200 mg/kg body weight per day. The final body weight and body weight gain of the high-dose group were significantly lower than in the controls. Minimal changes in haematological parameters were observed in the high-dose group. Both the absolute and relative weights of prostate and testis were significantly decreased in the high-dose group (2200 mg/kg body weight per day). (Other lower organ weights in this group were attributed to the lower mean body weight.) Other effects observed at the high dose included degeneration of the seminiferous tubular germinal epithelium and significantly reduced weight of right cauda, right epididymis, and right testis. Epididymal spermatozoal concentrations were significantly reduced in a dose-related manner at the two highest doses. However, histopathological evidence of hypospermia and a decrease in fertility index were observed only at the highest dose. Ten of 30 females mated to high-dose males were found to be sperm positive, but none was pregnant at necropsy. Fertility indices were significantly lower at the high dose. At the lower two doses, there were no exposure-related effects observed on maternal body weight, maternal clinical observations, or litter data. A NOEL of 20 mg/kg body weight per day can be designated, based upon a significant and dose-related decrease in epididymal spermatozoal concentration at the two highest doses and associated effects on fertility at the highest dose (LOAEL = 200 mg/kg body weight per day).

Concentrations of BBP of 0.2, 0.4, and 0.8% (108, 206, and 418 mg/kg body weight per day for males; 106, 217, and 446 mg/kg body weight per day for females) were administered in the diet to males for 10 weeks and to females for 2 weeks premating. Two litters were

produced, and no adverse effects were observed on fertility, pregnancy, or offspring development (TNO Biotechnology and Chemistry Institute, 1993).

Sharpe et al. (1995) administered a single dose level of BBP via drinking-water to pregnant Wistar rats, to determine the effects of gestational and lactational exposure upon male offspring. Dams were exposed for 2 weeks prior to mating and throughout gestation until weaning. This procedure was then repeated on the same dams, and observations were also carried out on the second litters. Based upon measurement of drinking-water consumption in six animals, intake of BBP was estimated to range from 126 to 366 µg/kg body weight per day,

from postnatal days 1-2 to postnatal days 20-21, respectively. There
was a significant reduction in daily sperm production in the
BBP-exposed animals examined at 90-95 days. Sperm production in the
positive control group, which received 100 µg diethylstilbestrol
(DES)/litre in drinking-water, was also reduced (P < 0.01); the
negative control group (which received 1000 µg octylphenol
polyethoxylate/litre) was not evaluated. The authors questioned the
relevance of the effects to humans on the basis that this would
require detailed dose-response data and measurement of the actual
levels of the administered chemical in the male rats. Moreover, these
results vary from those reported by Sharpe et al. (1995) in an
investigation of effects on male offspring.

Ashby et al. (1997a) exposed Alpk:AP$_f$SD rats during gestation
and lactation to 1000 µg BBP/litre in drinking-water or 50 µg
DES/litre in drinking-water (positive control). Negative controls
received 100 µl ethanol/litre in drinking-water. Glass drinking-water
bottles were used in the experiment, as the authors had determined
that 60% of BBP was adsorbed onto plastic drinking-water bottles
within 24 h (Ashby et al., 1997b). The authors reported that the
overall exposures were 183 µg BBP/kg body weight per day and 8.6 µg
DES/kg body weight per day. There were no effects upon weight of right
testis after decapsulation, total sperm count (right testis), sperm
count per gram of right testis, or total sperm count in right cauda on
either postnatal day 90 or postnatal day 137. The authors noted the
contrast between these results and those reported by Sharpe et al.
(1995).[1]

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[1] It is noted that TNO Nutrition and Food Research Institute (1997)
   is conducting an experiment in which the protocol was designed "to
   investigate the reproducibility of, and expand on, the findings of
   Sharpe et al. ... related to the development of the reproductive
   system in Wistar rats exposed *in utero* and during lactation to
   butyl benzyl phthalate in drinking water." Data from this study have
   not yet been published.

It should be noted that there were significant differences
between these studies with respect to exposure of the dams. In the
Sharpe et al. (1995) study, the dams were exposed for 2 weeks prior to
mating, throughout gestation and weaning, and subsequently for another
2 weeks prior to mating, during gestation, and during lactation. In
the study by Ashby et al. (1997a), dams were exposed only during
gestation and lactation.

Although BBP has been estrogenic in human breast cancer cells
 in vitro (Jobling et al., 1995; Soto et al., 1995; Meek et al.,
1996), results in yeast have been both positive (Coldham et al., 1997;
Harris et al., 1997) and negative, the latter for both BBP and its
principal metabolites (Gaido et al., 1997); it should be noted,
however, that administered concentrations were unclear in two of the
studies (Coldham et al., 1997; Harris et al., 1997). However, neither
BBP nor its metabolites monobutyl benzyl phthalate and monobenzyl
phthalate have been uterotrophic *in vivo* in rats (Monsanto Europe
SA, 1995a, 1996a) or in rats and mice (Monsanto Europe SA, 1995b,
1996b), respectively. There was no estrogenic effect in an acute *in
 vivo* assay (Milligan et al., 1998) in mice (stimulation of increased

uterine vascular permeability).

The developmental toxicity of BBP following dietary administration has been well investigated by the NTP in studies in both rats and mice (NTP, 1989, 1990; Price et al., 1990) and in a series of investigations in rats by Ema et al. (1990, 1991a,b,c, 1993, 1994, 1995) following both dietary and gavage administration. In general, developmental effects of BBP have been observed only at dose levels that induced significant maternal toxicity; in pair feeding studies, however, malformations observed at high doses were not fully attributable to maternal toxicity (Ema et al., 1992). In a well-conducted NTP (1989) study in rats, at 1100 mg/kg body weight per day there were significant effects in the mothers but minimal effects in the offspring. At the highest dose (1640 mg/kg body weight per day), there was an increased incidence of rudimentary extra lumbar ribs. Results of studies by Ema and colleagues in which BBP was administered in the diet to rats for various periods, including the full 21 days of gestation, were similar. Although the no-observed-adverse-effect levels (NOAELs) for both maternal and developmental toxicity were less in the NTP (1990) study in mice (182 mg/kg body weight per day), this was primarily a function of wide dose spacing, with maternal (decreased weight gain) and developmental effects being observed at 910 mg/kg body weight per day. At both 910 and 2330 mg/kg body weight per day, there was a significant increase in the percentage of fetuses malformed per litter. Ema et al. (1998) observed a significant decrease in uterine decidual growth at 750 mg/kg body weight and higher following administration on days 0–8 to pseudopregnant rats. Functional effects have not been investigated in available studies.

Metabolites of BBP have induced effects on the testes similar to those of BBP, with the monobutyl ester being more potent in this regard (Mikuriya et al., 1988). Similarly, profiles of effects (e.g., fusion of sternebrae, cleft palate) in the offspring observed at maternally toxic doses of the metabolites of BBP are similar to those induced by BBP itself, with effects being observed at lower doses of monobenzyl than of monobutyl phthalate (see, for example, Ema et al., 1996a,b,c).

In a recent multigeneration study by continuous breeding in rats exposed to DBP for which the sole metabolite is monobutyl phthalate, testicular effects observed in the F_1 generation were attributed to impairment of normal androgen signalling in the fetus, although available data were considered insufficient to conclude that the monoester was responsible (Foster, 1997). Multigeneration studies for BBP have not been identified.

8.7 Peroxisomal proliferation

BIBRA (1985) investigated peroxisomal proliferation of BBP and reported an increase in relative liver and relative kidney weights, an increase in cyanide-insensitive palmitoyl-CoA oxidation, and an increase in lauric acid 11- and 12-hydroxylase activity in male F344 rats at 639 mg/kg body weight per day. In female rats, an increase in relative liver and relative kidney weights was reported at 679 mg/kg body weight per day. These were the lowest levels of exposure. The NTP (1997a) reported an increase in peroxisomal proliferation in female

F344/N rats after exposure to 300 mg/kg body weight per day for either
1 or 12 months. In a comparative study, whereas DEHP induced a "very
marked" increase in peroxisomal proliferation, that for BBP was
considered "moderate" (Barber et al., 1987).

8.8 Immunological and neurological effects

Data additional to those presented in sections 8.2 and 8.3
relevant to assessment of the potential immunotoxicity and
neurotoxicity of BBP were not identified.

9. EFFECTS ON HUMANS

Although in an early study (Mallette & von Haam, 1952) BBP was
reported to have a moderately irritating effect upon 15-30 volunteers,
Hammond et al. (1987) observed neither primary irritation nor
sensitization reactions in a patch test with 200 volunteers. Other
identified data in humans relevant to the assessment of the potential
adverse effects of BBP are restricted to limited studies of
respiratory/neurological effects or cancer in populations of workers
generally exposed to mixtures of plasticizers, of which BBP was a
minor component (Nielsen et al., 1985; Hagmar et al., 1990).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

10.1.1 Pelagic organisms

Data on acute toxicity are available for approximately two dozen
species, including microorganisms, algae, invertebrates, and fish
(Table 2). The lowest reported acute toxicity value was a 96-h LC_{50}
of 510 µg/litre for the shiner perch (*Cymatogaster aggregata*) in a
flow-through study using measured concentrations (Ozretich et al.,
1983). Values of the LC_{50} for most other fish species exceeded 1000
µg/litre. The most sensitive invertebrate species in acute toxicity
tests was the mysid shrimp (*Mysidopsis bahia*), with a 96-h LC_{50} of
900 µg/litre in a static bioassay using nominal concentrations
(Gledhill et al., 1980). Reported LC_{50} values for other invertebrates
exceeded 1000 µg/litre.

Data on chronic toxicity are available for about a dozen species,
including algae, invertebrates, and fish. The lowest reported chronic
toxicity value was a 96-h EC_{50} of 110 µg/litre, reported for the
green alga *Selenastrum*, based on chlorophyll *a* measurements and
cell number reductions using nominal concentrations (Suggatt & Foote,
1981). The most sensitive invertebrate species in chronic toxicity
tests was the mysid shrimp (*Mysidopsis bahia*), with a 28-day
lowest-observed-effect concentration (LOEC) of 170 µg/litre, based on
reproduction and growth in a flow-through study using measured
concentrations (Springborn Bionomics, 1986a). The most sensitive fish
species in chronic toxicity tests was the fathead minnow (*Pimephales
 promelas*), with a 30-day LOEC of 360 µg/litre based on hatching of
eggs and survival and growth of larvae using measured concentrations
(LeBlanc, 1984).

Table 2: Toxicity to aquatic organisms.

Organism	Effect	Reference
Acute toxicity		
mixed microbial cultures (2900 µg/litre)	8% inhibition of oxygen consumption at solubility limit with Organisation for Economic Co-operation and Development (OECD) Respiration Inhibition Kinetic Analysis (RIKA)[a] Screening Test	Volskay & Grady, 1988; Volskay et al., 1990
selected pure bacterial cultures 625-625 000	little or no inhibition of growth in cultures amended with µg/litre	Painter & Jones, 1990
unacclimated wastewater treatment plant sludge at 3000 µg/litre, nitrification of ammonia	8.4% chemical oxygen demand (COD) removal inhibition after 3 h no effect on	Adams & Bianchini-Akbeg, 1989
Photobacterium phosphoreum sediment ng/g dry weight	5-min Apparent Effects Threshold[b] (AET), Puget Sound (reduced luminescence), 63 sediment	Tetra Tech Inc., 1986; Barrick et al., 1988
Photobacterium phosphoreum ng/g organic carbon	5-min, Puget Sound (reduced sediment luminescence), 4900	Barrick et al., 1988
variety of algae, invertebrates, and fish 5000 µg/litre	acute toxicity = 500-	TOXNET[c]
Hydra littoralis µg/litre (mortality "tulip" stage)	96-h EC_{50} = 1100 and presence of	Monsanto Company, 1986a

polychaetes (Nereis/Neanthes virens)   96-h LC_{50} > 3000 µg/litre   Monsanto Company, 1986b

Table 2 (continued)

Organism   Effect
Reference

Organism	Effect	Reference
oyster (Crassostrea gigas) (increased abnormalities), >470 ng/g dry weight sediment	AET, Puget Sound	Tetra Tech Inc., 1986; Barrick et al., 1988
oyster (Crassostrea gigas) (increased abnormalities), >9200 ng/g organic carbon	AET, Puget Sound	Barrick et al., 1988
oyster (Crassostrea virginica) (shell deposition)	96-h EC_{50} = 1300 µg/litre	Monsanto Company, 1986c
amphipod (Rhepoxynius abronius) (increased mortality), >470 ng/g dry weight sediment	AET, Puget Sound	Tetra Tech Inc., 1986
amphipod (Rhepoxynius abronius) (increased mortality), 900 ng/g dry weight sediment	AET, Puget Sound	Barrick et al., 1988
amphipod (Rhepoxynius abronius) (increased mortality), 42 000 ng/g organic carbon	AET, Puget Sound	Barrick et al., 1988
daphnids	48-h LC_{50} = 1000–3700 µg/litre	Nabholz, 1987
Daphnia magna	24-h LC_{50} > 460 000 µg/litre	LeBlanc, 1980
Daphnia magna	24-h EC_{50} = 3800 µg/litre	Adams & Heidolph, 1985
Daphnia magna	48-h EC_{50} > 960 µg/litre	Adams et al., 1995
Daphnia magna	48-h EC_{50} > 1400 µg/litre	CMA, 1984

Organism	Reference	Effect
Daphnia magna µg/litre	Zeigenfuss et al., 1986	48-h LC_{50} = 1800
Daphnia magna µg/litre	Adams & Heidolph, 1985	48-h EC_{50} = 1800
Daphnia magna µg/litre	Gledhill et al., 1980	48-h EC_{50} = 3700

Table 2 (continued)

Organism	Reference	Effect
Daphnia magna µg/litre	LeBlanc, 1980	48-h LC_{50} = 92 000
Daphnia magna µg/litre (no food) to (2000 µg/litre algae yeast as food)	Barera & Adams, 1983	48-h LC_{50} = 1600 >10 000 µg/litre or 30 000 µg/litre trout chow/alfalfa
Daphnia magna µg/litre (no organic µg/litre (triethylene	Barera & Adams, 1983	48-h LC_{50} = 1000 solvent) to 2200 glycol solvent)
Daphnia magna day EC_{50} > 760 through); 21-day EC_{50} (static renewal)	Adams & Heidolph, 1985	2-, 7-, 14-, and 21- µg/litre (flow- = 680 µg/litre
Daphnia magna µg/litre (no fulvic acid) µg/litre (250 mg natural µg/litre (250 mg acid/litre)	Monsanto Company, 1978	48-h LC_{50} = 3700 48-h LC_{50} = 2430 fulvic acid/litre) 48-h LC_{50} = 1910 purchased fulvic
Mysid shrimp (Mysidopsis bahia) µg/litre	CMA, 1984	48-h LC_{50} = 1700
Mysid shrimp (Mysidopsis bahia) µg/litre	Gledhill et al., 1980	96-h LC_{50} = 900

Mysid shrimp (Mysidopsis bahia)   96-h LC_{50} > 740 µg/litre   Monsanto Company, 1988

                                                     (estimate = 1100 µg/litre)

Mysid shrimp (Mysidopsis bahia)   96-h LC_{50} = 9630 µg/litre   Suggatt & Foote, 1981

Grass shrimp (Paleomonetes vulgaris)   96-h LC_{50} > 2700 µg/litre   Monsanto Company, 1986d

Pink shrimp (Penaeus duorarum)   96-h LC_{50} > 3400 µg/litre   Springborn Bionomics, 1986b

Table 2 (continued)

Organism	Effect Reference

Crayfish (Procambarus sp.)   96-h LC_{50} > 2400 µg/litre   Monsanto Company, 1986e

Chironomus tentans   48-h LC_{50} = 1600 µg/litre   Zeigenfuss et al., 1986

Chironomus tentans   48-h LC_{50} = 1640 µg/litre   Monsanto Company, 1982b

Chironomus tentans   48-h LC_{50} = 3600 µg/litre   Monsanto Company, 1981a

Paratanytarsus dissimilis   48-h LC_{50} > 3600 µg/litre   Monsanto Company, 1981a

Midge (Paratanytarsus parthenogenetica)   48-h LC_{50} = 7200 µg/litre   Monsanto Company, 1981b;

CMA, 1984

Midge (Paratanytarsus parthenogenetica)   48-h LC_{50} = 13 400 µg/litre   Monsanto Company, 1981c

Midge (Paratanytarsus parthenogenetica)   96-h LC_{50} > 3600 µg/litre   Adams et al., 1995

Mayfly (Hexagenia sp.)   96-h LC_{50} = 1100 µg/litre   Monsanto Company, 1986f

Fathead minnow (Pimephales promelas)   96-h LC_{50} = 2100 µg/litre (hardness   Gledhill et al., 1980

                                                     40 000 µg calcium carbonate/litre)

Fathead minnow (Pimephales promelas)   96-h LC_{50} = 5300 µg/litre (hardness   Gledhill et al., 1980

160 000 µg calcium
carbonate/litre)

Fathead minnow (Pimephales promelas)   96-h LC_{50} > 780
µg/litre (static test)   Adams et al., 1995

Fathead minnow (Pimephales promelas)   96-h LC_{50} = 1500
µg/litre   CMA, 1984; Adams et al., 1995
                                        (flow-through test)

Fathead minnow (Pimephales promelas)   96-h LC_{50} > 1600
µg/litre (static test)   CMA, 1984

Fathead minnow (Pimephales promelas)   96-h LC_{50} = 2320
µg/litre   Gledhill et al., 1980

Fathead minnow (Pimephales promelas)   14-day LC_{50} = 2250
µg/litre   Gledhill et al., 1980

Table 2 (continued)

Organism   Effect
Reference

Bluegill (Lepomis macrochirus)   24-h LC_{50} = 62 000
µg/litre   Buccafusco et al., 1981

Bluegill (Lepomis macrochirus)   96-h LC_{50} = 43 000
µg/litre   Buccafusco et al., 1981

Bluegill (Lepomis macrochirus)   96-h LC_{50} = 1700
µg/litre   Gledhill et al., 1980;

CMA, 1984

Rainbow trout (Oncorhynchus mykiss)   96-h LC_{50} = 3300
µg/litre   Gledhill et al., 1980

Rainbow trout (Oncorhynchus mykiss)   96-h LC_{50} = 820
µg/litre (flow-through test) CMA, 1984; Adams et al., 1995

Sheepshead minnow (Cyprinodon variegatus)   48-h LC_{50} = 3300
µg/litre   AQUIRE[d]

Sheepshead minnow (Cyprinodon variegatus)   96-h LC_{50} > 680
µg/litre (static test)   CMA, 1984; Adams et al., 1995

Sheepshead minnow (Cyprinodon variegatus)   96-h LC_{50} = 3000
µg/litre   Gledhill et al., 1980

Sheepshead minnow (Cyprinodon variegatus)   96-h LC_{50} = 440 000
µg/litre   Heitmuller et al., 1981

Shiner perch (Cymatogaster aggregata)   96-h LC_{50} = 510
µg/litre   Ozretich et al., 1983

English sole (Parophrys vetulus)   96-h LC_{50} = 660 µg/litre (static   Randall et al., 1983   replenish), 550 µg/litre (flow-through)

Chronic toxicity

Algae   96-h EC_{50} = 200 µg/litre   CMA, 1984

Anacystis   96-h EC_{50} = 1000 µg/litre (cell count)   AQUIRE[d]

Microcystis   96-h EC_{50} = 1 000 000 µg/litre (cell count)   Gledhill et al., 1980

Dunaliella   96-h EC_{50} = 1000 µg/litre (cell count)   Gledhill et al., 1980

Navicula   96-h EC_{50} = 600 µg/litre (cell count)   Gledhill et al., 1980

Table 2 (continued)

Organism	Effect	Reference

Skeletonema   96-h EC_{50} = 600 µg/litre (cell count)   Gledhill et al., 1980

Skeletonema EC_{50} = 190 µg/litre (cell count)   Suggatt & Foote, 1981

Skeletonema EC_{50} = 170 µg/litre (chlorophyll a)   Suggatt & Foote, 1981

Selenastrum   96-h EC_{50}= 400 µg/litre (cell count)   Gledhill et al., 1980

Selenastrum   96-h EC_{50}= 110 µg/litre (chlorophyll a)   Suggatt & Foote, 1981

Selenastrum   96-h EC_{50} = 130 µg/litre (cell count)   Suggatt & Foote, 1981

Selenastrum   96-h EC_{50} = 600 µg/litre (cell count)   AQUIREd

Selenastrum capricornutum   96-h EC_{50} = 210 µg/litre (cell count)   Adams et al., 1995

Selenastrum capricornutum   96-h EC_{50} = 520 µg/litre (red blood cells,   Tucker et al., 1985   reduced dry weight)

Organism	Effect	Reference
Selenastrum capricornutum	5-day EC_{50} = 720 µg/litre (cell count)	Monsanto Company, 1980b
Selenastrum capricornutum	14-day EC_{50} = 520 µg/litre (cell count)	Monsanto Company, 1980b
Daphnids	21-day NOEC = 440-630 µg/litre	Nabholz, 1987
Daphnia and fathead minnow (Pimephales promelas)	chronic toxicity = 100-800 µg/litre	TOXNET[c]
Daphnia magna	21-day LOEC = 350 µg/litre; NOEC = 220 µg/litre (reproduction) (chronic renewal)	Monsanto Company, 1982c
Daphnia magna	21-day LOEC = 760 µg/litre; NOEC = 260 µg/litre (reproduction) (flow-through)	Adams & Heidolph, 1985

Table 2 (continued)

Organism	Effect	Reference
Daphnia magna	21-day LOEC = 700 µg/litre; NOEC = 350 µg/litre (growth, survival, and reproduction) (static)	Adams & Heidolph, 1985
Daphnia magna	14-day (Springborn = 21-day) LOEC = 1400 µg/litre; NOEC = 280 µg/litre (survival and reproduction)	CMA, 1984; Springborn Bionomics, 1984; Rhodes et al., 1995
Daphnia magna	42-day LOEC = 760 µg/litre; NOEC = 260 µg/litre (decreased reproduction, both generations; decreased survival in second generation)	Gledhill et al., 1980
Mysid shrimp (Mysidopsis bahia)	28-day LOEC = 170 µg/litre; NOEC = 75 µg/litre (reproduction and growth)	Springborn Bionomics, 1986a

Organism	Effect	Reference
Fathead minnow (Pimephales promelas) (decreased growth, embryo-larvae study)	30-day LOEC = 360 µg/litre; NOEC = 140 µg/litre	LeBlanc, 1984
Fathead minnow (Pimephales promelas) (estimated)	maximum acceptable toxicant concentration (MATC) > 360 µg/litre; chronic LC01 = 547 µg/litre	Sun et al., 1995
Fathead minnow (Pimephales promelas)	30-day mean chronic value = 220 µg/litre	Pickering, 1983
Bluegill (Lepomis macrochirus)	NOEC = 380 µg/litre	Verschueren, 1983

Table 2 (continued)

Organism	Effect	Reference
Rainbow trout (Oncorhynchus mykiss) (hatchability, growth, survival)	109-day NOEC > 200 µg/litre	Monsanto Company, 1986g; Rhodes et al., 1995
English sole (Parophrys vetulus)	sublethal effects at all exposures, lowest = 100 µg/litre	TOXNETc

[a] According to Volskay et al. (1990).
[b] The concentration above which statistically significant adverse effects are always expected relative
   to appropriate reference conditions.
[c] Toxicology Data Network, National Library of Medicine, US Department of Health and Human Services,
   Bethesda, MD.
[d] Aquatic Information Retrieval Database, US Environmental Protection Agency.

10.1.2 Benthic organisms

There were no acute or chronic toxicity studies identified for BBP in sediments.

Tetra Tech Inc. (1986) calculated a sediment quality value[1] of 55 000 ng BBP/g dry weight for sediment containing 1% organic carbon using the equilibrium partitioning approach. The assumption behind this approach is that non-polar organic compounds partition to the organic carbon fraction of the sediments to varying degrees depending upon their organic carbon/water partition coefficients (Di Toro et

al., 1991).

10.2 Terrestrial environment

No studies on the effects of BBP on wild mammals were identified. Information about the effects of BBP on laboratory mammals is presented in section 8.

No studies on the effects of BBP on plants were identified.

[1] Sediment quality values represent concentrations of chemicals in sediments that are expected to be associated with adverse biological effects based either on field evidence or on theoretical predictions (Tetra Tech Inc., 1986).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

Following oral administration to rats, BBP is readily hydrolysed in the gastrointestinal tract and the liver to phthalate monoesters (monobutyl and monobenzyl phthalate), which are rapidly eliminated, predominantly in urine.

Available data in humans are inadequate to serve as a basis for assessment of the effects of long-term exposure to BBP in human populations. The remainder of this section, therefore, addresses effects in experimental animals.

The acute toxicity of BBP is relatively low, with oral LD_{50} values in rats being greater than 2 g/kg body weight. Target organs following acute exposure include the haematological and central nervous systems.

Available data are inadequate to assess the irritant or sensitizing effects of BBP in animal species.

The repeated-dose toxicity of BBP has been well investigated in recent studies, primarily in the rat, in which dose-response was well characterized. Effects observed consistently have been decreases in body weight gain (often accompanied by decreases in food consumption) and increases in organ to body weight ratios, particularly for the kidney and liver. In addition, histopathological effects on the pancreas and kidney and haematological effects have also been observed. At higher doses, degenerative effects on the testes and, occasionally, histopathological effects on the liver have been reported. In specialized investigations, peroxisomal proliferation in the liver has been observed, although potency in this regard was less than that for other phthalates, such as DEHP.

The chronic toxicity and carcinogenicity of BBP have been investigated in NTP bioassays in rats (including standard and feed-restricted protocols) and mice. An increase in mononuclear cell leukaemias observed in female F344 rats was not confirmed in a repeat

study. It was concluded that there was "some evidence" of carcinogenicity in male rats, based on an increased incidence of pancreatic tumours, and equivocal evidence in female rats, based on marginal increases in pancreatic and bladder tumours. Dietary restriction prevented full expression of the pancreatic tumours and delayed appearance of the bladder tumours. There was no evidence of carcinogenicity in mice.

The weight of evidence of the genotoxicity of BBP is clearly negative. However, available data are inadequate to conclude unequivocally that BBP is not clastogenic, although in identified studies it has induced, at most, weak activity of a magnitude consistent with secondary effects on DNA.

Therefore, BBP has induced an increase in pancreatic tumours primarily in one sex of one species, the full expression of which was prevented in a dietary restriction protocol, and a marginal increase in bladder tumours in the other sex, which was delayed upon dietary restriction. Available data are consistent with the compound not interacting directly with DNA. On this basis, BBP can be considered, at most, possibly carcinogenic to humans, likely inducing tumours through a non-genotoxic (although unknown) mechanism.

In a range of studies, including those designed to investigate the reproductive effects of BBP on the testes and endocrine hormones of male rats, a modified mating protocol conducted by the NTP, and a one-generation study, adverse effects on the testes and, consequently, fertility have generally been observed only at doses higher than those that induce effects on other organs (such as the kidney and liver), although decreases in sperm counts have been observed at doses similar to those that induce effects in the kidney and liver. This is consistent with the results of repeated-dose toxicity studies.

Reductions in testes weight and daily sperm production in offspring were reported at a relatively low level in rats exposed *in utero* and during lactation in a study in which dose-response was not investigated. However, such effects were not observed in a recent study in another strain of rats in which only increases in absolute and relative liver weights were observed at postnatal day 90. Additional investigation of potential effects on the reproductive systems of male and female animals exposed *in utero* and during lactation in studies designed to address dose-response is desirable and under way.

Although BBP has been estrogenic in human breast cell cancer lines *in vitro*, results in yeast cells have been mixed. Neither BBP nor its principal metabolites have been uterotrophic *in vivo* in rats or mice. Although available data do not support the conclusion that BBP is estrogenic, other potential endocrine-mediated effects such as anti-androgenic activity associated with DBP are not precluded.

There is considerable emphasis currently on development of more sensitive frameworks for testing and assessment of endocrine-disrupting substances; compounds such as phthalates are likely early candidates for additional testing.

In several well-conducted studies in rats and mice, BBP has

induced marked developmental effects, but only at dose levels that induce significant maternal toxicity.

Although the potential neurotoxicity of BBP has not been well investigated, histopathological effects on the central and peripheral nervous systems have not been observed following short-term exposure to relatively high dietary concentrations. Available data are inadequate to assess the potential immunotoxicity of BBP.

Effect levels in available studies for the oral route are summarized in Table 1. Based on consideration of the complete database on repeated-dose toxicity by the oral route (including subchronic, chronic, and reproductive/developmental studies), effects that occur at lowest concentrations in rats are increases in organ to body weight ratios, primarily for the liver and kidney, and histopathological effects on the pancreas and kidney at dose levels in the range of 120 to just greater than 300 mg/kg body weight per day. Specifically, these include increases in ratios of liver to body weight and pancreatic lesions in the Wistar rat observed in a 90-day study (Hammond et al., 1987), increases in (absolute and relative) kidney weight and relative liver weight and proximal tubular regeneration in a 2-week reproductive study (Agarwal et al., 1985), and increased relative kidney weight at interim (15 month; not determined at termination) sacrifice in male F344 rats in the 2-year NTP bioassay (NTP, 1997a). Although nephropathy was also increased at all doses (300 mg/kg body weight per day and higher) in the kidney of female F344 rats in the 2-year NTP bioassay (NTP, 1997a), incidence was high in all groups, with no evidence of dose-response (incidence or severity) and no increase in severity between the interim and final sacrifices.

Increases in hepatic peroxisomal proliferation in F344 rats also occur at doses similar to those at which the effects mentioned above have been observed following exposure for 1 or 12 months (NTP, 1997a). Decreases in body weight in mice (of unspecified statistical significance) have also been observed in this dose range in a 90-day study, although food consumption was not reported (NTP, 1982). Decreases in epididymal spermatozoal concentrations have also been reported at these levels, although without accompanying histopathological effects on the testes or adverse impact on fertility (NTP, 1997a).

11.1.2 Criteria for setting guidance values for BBP

The following guidance is provided as a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities.

Benchmark doses have been developed for histopathological lesions in the pancreas of male Wistar rats in the 90-day study (Hammond et al., 1987) and renal lesions in male F344 rats in the 2-week reproductive study conducted by the NTP (Agarwal et al., 1985). Primarily for purposes of comparison, a benchmark dose for renal lesions in female F344/N rats in the 2-year carcinogenesis bioassays conducted by the NTP is also presented (NTP, 1997a). Information on

the incidence of these lesions, resulting benchmark doses calculated

using the THRESH program (Howe, 1995), and associated parameter estimates and statistics of fit are presented in Table 3. Each benchmark dose is based upon a 5% effect level; 95% lower confidence limits are also presented.

Histopathological effects have not been associated with increases in organ to body weight ratios in the same sex except at much higher doses, nor have decreases in epididymal spermatozoal concentrations at lowest doses been accompanied by histopathological effects and adverse impact on fertility. Owing principally to these considerations and less to the inadequacy of current statistical techniques to adequately model continuous data for these end-points and for peroxisomal proliferation, benchmark doses for these end-points have not been developed; for completeness, however, relevant effect levels are included in Table 3 for comparison.

The fit of the model was best for pancreatic lesions in male Wistar rats in the subchronic study by Hammond et al. (1987) (P = 0.98), adequate for proximal tubular regeneration in the kidney of male rats in the 2-week reproductive protocol (Agarwal et al., 1985) (P = 0.39), and inadequate for nephropathy in female rats in the 2-year bioassay (NTP, 1997a) (P = 0.03). Inadequate fit for the latter is attributable to high incidence in all dose groups and little evidence of dose-response. On this basis and consideration of the fact that pancreatic lesions and tumours were also observed in the NTP 2-year bioassay in males of another strain of rats, the pancreatic lesions in the Hammond et al. (1987) study have been selected as the point of departure for development of a tolerable intake.

For comparison, a benchmark dose calculated using the THRESH program (Howe, 1995) and associated parameter estimates and statistics of fit for pancreatic focal hyperplasia (acinus) in male F344 rats in the 2-year NTP bioassay are presented in Table 4. Although the benchmark dose and associated lower 95% confidence limit are slightly less than those calculated on the basis of the Hammond et al. (1987) study in Wistar rats, it should be noted that the distinction between hyperplasia and adenomas in the carcinogenesis bioassay was not readily apparent. A tumorigenic dose (TD_{05}) calculated on the basis of multistage modelling (Global 82) of the incidence of pancreatic adenomas or carcinomas (acinus) in male rats in the NTP bioassay is also presented in Table 4 and, as would be expected, is greater than the benchmark dose for hyperplasia. Data presented in the published account were insufficient to develop a benchmark dose on the basis of hyperplasia and adenomas combined.

Table 3: Benchmark doses for non-neoplastic effects.

Study calculating (reference)		Parameter estimates		Data for benchmark dose[a]
	Effect levels Response	Benchmark dose	Dose Goodness of fit	

Study (reference)	Effect levels	Response	Benchmark dose	Parameter estimates Goodness of fit	Data for calculating benchmark dose[a]
Subchronic dietary study Wistar rats, 27–45/group 3-month duration (Monsanto Company, 1980a; Hammond et al., 1987)	LOAEL = 381 mg/kg body weight per day (based upon histopathological lesions in males in pancreas at two highest doses) (males) LOEL = 171 mg/kg body weight per day (based on increases in organ to body weight ratios at all doses for the kidney, liver, and caecum) (females)	Lesions in pancreas: 0/27 (0%) 0/14 (0%) 8/15 (53%) 13/14 (93%)	5% dose: 167 mg/kg body weight per day 95% lower confidence limit: 132 mg/kg body weight per day	Males: Chi-square goodness of fit: 9.3×10^{-4} Degrees of freedom: 1 P-value: 0.98	control 151 mg/kg body weight per day 381 mg/kg body weight per day 960 mg/kg body weight per day
Reproductive study F344 male rats, 10/group 14-day dietary administration (Kluwe et al., 1984; Agarwal et al., 1985)	LOAEL = 312.5 mg/kg body weight per day (based upon significant increase in the relative weight of liver and both the absolute and relative weights of kidney and proximal tubular regeneration at all levels of exposure)	Kidney, proximal tubular regeneration: 0/10 2/10 2/10 4/10 3/10	5% dose: 228 mg/kg body weight per day 95% lower confidence limit: 117 mg/kg body weight per day	Males: control Chi-square goodness of fit: 3.01 Degrees of freedom: 3 P-value: 0.39	312.5 mg/kg body weight per day 625 mg/kg body weight per day 1250 mg/kg body weight per day 2500 mg/kg body weight per day

Table 3 (continued)

Study (reference)	Effect levels	Response	Benchmark dose	Parameter estimates Goodness of fit	Data for calculating benchmark dose[a]

Study (reference) Response	Effect levels	Parameter estimates 5% dose: 50 mg/kg body weight per day	Data for benchmark dose Goodness of fit
Carcinogenicity bioassay F344/N rats, nephropathy: 60/sex/group Dietary administration for 2 years	LOEL = 120 mg/kg body weight per day (based on increased relative kidney weight in males at interim sacrifice) (not determined at terminal sacrifice)	95% lower confidence limit: 28 mg/kg body weight per day	Females: Chi-square goodness of fit: 7.09 Degrees of freedom: 2 P-value: 2.9×10^{-2}
(NTP, 1997a) 34/50 47/50 (P < 0.01) 43/50 (P < 0.05) 45/50 (P < 0.01)	Increase in renal nephropathy in females at all doses (300 mg/kg body weight and above); however, unacceptable goodness of fit for benchmark dose		control 300 mg/kg body weight per day 600 mg/kg body weight per day 1200 mg/kg body weight per day
F344/N female rats, 5/group Dietary administration for 1 or 12 months (NTP, 1997a)	LOEL = 300 mg/kg body weight per day (based on increase in peroxisomal proliferation)		

Table 3 (continued)

Study calculating (reference) Response	Parameter estimates Effect levels Benchmark dose	Data for benchmark dose[a] Dose Goodness of fit
F344 males, 15/group Modified mating protocol (NTP, 1997a)	LOAEL = 200 mg/kg body weight per day (decrease in epididymal spermatozoal concentration without histopathological evidence of hypospermia or decrease in fertility) (It should be noted that the dose levels in this protocol increase by a factor of 10.)	

ª Benchmark doses were calculated with the THRESH program (Howe, 1995). The approach to the use of benchmark doses in risk
     assessment is described by US EPA (1995).

     The TDI is developed, therefore, as follows:

TDI =   <u>132 mg/kg body weight per day</u>
                         100

     =   1.3 mg/kg body weight per day

where:

132 mg/kg body weight per day is the lower 95% confidence limit for the benchmark dose (167 mg/kg body weight per day) associated with a 5% increase in the incidence of pancreatic lesions in male Wistar rats in the subchronic study of Hammond et al. (1987). It is noted that increased excretion in faeces at higher doses observed in one study might impact on the dose-response curve and resulting benchmark dose, although it was not possible to address this quantitatively.

100 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation). An additional factor for extrapolation from subchronic to chronic has not been incorporated as, on the basis of a fairly robust database, there is no indication that effect levels are lower in chronic studies than in investigations of shorter duration; moreover, the compound is rapidly eliminated. Also, the incidence of pancreatic lesions in the Wistar rat in the subchronic study on which the benchmark dose is based is higher than that observed in the F344/N rat in the 2-year carcinogenesis bioassay. Available data were considered insufficient to replace default values for toxicokinetic and toxicodynamic components of interspecies and intraspecies variation with data-derived values.

     This TDI is similar to values that could be developed based on the LOELs for the continuous end-points such as peroxisomal proliferation and increases in organ to body weight ratios included in Table 1.

     Data on the toxicity of BBP following repeated exposure by inhalation are limited, with information relevant to characterization of exposure-response being confined to results of two short-term and one subchronic study in rats, with the range of end-points examined in the latter investigation being more limited (Hammond et al., 1987). In the short-term study with lowest concentrations, effects on body weight gain and serum glucose were observed at 526 mg/m³; there were no effects on haematology, blood chemistry, urinalysis, organ weights, or histopathology at 144 mg/m³. Increases in organ weights were observed at 218 mg/m³ in the subchronic study, although there were no histopathological effects at the highest dose (789 mg/m³); the NOEL was 51 mg/m³. Although the database for inhalation is somewhat limited, it is of interest to note that the NOELs for effects by this route are similar to those for ingestion. For example, the NOEL in the

investigation in which the range of end-points examined was more extensive (144 mg/m³) is equivalent to a dose approximately threefold

less than the point of departure (i.e., the 95% lower confidence limit) for the TDI presented above.[1]

11.1.3 Sample risk characterization

Based upon a sample estimate (section 6.2), intake of BBP for the general population ranges from 2 μg/kg body weight per day in adults to 6 μg/kg body weight per day in children. Food is by far the greatest source, contributing essentially all of the intake.

The maximum and minimum estimates of total daily intake are 200 and 650 times less, respectively, than the TDI derived above for the general population.

Identified data were inadequate to provide sample estimates of exposure to BBP in the occupational environment or from consumer products and hence sample risk characterizations for these scenarios. It should be noted, though, that the inclusion of concentrations in indoor air in the estimates of exposure for the general population should account, at least to some extent, for exposure from consumer products.

11.2 Evaluation of environmental effects

BBP may be released to the environment from a number of industrial and municipal sources. Most releases are reported to be to the atmosphere, but BBP is also released to the aquatic environment from industrial and municipal liquid effluents.

Once in the environment, BBP partitions to soil, surface water, sediments, and biota, and the substance has been detected in each of these compartments. Likely sinks are soil and sediment.

BBP is removed from the atmosphere by photooxidation and by rainwater, with a half-life of a few hours to a few days. BBP is not persistent in water, sediments, or soil under aerobic conditions, with a half-life of a few days. Under anaerobic conditions, BBP is more persistent, with a half-life of a few months. BBP is readily metabolized by vertebrates and invertebrates. Reported BCFs are less than 1000, based on total residues, and well under 100, based on intact BBP residues.

[1] Based on the following conversion: 1 mg/m^3 in air = 0.31 mg/kg body weight per day ingested in rats (Health Canada, 1994).

Table 4: Benchmark dose for pancreatic hyperplasia and tumorigenic dose (NTP 2-year bioassay).

Study benchmark dose (reference)	Effect levels	Data for calculating benchmark dose	Parameter estimates	Dose	Goodness of fit
Response					

Carcinogenicity bioassay	Pancreas, acinus, focal hyperplasia	Males:	
F344/N rats		control	4/50
Dietary administration		120 mg/kg body weight per day	7/49
for 2 years		weight per day	9/50
(NTP, 1997a)		240 mg/kg body weight per day	12/50 (P < 0.05)
		500 mg/kg body weight per day	

5% dose: 130 mg/kg body weight per day
P-value for lack of fit: 0.916
95% lower confidence limit: 73 mg/kg body weight

Carcinogenicity bioassay	Pancreas, acinus, adenoma, or carcinoma	Males:	
F344/N rats		control	3/50
Dietary administration		120 mg/kg body weight per day	2/49
for 2 years		per day	3/50
(NTP, 1997a)		240 mg/kg body weight per day	
		500 mg/kg body weight per day	

TD_{05}: 320 mg/kg body weight per day
P-value for lack of fit: 0.854
95% lower confidence limit: 160 mg/kg body weight per day
11/50 (P = 0.014)
P = 0.003 for trend

In acute toxicity tests on approximately two dozen species and chronic tests on about a dozen species, adverse effects occur at exposure concentrations equal to or greater than 100 µg/litre. Although higher concentrations have sometimes been reported, concentrations in surface waters are generally less than 1 µg/litre. Therefore, it is likely that BBP poses low risk to aquatic organisms.

No information about the effects of BBP on sediment-dwelling organisms, soil invertebrates, terrestrial plants, or birds has been identified on which to base an estimate of risk to these organisms.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

IARC (1987) has classified BBP in Group 3: "the agent is not classifiable as to its carcinogenicity to humans." There were no adequate data for humans, and evidence in animals was inadequate.

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventive and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0834) reproduced in this document.

13.1 Human health hazards

BBP has the potential to adversely affect reproductive function, although effects on kidney, liver, and pancreas are noted at generally lower doses.

13.2 Advice to physicians

In case of poisoning, treatment is supportive.

13.3 Spillage

In the event of spillage, measures should be undertaken to prevent BBP from reaching drains or watercourses because of its toxicity to aquatic organisms.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards may be obtained from UNEP Chemicals (IRPTC), Geneva. The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

INTERNATIONAL CHEMICAL SAFETY CARD

BUTYL BENZYL PHTHALATE   ICSC: 0834
                                                   March 1998

CAS #   85-68-7   Benzyl Butyl phthalate
RTECS #   TH9990000   1,2-Benzenedicarboxylic acid, butyl
phenymethyl ester

                                           BBP
        $1,2-C_6H_4(COOCH_2C_6H_5)(COOC_4H_9)/C_{19}H_{20}O_4$

                                    Molecular Mass: 312.4

    TYPES OF HAZARD/   ACUTE HAZARDS/   PREVENTION
FIRST AID/

EXPOSURE	SYMPTOMS	FIRE FIGHTING

FIRE   Combustible. Gives off   NO open flames.   Water spray, powder, irritating or toxic fumes carbon dioxide. (or gases) in a fire.

EXPLOSION

EXPOSURE

Inhalation   Cough. Sore throat.   Ventilation, local exhaust,   Fresh air, rest. or breathing protection.

Skin   Redness.   Protective gloves.   Remove contaminated clothes. Rinse and then wash skin with water and soap.

Eyes   Redness.   Safety spectacles.   First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.

Ingestion   Do not eat, drink, or smoke   Rinse mouth. Rest. during work.

SPILLAGE DISPOSAL	PACKAGING & LABELLING

Collect leaking and spilled liquid in sealable metal   Marine pollutant.
containers as far as possible. Absorb remaining liquid   EU Classification
in sand or inert absorbent and remove to safe place.   Symbol:
Do NOT let this chemical enter the environment. (Extra   UN Classification

personal protection: A/P2 filter respirator for organic
vapour and harmful dust).

EMERGENCY RESPONSE	STORAGE

NFPA Code: H1; F1; R0;   Separated
from strong oxidants.

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE: ROUTES OF
EXPOSURE:
COLOURLESS OILY LIQUID   The substance
can be absorbed into the body
                                                         by inhalation
of its vapour.

CHEMICAL DANGERS: INHALATION
RISK:
The substance decomposes on heating producing toxic   No indication
can be given about the rate in
fumes (phthalic anhydride). Reacts with oxidants.   which a
harmful concentration in the air is
                                                         reached on
evaporation of this substance
                                                         at 20°C.

OCCUPATIONAL EXPOSURE LIMITS: EFFECTS OF
SHORT-TERM EXPOSURE:
TLV not established.   The substance
irritates the eyes, the skin
                                                         and the
respiratory tract.

                                                         EFFECTS OF
LONG-TERM OR REPEATED EXPOSURE:
                                                         The substance
may have effects on the liver and
                                                         kidneys,
resulting in impaired functions.

PHYSICAL PROPERTIES

Boiling point:	370°C
Melting point:	-35°C
Relative density (water = 1):	1.1
Solubility in water:	none
Vapour pressure, Pa at 20°C:	<0.1
Relative vapour density (air = 1):	10.8
Flash point:	199°C
Octanol/water partition coefficient as log Pow:	4.77

ENVIRONMENTAL DATA

The substance is very toxic to aquatic organisms. In the food chain important to humans,
bioaccumulation takes place, specifically in fish.

NOTES

Saniticizer 160, Sicol 160, Unimoll BB and Palatinol BB are trade names. Also consult
ICSC #0271 Di(2-ethylhexyl)phthalate.

ADDITIONAL INFORMATION

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APPENDIX 1 -- SOURCE DOCUMENTS

Government of Canada (in press)

    Copies of the Canadian Environmental Protection Act *Priority
 Substances List assessment report* (Government of Canada, in press)
and unpublished supporting documentation for BBP may be obtained from:

    Commercial Chemicals Branch
    Environment Canada
    14th Floor, Place Vincent Massey
    351 St. Joseph Blvd.
    Hull, Quebec
    Canada K1A 0H3

or

    Environmental Health Centre
    Health Canada
    Address Locator: 0801A
    Tunney's Pasture
    Ottawa, Ontario
    Canada K1A 0L2

    Initial drafts of the supporting documentation and Assessment
Report for BBP were prepared by staff of Health Canada and Environment
Canada.

    The environmental sections were reviewed externally by Dr G.
Coyle (Monsanto Company), Dr T. Parkerton (Exxon Biomedical Sciences
Inc.), Mr A. Sardella (Monsanto Canada), and Dr D. Spry (Ontario
Ministry of Environment and Energy).

    Sections of the supporting documentation pertaining to human
health were reviewed externally by Dr R. Nair (Solutia Inc.) to
address adequacy of coverage. Accuracy of reporting, adequacy of
coverage, and defensibility of conclusions with respect to hazard
identification and dose-response analyses were considered in written

review by staff of the Information Department of BIBRA International and at a panel meeting of the following members convened by Toxicology Excellence for Risk Assessment on 27 April 1998 in Cincinnati, Ohio, USA:

Dr M. Abdel-Raman, University of Medicine and Dentistry of New Jersey

Dr J. Christopher, California Environmental Protection Agency

Dr G. Datson, Procter & Gamble Co.

Dr J. Donohue, US Environmental Protection Agency

Dr M. Dourson, Toxicology Excellence for Risk Assessment

Ms D. Proctor, ChemRisk

Ms R. Rudel, Silent Spring Institute (submitted written comments; not available to attend panel meeting)

Dr A. Stern, New Jersey Department of Environmental Protection

APPENDIX 2 -- CICAD PEER REVIEW

The draft CICAD on BBP was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Chemical Industry Institute of Toxicology (CIIT), Research Triangle Park, USA

Department of Health, London, United Kingdom

Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany

Health and Safety Executive, Bootle, United Kingdom

Health Canada, Ottawa, Canada

József Fodor National Center of Public Health, Budapest, Hungary

Karolinska Institute, Stockholm, Sweden

National Chemicals Inspectorate (KEMI), Solna, Sweden

National Food Administration, Uppsala, Sweden

National Institute for Working Life, Solna, Sweden

National Institute of Public Health, Oslo, Norway

National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands

Nofer Institute of Occupational Medicine, Lodz, Poland

Norwegian University of Science and Technology, Trondheim, Norway

Mr Frank Sullivan, Consultant Toxicologist, Brighton, United Kingdom

United States Department of Health and Human Services (Agency for Toxic Substances and Disease Registry, Atlanta, USA; National Institute of Environmental Health Sciences, Research Triangle Park, USA)

APPENDIX 3 -- CICAD FINAL REVIEW BOARD

Tokyo, Japan, 30 June - 2 July 1998

Members

Dr R. Benson, Drinking Water Program, United States Environmental Protection Agency, Denver, CO, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Mr R. Cary, Health Directorate, Health and Safety Executive, Merseyside, United Kingdom

Dr C. DeRosa, Agency for Toxic Substances and Disease Registry, Center for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Institute of Terrestrial Ecology, Cambridgeshire, United Kingdom

Dr H. Gibb, National Center for Environmental Assessment, United States Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M.E. Meek, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada (*Chairperson*)

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan (*Vice-Chairperson*)

Professor S.A. Soliman, Department of Pesticide Chemistry, Alexandria University, Alexandria, Egypt

Ms D. Willcocks, Chemical Assessment Division, Worksafe Australia, Camperdown, Australia (*Rapporteur*)

Professor P. Yao, Chinese Academy of Preventive Medicine, Institute of

Occupational Medicine, Beijing, People's Republic of China

Observers

Professor F.M.C. Carpanini,[1] Secretary-General, ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), Brussels, Belgium

[1] Invited but unable to attend.

Dr M. Ema, Division of Biological Evaluation, National Institute of Health Sciences, Osakai, Japan

Mr R. Green,[1] International Federation of Chemical, Energy, Mine and General Workers' Unions, Brussels, Belgium

Dr B. Hansen,[1] European Chemicals Bureau, European Commission, Ispra, Italy

Mr T. Jacob,[1] Dupont, Washington, DC, USA

Dr H. Koeter, Organisation for Economic Co-operation and Development, Paris, France

Mr H. Kondo, Chemical Safety Policy Office, Ministry of International Trade and Industry, Tokyo, Japan

Ms J. Matsui, Chemical Safety Policy Office, Ministry of International Trade and Industry, Tokyo, Japan

Mr R. Montaigne,[1] European Chemical Industry Council (CEFIC), Brussels, Belgium

Dr A. Nishikawa, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan

Dr H. Nishimura, Environmental Health Science Laboratory, National Institute of Health Sciences, Osaka, Japan

Ms C. Ohtake, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr T. Suzuki, Division of Food, National Institute of Health Sciences, Tokyo, Japan

Dr K. Takeda, Mitsubishikagaku Institute of Toxicological and Environmental Sciences, Yokohama, Japan

Dr K. Tasaka, Department of Chemistry, International Christian University, Tokyo, Japan

Dr H. Yamada, Environment Conservation Division, National Research Institute of Fisheries Science, Kanagawa, Japan

Dr M. Yamamoto, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr M. Yasuno, School of Environmental Science, The University of Shiga Prefecture, Hikone, Japan

[1] Invited but unable to attend.

Dr K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

Secretariat

Ms L. Regis, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

Dr P. Toft, Associate Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au phtalate de butyle et de benzyle a été préparé conjointement par la Direction de l'Hygiène du Milieu (Santé Canada) et par la Direction de l'Evaluation des Produits chimiques commerciaux (Environnement Canada) d'après la documentation préparée parallèlement dans le cadre du Programme d'évaluation des substances d'intérêt prioritaire mené en vertu de la *Loi canadienne sur la protection de l'environnement* (LCPE). L'objectif de l'évaluation des substances d'intérêt prioritaire en vertu de la LCPE est d'évaluer les effets potentiels sur la santé humaine de l'exposition indirecte aux substances présentes dans l'environnement, ainsi que les effets de ces substances sur l'environnement. Les analyses ont porté sur les données connues à fin avril 1998. On trouvera à l'appendice 1 des informations sur les modalités de l'examen par des pairs et sur les sources documentaires. Les renseignements concernant l'examen du CICAD par des pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Tokyo (Japon) du 30 juin au 2 juillet 1998. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC N° 0834) pour le phtalate de butyle et de benzyle, établie par le Programme international sur la Sécurité chimique (IPCS, 1993) est également reproduite dans ce document.

Le phtalate de butyle et de benzyle (N° CAS 85-68-7), ou PBB, est un liquide huileux limpide utilisé comme plastifiant principalement dans le poly(chlorure de vinyle) (PVC) pour les revêtements de sol, les mousses de vinyle et les sous-couches de tapis et, dans une moindre mesure, dans les plastiques cellulosiques et le polyuréthane. La plupart des rejets se font dans l'air. Une fois dans l'environnement, le PBB se répartit entre l'atmosphère, le sol, les eaux de surface, les sédiments et les biotes, et a été détecté dans chacun de ces compartiments.

Le PBB est éliminé de l'atmosphère par photo-oxydation et par la pluie, avec une demi-vie de quelques heures à quelques jours. En aérobiose, il ne persiste pas dans l'eau, les sédiments ni les sols,

sa demi-vie étant de quelques jours. En anaérobiose, il est plus persistant, avec une demi-vie de quelques mois. Les vertébrés et les invertébrés le métabolisent facilement. Les facteurs de bioconcentration signalés sont inférieurs à 1000 si l'on tient compte des résidus totaux, et sont bien inférieurs à 100 d'après les résidus intacts.

Les données disponibles sur l'homme sont insuffisantes pour servir de base à l'évaluation des effets d'une exposition à long terme au PBB sur les populations humaines.

La toxicité aiguë du PBB est relativement faible, la DL_{50} orale chez le rat étant supérieure à 2 g/kg de poids corporel. Après exposition aiguë, les cibles principales sont le sang et le système nerveux central.

Les données disponibles sont insuffisantes pour évaluer les effets irritants et sensibilisants du PBB chez l'animal.

La toxicité du PBB après administration de doses répétées a été largement étudiée lors d'études récentes, principalement chez le rat, espèce pour laquelle une relation dose-réponse a été bien caractérisée. Les effets régulièrement observés consistaient en une diminution de la prise de poids (souvent accompagnée d'une diminution de la consommation alimentaire) et en une augmentation du rapport du poids des organes (notamment du foie et des reins) au poids total. On a également observé des effets histopathologiques sur le pancréas et les reins et des effets hématologiques. Aux fortes doses, une dégénérescence des testicules et parfois des effets histopathologiques sur le foie ont été rapportés. Des investigations spécialisées ont montré une prolifération des peroxysomes du foie, bien que le PBB ait fait preuve dans cette étude d'une activité plus faible que les autres phtalates, par exemple le phtalate de bis(2-éthylhexyle).

La toxicité chronique et la cancérogénicité du PBB ont été étudiées lors d'essais biologiques de l'US National Toxicology Program (NTP) chez le rat (avec des protocoles alimentaires standard et restrictifs) et chez la souris. Il a été conclu qu'il y avait "certaines preuves" de cancérogénicité chez le rat mâle, d'après une incidence accrue des tumeurs du pancréas, et des preuves non concluantes chez les rats femelles d'après une augmentation marginale des tumeurs du pancréas et de la vessie. L'administration d'une alimentation restreinte empêchait l'expression complète des tumeurs du pancréas et retardait l'apparition des tumeurs de la vessie. Aucune preuve de cancérogénicité n'a été trouvée chez la souris.

Les résultats des études de génotoxicité portant sur le PBB sont clairement négatifs. Cependant, les données disponibles sont insuffisantes pour permettre de conclure formellement à l'absence de clastogénicité du PBB, bien que dans certaines études il ait induit au maximum une activité clastogène faible, d'une intensité compatible avec des effets secondaires sur l'ADN.

En résumé, le PBB a induit une augmentation des tumeurs du pancréas chez les animaux d'un sexe d'une espèce, effet dont l'expression totale était empêchée par une restriction alimentaire, et une augmentation marginale des tumeurs de la vessie chez les animaux

de l'autre sexe, effet retardé par la restriction alimentaire. En ce qui concerne la génotoxicité, les résultats ont été négatifs et, bien qu'on ne puisse exclure un faible potentiel clastogène, les données disponibles permettent de penser que le composé n'exerce pas

d'interaction directe avec l'ADN. D'après ces résultats, le PBB peut être considéré au maximum comme éventuellement cancérogène pour l'homme, susceptible d'induire des tumeurs par un mécanisme non génotoxique (mais inconnu).

Dans diverses études, y compris celles portant sur les effets du PBB sur les testicules et les hormones endocrines chez le rat mâle, des études avec un protocole modifié d'accouplement réalisées par le NTP, et une étude sur une seule génération, on n'a en général observé d'effets indésirables sur les testicules et par conséquent sur la fécondité qu'aux doses supérieures à celles qui induisent des effets sur les autres organes (comme le foie et les reins), bien qu'une diminution du nombre de spermatozoïdes ait été observée à des doses analogues à celles qui induisent des effets sur le rein et le foie. Ces résultats sont compatibles avec ceux des études de toxicité portant sur des doses répétées.

Une diminution du poids des testicules et de la production quotidienne de spermatozoïdes chez la descendance a été observée à une dose relativement faible chez des rats exposés *in utero* et pendant l'allaitement lors d'une étude dans laquelle la relation dose-réponse n'était pas examinée. Cependant, de tels effets n'ont pas été observés lors d'une étude récente de conception similaire mais non identique réalisée sur une autre souche de rats, chez lesquels seule une augmentation du poids relatif et absolu du foie a été observée 90 jours après la naissance. Des investigations supplémentaires sur les effets potentiels du composé sur le système reproducteur d'animaux mâles et femelles exposés *in utero* et pendant l'allaitement dans le cadre d'études portant également sur la relation dose-réponse sont souhaitables, et sont en cours.

Bien que le PBB ait des effets estrogéniques dans des lignées de cellules humaines de cancer du sein *in vitro*, les résultats en cellules de levure sont peu concluants. Ni le PBB ni ses principaux métabolites ne sont utérotrophiques *in vivo* chez le rat ou la souris. Si les données disponibles ne permettent pas de conclure que le PBB a des propriétés estrogéniques, d'autres effets potentiels à médiation endocrinienne, par exemple un effet anti-androgène associé au phtalate de dibutyle, ne sont pas exclus.

On s'intéresse actuellement à la mise au point de cadres plus sensibles d'essai et d'évaluation des substances perturbant l'équilibre endocrinien; des composés comme les phtalates sont susceptibles d'être parmi les premiers candidats à soumettre à des essais supplémentaires.

Lors de plusieurs études bien conduites chez des rats et des souris, le PBB a induit des effets notables sur le développement, mais seulement à des doses qui entraînent une toxicité significative chez la mère.

Bien que la neurotoxicité potentielle du PBB n'ait pas été

largement explorée, il n'a pas été observé d'effets histopathologiques sur le système nerveux central et périphérique après exposition à court terme à des doses relativement élevées dans l'alimentation. Les données disponibles sont insuffisantes pour permettre d'évaluer la toxicité immunologique potentielle du PBB.

Une dose journalière tolérable estimative (DJT) de 1300 µg/kg de poids corporel par jour a été calculée pour le PBB, d'après la limite inférieure de confiance à 95% pour la dose associée à une augmentation de 5% de l'incidence des lésions pancréatiques chez le rat mâle lors d'un essai biologique subchronique par voie orale, divisée par un facteur d'incertitude de 100 (10 pour la variation interspécifique et 10 pour la variation intraspécifique). D'après les concentrations rencontrées dans les divers milieux de l'environnement, il apparaît (d'après des estimations) que la totalité de l'apport estimé est imputable à l'alimentation; cet apport est évalué, pour la population générale, à 2-6 µg/kg de poids corporel par jour. Ces estimations sont 200 à 650 fois plus faibles que la DJT. Les données sont insuffisantes pour estimer l'exposition dans le milieu de travail ou par des produits de consommation.

Divers tests de toxicité réalisés sur des organismes aquatiques ont montré que des effets indésirables se produisent lors d'expositions à des concentrations supérieures ou égales à 100 µg/litre. Comme les concentrations de PBB dans les eaux de surface sont en général inférieures à 1 µg/litre, il est probable que ce composé comportera peu de risques pour les organismes aquatiques.

On ne dispose d'aucune information sur les effets du PBB sur les organismes benthiques, les invertébrés du sol, les plantes terrestres ou les oiseaux, qui permettrait d'estimer le risque pour ces organismes.

RESUMEN DE ORIENTACION

Este CICAD sobre el butil-bencil-ftalato, preparado conjuntamente por la Dirección de Higiene del Medio del Ministerio de Sanidad del Canadá y la División de Evaluación de Productos Químicos Comerciales del Ministerio de Medio Ambiente del Canadá, se basa en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la *Ley Canadiense de Protección del Medio Ambiente* (CEPA). Las evaluaciones de sustancias prioritarias prevista en la CEPA tienen por objeto valorar los efectos potenciales para la salud humana de la exposición indirecta en el medio ambiente general, así como los efectos ecológicos. En estos exámenes se incluyen los datos identificados hasta el final de abril de 1998. La información relativa al carácter del examen colegiado del documento original y su disponibilidad figura en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Tokio (Japón) del 30 de junio al 2 de julio de 1998. La lista de participantes en esta reunión figura en el apéndice 3. La ficha internacional de seguridad química (ICSC 0834) para el butil-bencil-ftalato, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en este documento.

El butil-bencil-ftalato (CAS N° 85-68-7) o BBP es un líquido oleoso transparente que se utiliza como plastificante sobre todo en el cloruro de polivinilo (PVC) para la fabricación de baldosas de vinilo, espumas de vinilo y entramado para alfombras y en menor medida también en los plásticos de celulosa y el poliuretano. La mayor parte del que se libera en el medio ambiente va al aire. Una vez en el medio ambiente, el BBP se distribuye entre la atmósfera, el suelo, el agua superficial, los sedimentos y la biota, y se ha detectado en cada uno de estos compartimentos.

El BBP se elimina de la atmósfera por fotooxidación y por el agua de lluvia, con una semivida que oscila entre algunas horas y varios días. No es persistente en el agua, los sedimentos o el suelo en condiciones aerobias, con una semivida de varios días. En condiciones anaerobias, el BBP es más persistente, siendo su semivida de varios meses. Los vertebrados e invertebrados lo metabolizan fácilmente. Se han notificado factores de bioconcentración inferiores a 1000, tomando como base los residuos totales, y muy por debajo de 100 a partir de los residuos de BBP intactos.

Los datos disponibles en el ser humano son insuficientes para poder evaluar los efectos de la exposición prolongada al BBP en poblaciones humanas.

La toxicidad aguda del BBP es relativamente baja, con valores de la DL_{50} por vía oral superiores a 2 g/kg de peso corporal en ratas. Los órganos afectados tras la exposición aguda son el sistema hematológico y el sistema nervioso central.

Los datos disponibles son insuficientes para evaluar los efectos irritantes y sensibilizantes del BBP en especies de animales.

En estudios recientes se ha investigado a fondo la toxicidad de dosis repetidas de BBP, particularmente en la rata, en la cual está bien caracterizada la relación dosis-respuesta. Los efectos observados han sido siempre una disminución del aumento del peso corporal (con frecuencia acompañada de una reducción del consumo de alimentos) y un incremento de la razón peso de los órganos/peso corporal, especialmente para el riñón y el hígado. Se han observado asimismo efectos en el páncreas y el riñón, así como hematológicos. Con dosis más elevadas, se han notificado efectos degenerativos en los testículos y, ocasionalmente, efectos histopatológicos en el hígado. En investigaciones especializadas se ha observado proliferación de peroxisomas en el hígado, aunque la potencia a este respecto fue inferior a la de otros ftalatos, como el bis(2-etilhexil)ftalato (DEHP).

Se han investigado la toxicidad crónica y la carcinogenicidad del BBP en biovaloraciones realizadas por el Programa Nacional de Toxicología de los Estados Unidos de América (con inclusión de protocolos normales y de alimentación limitada) en ratas y en ratones. Se llegó a la conclusión de que había "algunos indicios" de carcinogenicidad en ratas macho, basados en una mayor incidencia de tumores pancreáticos, e indicios equívocos en ratas hembra, basadas en un aumento marginal de la incidencia de tumores pancreáticos y de vejiga. La limitación de la alimentación impidió la expresión completa

de los tumores pancreáticos y retrasó la aparición de los tumores de vejiga. No hubo indicios de carcinogenicidad en ratones.

El valor demostrativo de los indicios de genotoxicidad del BBP es claramente negativo. Sin embargo, los datos disponibles son insuficientes para llegar a la conclusión inequívoca de que el BBP no es clastogénico, aunque en determinados estudios ha inducido, como máximo, una actividad débil de magnitud compatible con los efectos secundarios en el ADN.

Por consiguiente, el BBP ha inducido un aumento de los tumores pancreáticos fundamentalmente en un sexo de una especie, cuya expresión completa se evitó mediante un protocolo de alimentación limitada, y un aumento marginal de los tumores de vejiga en el otro sexo, que se retrasó con la limitación de la alimentación. El valor demostrativo de los indicios de genotoxicidad es negativo y, aunque no se puede descartar el potencial clastogénico, los datos disponibles son compatibles con el hecho de que el compuesto no tiene una interacción directa con el ADN. De acuerdo con esto, el BBP puede considerarse, como máximo, posiblemente carcinogénico para el ser humano, probablemente induciendo tumores a través de un mecanismo no genotóxico (aunque desconocido).

En una serie de estudios, en particular los diseñados para investigar los efectos reproductivos del BBP en los testículos y las hormonas endocrinas de las ratas macho, un protocolo modificado de acoplamiento realizado por el NTP y un estudio de una generación, en general se han observado efectos adversos en los testículos y, por consiguiente, en la fecundidad sólo con dosis superiores a las que inducen efectos en otros órganos (como el riñón y el hígado), si bien se ha puesto de manifiesto una reducción en el recuento de espermatozoides con dosis semejantes a las que inducen efectos en el riñón y el hígado. Esto está en consonancia con los resultados de los estudios de toxicidad con dosis repetidas.

En un estudio en el que no se investigó la relación dosis-respuesta se observó una reducción del peso de los testículos y de la producción diaria de espermatozoides en crías de ratas expuestas a una concentración relativamente baja en el útero y durante la lactancia. Sin embargo, estos efectos no se observaron en un estudio reciente de diseño parecido, pero no idéntico, realizado con otra estirpe de ratas en la cual sólo se observó un aumento del peso absoluto y relativo del hígado a los 90 días del nacimiento. Son convenientes, y se han emprendido ya, nuevas investigaciones de los efectos potenciales en el sistema reproductor de animales machos y hembras expuestos en el útero y durante la lactancia en estudios encaminados a examinar la relación dosis-respuesta.

Si bien el BBP ha sido estrogénico en líneas de células de cáncer de mama humano *in vitro*, los resultados en células de levadura han sido contradictorios. Ni el BBP ni sus principales metabolitos han sido uterotróficos *in vivo* en ratas o ratones. Aunque los datos disponibles no permiten llegar a la conclusión de que el BBP es estrogénico, no se pueden descartar otros posibles efectos debidos a factores endocrinos, como la actividad antiandrogénica asociada al dibutil-ftalato (DBP).

En la actualidad se concede una importancia considerable a la creación de sistemas más sensibles de prueba y evaluación de sustancias perturbadoras del sistema endocrino; compuestos como los ftalatos probablemente serán de los primeros que se someterán a pruebas adicionales.

En varios estudios bien realizados en ratas y ratones, el BBP indujo efectos pronunciados en el desarrollo, pero sólo a concentraciones que producen una toxicidad materna significativa.

Aunque no se ha investigado bien la posible neurotoxicidad del BBP, no se han observado efectos histopatológicos en los sistemas nerviosos central y periférico tras una exposición breve a concentraciones relativamente altas en los alimentos. Los datos disponibles son insuficientes para evaluar la posible inmunotoxicidad del BBP.

Se ha estimado para el BBP una ingesta diaria tolerable (IDT) muestral de 1300 µg/kg de peso corporal al día. Se basa en un límite de confianza inferior del 95% para la dosis de referencia asociada con un aumento del 5% de la incidencia de lesiones pancreáticas en ratas macho en una biovaloración subcrónica por vía oral, dividido por un factor de incertidumbre de 100 (10 por la variación interespecífica y 10 por la intraespecífica). Teniendo en cuenta las concentraciones en diversos medios parece (a partir de estimaciones muestrales) que los alimentos son la fuente de toda la ingesta estimada, que se considera que oscila, para la población general, entre 2 y 6 µg/kg de peso corporal al día. Estas estimaciones son 200-650 veces inferiores a la IDT. Los datos fueron insuficientes para estimar la exposición en el entorno ocupacional o a partir de productos de consumo.

En una serie de pruebas de toxicidad con organismos acuáticos se ha puesto de manifiesto que se producen efectos adversos a concentraciones de exposición iguales o superiores a 100 µg/l. Habida cuenta de que la concentración en el agua superficial suele ser inferior a 1 µg/l, es probable que el BBP represente un riesgo bajo para los organismos acuáticos.

No se dispone de información acerca de los efectos del BBP en los organismos de los sedimentos, los invertebrados del suelo, las plantas terrestres o las aves en la que pueda basarse una estimación del riesgo para estos organismos.

See Also: