Priority Existing Chemical Assessment Report No. 40

Australian Government

Department of Health
National Industrial Chemicals
Notification and Assessment Scheme

Butyl benzyl phthalate

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
GPO Box 58 Sydney NSW 2001 Australia www.nicnas.gov.au

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of the Australian people and the environment by assessing the risks of industrial chemicals and providing information to promote their safe use.

NICNAS assessments are carried out by staff employed by the Australian Government Department of Health in conjunction with the Australian Government Department of the Environment.

NICNAS has two major assessment programmes: the assessment of human health and safety and environmental effects of new industrial chemicals prior to importation or manufacture; and the assessment of chemicals already in use in Australia to address specific concerns about their health and/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals (PECs).

This PEC report has been prepared for the Director of NICNAS, in accordance with the Act. Under the Act, manufacturers and importers of PECs are required to apply for assessment. On completing a PEC assessment, the Director of NICNAS, in accordance with the Act, causes a draft report of the assessment to be prepared and makes it available to the applicants for factual corrections and to the public (including applicants and other interested parties) for comments. This consultation process for PECs thus includes two stages: each allows a statutory 28-day timeframe for the applicants to notify the Director of any errors and the public to submit any requests for variations of the draft report. Where variations are requested, the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment, and decisions made, are published in the *Commonwealth Chemical Gazette*.

In accordance with the Act, publication of the final report revokes the declaration of the chemical as a PEC; therefore, manufacturers and importers wishing to introduce the chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty under section 64 of the Act to provide any new information to NICNAS, including any additional information that becomes available as to an adverse effect of the chemical on occupational health and safety, public health or the environment.

PEC assessment reports are available on the NICNAS website at www.nicnas.gov.au. Hard copies are available (free) by contacting NICNAS at:

GPO Box 58 Sydney NSW 2001 AUSTRALIA
Freecall: 1800 638 528

Contents

Acronyms and glossary

ACC	American Chemistry Council
ACCC	Australian Competition and Consumer Commission
AGD	anogenital distance
AGI	anogenital index
AICS	Australian Inventory of Chemical Substances
AR	androgen receptor
AS/NZS	Australian/New Zealand Standard
ASEAN	Association of Southeast Asian Nations
atm	atmosphere
BBP	butyl benzyl phthalate
BMI	body mass index
BNBAS	Brazelton Neonatal Behavioral Assessment Scale
BW or bw	body weight
CAS	Chemical Abstracts Service
CASA	computer-aided semen analysis
CDC	Centers for Disease Control and Prevention
CED	critical effect dose
CERHR	Center for the Evaluation of Risks to Human Reproduction
CHMS	Canadian Health Measures Survey
CICAD	Concise International Chemical Assessment Document
CIR	Cosmetic Ingredient Review
CIUCUS	Complication of Ingredients Used in Cosmetics in the United States
CMR	carcinogenic, mutagenic, or toxic for reproduction
CosIng	Cosmetic Ingredients and Substances Database
CPSC	Consumer Product Safety Commission
DBP	dibutyl phthalate, di-n-butyl phthalate
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DiBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DiHP	diisoheptyl phthalate
DINP	diisononyl phthalate
DMP	dimethyl phthalate
DnOP	di-n-octyl phthalate
DPP	dipentyl phthalate
e.g.	*exempli gratia*, for example
EC	European Comission
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EHD	estimated human dose
EPA	Environmental Protection Agency
et al.	*et alii*, and others
EU RAR	European Union Risk Assessment Report
EU	European Union
F0	parental generation
F1	first filial/offspring generation
F2	second filial/offspring generation
FSH	follicle-stimulating hormone
g	gram
GD	gestational day
GI	gastrointestinal
GPMT	guinea pig maximisation test
Hb	haemoglobin

HBM	human biomonitoring
HEIMTSA	Health and Environment Integrated Methodology and Toolbox for Scenario Development
HI	hazard index
HMW	high molecular weight
HPV	high production volume
HSIS	Hazardous Substances Information System
i.e.	that is
IARC	International Agency for Research on Cancer
INCI	International Nomenclature Cosmetic Ingredient Dictionary
insl3	insulin-like hormone 3 (Leydig cell)
IPCS	International Programme on Chemical Safety
IQ	intelligence quotient
ISO	International Organization for Standardization
kg	kilogram
kPa	kilopascal
L	litre
LD50	median lethal dose
LH	luteinizing hormone
LMW	low molecular weight
LOAEL	lowest observed adverse effect level
m^3	cubic metre
MBP	monobutyl phthalate
MBzP	monobenzyl phthalate
MCL	mononuclear cell leukaemia
MEHP	monomethylhexyl phthalate
m-f	male-female
µg	microgram
mg	milligram
mL	millilitre
MOE	margin of exposure
mPa·s	millipascal-second
MW	molecular weight
NHANES	National Health and Nutrition Examination Survey
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
P90	90th percentile
P95	95th percentile
PEC	Priority Existing Chemical
PND	postnatal day
ppm	parts per million
PVC	polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SA/BW	surface area to body weight ratio
SCCP	Scientific Committee on Consumer Products
SD	Sprague-Dawley (rats)
SHBG	sex hormone-binding globulin
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TG	Test Guideline
USA	United States of America
vs	*versus*, against
w/w	weight/weight
WHO	World Health Organization

Glossary

NICNAS uses the International Programme on Chemical Safety risk assessment terminology (IPCS 2004), which includes:

- Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and
- Part 2: IPCS Glossary of Key Exposure Assessment Terminology.

The IPCS risk assessment terminology can be accessed at:
http://www.who.int/ipcs/methods/harmonization/areas/terminology/en/.

Overview

Background and scope of the assessment

The chemical 1,2-benzenedicarboxylic acid, butyl phenylmethyl ester (CAS No. 85-68-7), also known as butyl benzyl phthalate (BBP), was declared a Priority Existing Chemical (PEC) for public health risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 7 March 2006. The decision for the declaration was based on:

- the ubiquitous use of phthalates as solvents and plasticisers in industrial and consumer products;
- consumer products being potentially significant sources of repeated and long-term exposure of the public to BBP both directly and indirectly through migration and leaching from products;
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from BBP exposure; and
- overseas regulatory activities involving restrictions and reviews of the health risk of phthalates, including BBP, in certain consumer products.

The purpose and scope of this PEC assessment is to determine the health risks to adults and children from BBP being used in consumer products such as cosmetics, children's toys and childcare articles, particularly from repeated or prolonged exposure.

Manufacture and importation

Data collected through calls for information specific to the assessment of BBP indicate that BBP is not manufactured in Australia. It is introduced into Australia both in finished products (or articles) and in mixtures for local formulation and processing. No information on the import volume of BBP is available.

Uses

Information about specific concentrations of BBP in toys is not available. The information collected by NICNAS indicates that BBP might be used as a plasticiser (a substance added to make another substance more pliable) for toys, including play and exercise balls. In children's toys and childcare articles made from polyvinyl chloride (PVC), BBP is unlikely to be found as the dominant (primary) phthalate plasticiser, as its molecular weight is similar to that of dibutyl phthalate (DBP), a commonly used secondary plasticiser. Therefore, the chemical might be used as a secondary plasticiser (in conjunction with another plasticiser) or occur as a minor contaminant of other phthalates, including diethylhexyl phthalate (DEHP) or diisononyl phthalate (DINP). Specific concentrations of BBP in toys used in Australia are not available, and the types of non-PVC articles used as toys (play and exercise balls) in which BBP is reported to be used are not typical mouthing articles. In the absence of data on the use of BBP in children's toys, assumptions need to be made in modelling exposures that BBP completely substitutes for DBP in a mixed phthalate plasticiser, at a maximum concentration of 0.5 % w/w, with a total plasticiser concentration (DINP+BBP) in the PVC of 43 %.

Cosmetic uses of BBP were not reported in Australia. However, substitution of BBP for other phthalates subsequently prohibited in cosmetics in Australia (e.g. DBP) cannot be ruled out.

There is no current overseas information available on the use of BBP in children's toys and cosmetics. BBP is prohibited for use in cosmetics in the European Union (EU), Southeast Asia and China. The use of BBP in children's toys and childcare articles is restricted to 0.1 % by weight in the EU, the United States of America (USA) and Canada.

BBP has been reported to have a number of industrial uses in Australia, including in the manufacture of adhesives, sealants, coatings, paints and inks. It serves as a specialty plasticiser in PVC compounds, vinyl and acrylic lacquers, nitrocellulose lacquers and polyurethane wheels for forklifts.

Health effects

BBP is rapidly and almost completely absorbed following oral administration. The bioavailability of BBP from oral exposure is assessed as 100 % for both adults and children. Bioavailability from dermal absorption is unlikely to exceed 5 % of the applied dose in humans. Data on absorption of inhaled BBP are limited; therefore,

a default bioavailability of 100 % is considered appropriate for this route of exposure for the purposes of this assessment.

Following absorption, BBP is widely distributed into tissues, including the placenta, but there is no evidence of accumulation in the body. BBP is also rapidly metabolised and excreted in the urine, predominantly as metabolites, particularly monobenzyl phthalate (MBzP) and monobutyl phthalate (MBP).

BBP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans. BBP is not expected to be a potential eye or skin irritant, or skin sensitiser in humans.

Based on the weight of evidence, the available data do not support a mutagenic, genotoxic or carcinogenic potential for BBP in humans.

Toxic effects related to repeated BBP exposure that are regarded as relevant to a human health risk assessment include systemic toxicity (increased liver and/or kidney weight), fertility (mediated by testicular toxicity) and developmental toxicity (antiandrogenic effects, reduced birth weight, embryolethality and teratogenicity, particularly in male rats).

The available data indicate that BBP, as well as DEHP and DBP, are antiandrogens with a mode of action that involves alterations of steroidogenesis and gene expression critical for the male reproductive development. Although there are uncertainties regarding the exact mechanism by which BBP affects fertility, foetal hormonal levels, and growth and development in rodents, this plausible mode of action for phthalates is considered relevant to humans if the exposure to antiandrogenic phthalates, including BBP, is high and within a critical window of human development.

For the systemic effects, the no observed adverse effect level (NOAEL) of 151 mg/kg bw/day, derived from a 90-day oral study and based on histopathological changes in the pancreas and gross pathological changes in the liver of Wistar rats, is considered most appropriate for risk characterisation.

For fertility-related and developmental effects, the highest NOAEL of 50 mg/kg bw/day is derived from the collective results of the three multi-generation studies, based on reduced birth weight in both sexes at 100 mg/kg bw/day.

Public exposure and health risk

In this assessment, public health risks from modelled BBP exposure are assessed based on a margin of exposure (MOE) approach for children using toys and childcare articles only.

For the scenario involving children using toys, routes of exposure that were considered included dermal exposure during normal handling of toys and childcare articles, and oral exposure during inadvertent or intentional mouthing, sucking and chewing these products. The leaching (migration) rates of BBP as a component of a mixed phthalate plasticiser (DINP+BBP) under mouthing conditions are based on those measured in human volunteers for DINP—a common primary plasticiser found in toys. The migration rates of BBP from plasticised PVC through the human skin are estimated using the rates of DEHP (another common primary plasticiser) migrating from PVC film through rat skin, given the lack of available migration rate data from plasticised PVC or quantitative dermal absorption data for DINP or mixed phthalate plasticisers.

Studies conducted overseas indicated that children's mouthing behaviour, and hence the potential for oral exposure, is highest between 6–12 months of age with a reasonable typical and worst-case mouthing time of 0.8 hours/day and 2.2 hours/day, respectively. These are also considered applicable to the time a child spends handling toys.

The risk of adverse acute effects for children arising from handling and mouthing toys is low for BBP given the low acute toxicity of the chemical, its low skin and eye irritation potential and the absence of skin sensitising potential.

The long-term health risks for children include potential liver and kidney effects, fertility-related and developmental effects associated with repeated combined handling and mouthing of toys containing 0.5 % BBP and 42.5 % DINP. This risk assessment, which compares the BBP dose at which there is no observed adverse effect on target organs and/or systems in laboratory animals (i.e. NOAEL) with the estimated human dose (EHD) of BBP for children, results in MOEs above 24000 (see Table 7.1) in both typical and worst-case scenarios of toy use, indicating an adequate safety margin, i.e. a negligible risk of these adverse health effects occurring in children.

Cumulative risks can arise from exposure to multiple phthalates, acting on the same biological targets, from a range of sources (e.g. simultaneous use of cosmetics and children's toys and childcare articles). Determining risk from combined exposure to multiple phthalates takes into account any risk mitigation measures recommended in the PEC assessment for each phthalate. The estimated cumulative MOEs for the critical developmental effects of phthalates, including BBP, indicate an adequate safety margin for children's exposure to toys and childcare articles.

Given the uncertainties regarding the market availability, possibilities for substitution, the severe and irreversible (fertility-based and teratogenic) health effects and exposure levels of BBP in different population groups, a cautious approach to managing the potential risks associated with BBP is warranted. It is recommended that BBP be considered for listing in Schedule 10/Appendix C of the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)) to limit potential public exposure, including young children, to BBP from its possible use in cosmetics.

Recommendations

This section provides the recommendations arising from the assessment of 1,2-benzenedicarboxylic acid, butyl phenylmethyl ester (CAS No. 85-68-7), also known as butyl benzyl phthalate (BBP). The recommendation will be directed to the appropriate regulatory body with responsibility for regulating chemicals in consumer products.

Recommendation 1

It is recommended that BBP be referred to the Delegate for Chemicals Scheduling to consider listing it in **Schedule 10/Appendix C** of the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)) to limit potential public exposure, including young children, to BBP from its possible use in cosmetics.

Recommendation 1 is based on the following findings of the PEC assessment:

- The assessment conclusions support the current hazard classification of BBP in the Hazardous Substances Information System (HSIS) (Safe Work Australia) as a Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child' and as a Reproductive Toxicant Category 3 with the risk phrase R62 'Possible risk of impaired fertility.'
- BBP represents a hazardous phthalate for reproductive (testicular toxicity) and developmental toxicity (reduced birth weight, embryolethality and teratogenicity), and is considered to have a toxicity profile equivalent to dibutyl phthalate (DBP)—a phthalate of similar molecular weight and sharing the same monoester metabolite, monobutyl phthalate (MBP). DBP also has the same hazard classification as BBP in the HSIS.
- While there is no current indication of BBP being used in cosmetics in Australia, BBP may be considered as a possible substitute for other phthalates that are subject to regulation (e.g. DEHP and DBP), based on its properties, functions and uses. In this case, exposure to BBP, which is currently low, may increase. Possible substitution of BBP for hazardous phthalates should be prevented by imposing a similar regulatory measure on all phthalates classified as toxic to reproduction (e.g. DEHP, DBP and BBP).
- Reproductive toxicity induced by BBP might have serious long-term effects and affect the development and reproduction of future populations if the exposure occurs within a critical window of human development.
- A cautious approach to managing the potential risks associated with BBP is warranted, given the uncertainties regarding the market availability, possibilities for substitution, the severe and irreversible (fertility-based and teratogenic) health effects and exposure levels in different population groups.

Secondary Notification

Under section 64 of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), the Secondary Notification of a chemical that has been assessed under the Act may be required where change of any circumstances that may warrant a reassessment of its hazards, exposures or risks occurs.

In the case of BBP, specific circumstances include:

- additional information becoming available on the adverse health effects of BBP;
- BBP being used in toys and childcare articles at a concentration of >0.5 %;
- additional sources of potentially high public exposure to BBP other than toys and childcare articles being identified;
- additional information or events that change the assumptions in estimating the cumulative risks in this assessment.

The Director of NICNAS must be notified within 28 days of the introducer becoming aware of any of the above or other circumstances prescribed under section 64(2) of the Act. A person who fails to comply with these secondary notification requirements would be committing an offence under this Act.

1 Introduction

1.1 Declaration

The chemical 1,2-benzenedicarboxylic acid, butyl phenylmethyl ester (CAS No. 85-68-7), also known as butyl benzyl phthalate (BBP), was one of nine phthalate chemicals declared a Priority Existing Chemical (PEC) under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 7 March 2006 (*Chemical Gazette* 2006) for assessment of the public health risk from its use in children's toys, childcare articles and cosmetics. The basis for the declaration was the actual and potential use of BBP in children's toys, childcare articles and cosmetics.

1.2 Objectives

The objectives of this assessment are to:

- characterise the properties of BBP;
- determine the use and function of BBP in Australia in the specific consumer applications of children's toys, childcare articles and cosmetics;
- determine the extent of exposure of adults and children to BBP from these applications;
- determine any adverse health effects associated with exposure to BBP;
- characterise the risks to humans posed by exposure to BBP from use in these applications;
- determine the extent to which any risk is capable of being reduced; and
- recommend appropriate risk mitigation measures.

These consumer applications are defined below from directives, regulations and amendments from the *Official Journal of the European Union* (various dates):

- Toys—products or materials designed or clearly intended for use in play by children of less than 14 years of age.
- Childcare articles—articles designed for use by children to facilitate sleep, relaxation, hygiene, feeding, the teething process or sucking on the part of children, e.g. dummies, teething rings, teats, and feeding bottles.
- Cosmetics—substances or preparations intended for placement in contact with any external part of the human body including the mucous membranes of the oral cavity and teeth, with a view to altering the odours of the body, or changing its appearance, or cleansing it, or maintaining it in good condition or perfuming it, or protecting it, e.g. soaps, shampoos, face creams, masks, mascara, and nail polish.

1.3 Sources of information

Information for this assessment was obtained from various sources including Australian industry, governments, overseas regulatory agencies and publicly available literature sources.

1.3.1 Industry

In August 2004, information was requested from industry in Australia regarding the import and/or manufacture of phthalates either as raw materials or in products.

In March 2006, as part of the declaration of certain phthalates (including BBP) as PECs, importers and manufacturers of BBP as a raw material for use in children's toys, childcare articles and cosmetics, and importers of finished cosmetic products containing BBP, were required to apply for assessment and supply information on the use of BBP in Australia. Unpublished information on the health effects of phthalates (including BBP) was also sought.

This call for information was followed in July 2006 by a voluntary call for information to importers of toys and childcare articles containing phthalates (including BBP). Similarly, unpublished information on health effects and exposure to phthalates from migration and leaching from these articles was requested.

Information provided to NICNAS by the Australian industry is mainly on uses of phthalates, including BBP.

1.3.2 Literature review

For this assessment, the following key documents were reviewed:

Assessments by NICNAS:

- Existing Chemical hazard assessment report on butyl benzyl phthalate (BBP) (NICNAS 2008a);
- *Phthalates hazard compendium*—A summary of physicochemical and human health hazard data for 24 ortho-phthalate chemicals (NICNAS 2008b);
- PEC assessment report on diethylhexyl phthalate (DEHP) (PEC No. 32; NICNAS 2010);
- PEC assessment report on diethyl phthalate (DEP) (PEC No. 33; NICNAS 2011);
- PEC assessment report on diisononyl phthalate (DINP) (PEC No. 35; NICNAS 2012);
- PEC assessment report on dibutyl phthalate (DBP) (PEC No. 36; NICNAS 2013); and
- PEC assessment report on dimethyl phthalate (DMP) (PEC No. 37; NICNAS 2014);

Assessments by international bodies:

- Concise International Chemical Assessment Document (CICAD) 17 on butyl benzyl phthalate (WHO 1999);
- Monographs on the evaluation of carcinogenic risks to humans, volume 73: *Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances* by the International Agency for Research on Cancer (IARC 1999);
- Monograph on the potential human reproductive and developmental effects of butyl benzyl phthalate by the National Toxicology Program—Center for the Evaluation of Risks to Human Reproduction (NTP–CERHR 2003);
- European Union Risk Assessment Report (EU RAR) on benzyl butyl phthalate by the European Chemicals Bureau (ECB 2007);
- Review of new available information for benzyl butyl phthalate by the European Chemicals Agency (ECHA 2010);
- Toxicity review of benzyl-n-butyl phthalate by the United States Consumer Product Safety Commission staff (US CPSC 2010).

Information from these documents was supplemented with new, relevant data identified from literature searches on PubMed, TOXNET®, ScienceDirect and SciFinder. The most recent searches were conducted in April 2015. For more details, refer to the **References** section of this report.

All citations, except those marked with an asterisk (*), were reviewed for the purposes of this assessment. Those citations marked with an asterisk were quoted from the key documents as secondary citations.

1.4 Peer review

The report has been subjected to internal peer review within NICNAS during all stages of preparation.

1.5 Applicants

Following the declaration of BBP as a PEC, the organisations applying for assessment of this chemical are listed below:

Brenntag Australia Pty Ltd
260–262 Highett Road
Highett VIC 3190

Ferro Corporation (Australia) Pty Ltd
21–23 South Link
Dandenong VIC 3175

NSW Environment Protection Authority
Level 14, 59–61 Goulburn Street
SYDNEY NSW 2000

Sigma Aldrich Pty Ltd
12 Anella Avenue
CASTLE HILL NSW 2154

Vinyl Council of Australia
65 Leakes Road
Laverton North VIC 3026

In accordance with the Act, NICNAS makes a draft report of the assessment available to the applicants for comment during the correction and variation stages of the PEC consultation process.

2 Background

2.1 International perspective

BBP is a member of the group of esters of phthalic acid commonly known as phthalates, used ubiquitously as solvents and plasticisers worldwide.

The Phthalate Esters Panel of the American Chemistry Council (ACC 2006 revised) derived three categories of phthalates based on use, physicochemical and toxicological properties. Low molecular weight (LMW) phthalates are defined as those produced from alcohols with carbon side-chain lengths of ≤C3. High molecular weight (HMW) phthalates are those produced from alcohols with straight or ring-structured carbon chain lengths of ≥C7. A similar definition of HMW phthalates is used by the Organisation for Economic Co-operation and Development (OECD 2004). Transitional phthalates were defined as those produced from alcohols with straight or branched carbon chain lengths of C4–6.

Structurally, BBP is an asymmetric diester, consisting of one linear and one ring-structured ester side chain. On the basis of the ester side-chain length (butyl C4 and benzyl C5), BBP belongs to the transitional C4–6 phthalate group.

The physicochemical properties of phthalates that impart usefulness as plasticisers also permit their migration and leaching from polymer matrices. Some phthalates such as DEHP and DINP can be present in high concentrations (up to approximately 40–50 % w/w) in polymer materials. The potential for leaching from plastics and the widespread use in a variety of consumer products including cosmetics, together with the reproductive toxicity profile of phthalates in general, have led to concerns over the potential health impacts of phthalates, including BBP. Particular concerns exist when there is the potential for exposure to phthalates of young children from use of toys and childcare articles, or for prolonged exposure of the general population through cosmetic use.

Historically, studies of the health effects of certain phthalates have identified reproductive toxicity, especially to the testes and testicular hormones, to be of particular concern. Accordingly, overseas jurisdictions have taken regulatory action on a number of phthalates, particularly transitional phthalates (DEHP, DBP and BBP), and HMW phthalates (DINP, DIDP (diisodecyl phthalate) and DnOP (di-n-octyl phthalate)), for particular uses.

In the EU, BBP is banned in all children's toys, childcare articles and in cosmetics, including nail polish, on the basis that BBP is classified as toxic for reproduction (i.e. Reprotoxic Substances Category 1B 'Evidence of effects in animals').

In particular, BBP is currently listed in the:

- European Commission (EC) Cosmetic Ingredients and Substances (CosIng) Annex II (List of substances prohibited in cosmetic products);
- Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Annex XIV (List of substances subject to authorisation, <http://echa.europa.eu/addressing-chemicals-of-concern/authorisation>); and
- Entry 51 in the REACH Annex XVII (List of restrictions on the manufacture, placing on the market and use of certain dangerous substances, preparations and articles, <http://echa.europa.eu/eu/addressing-chemicals-of-concern/restrictions/list-of-restrictions>): BBP (together with DEHP and DBP) 'shall not be used as substances or in mixtures, in concentrations greater than 0.1% by weight of the plasticised material, in toys and childcare articles. Toys and childcare articles containing these phthalates in a concentration greater than 0.1% by weight of the plasticised material shall not be placed on the market.'.

BBP is also listed on the Cosmetic Directive Annex II (List of substances which must not form part of the composition of cosmetic products) regulated by the Association of Southeast Asian Nations (ASEAN), as well as on China's list of banned substances for cosmetic uses (Galleria Chemica).

In the USA, the Congress has prohibited the use of BBP (together with DEHP and DBP) in any amount greater than 0.1 % in children's toys and childcare articles (*Consumer Product Safety Improvement Act 2008*, <http://www.cpsc.gov//PageFiles/113865/cpsia.pdf>).

A similar restriction on the three phthalates in children's toys and childcare articles has been issued by the Canadian Government (*Canada Gazette* 2010).

The chemical is also a candidate for further restrictions as it is listed in the:

- EC Endocrine Disruptors priority list with Category 1 classification (i.e. Evidence of endocrine disrupting activity in at least one species using intact animals; EC 2015).
- US Environmental Protection Agency's Phthalates Action Plan (US EPA 2012a revised), which is an initiative to address the manufacturing, processing, distribution in commerce, and/or use of eight phthalates, including BBP.
- US EPA's Universe of Chemicals list for potential endocrine disruptor screening and testing (US EPA, 2012b).

2.2 Australian perspective

In 1999, concern over the potential adverse health effects of phthalates, including reproductive and developmental toxicity, led to phthalates being nominated for inclusion in the NICNAS Candidate List (from which chemicals may be selected and recommended to the Minister for declaration as PECs).

As a result of literature searches and calls for information by NICNAS to industry in 2004 and 2006, one terephthalate and 24 ortho-phthalates, including BBP, were identified as currently or potentially in industrial use in Australia. The chemical BBP, together with eight other phthalates, was also identified to be in actual or potential use in cosmetics, children's toys and childcare articles in Australia.

In 2008, following industry and public comment, NICNAS released a series of hazard assessments on 25 phthalates (available at http://nicnas.gov.au/). NICNAS also released a phthalates compendium in which the uses and hazards associated with 24 ortho-phthalates were summarised and compared (NICNAS 2008b).

BBP is currently listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia) as:

- a Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child'; and
- a Reproductive Toxicant Category 3 with the risk phrase R62 'Possible risk of impaired fertility'.
- cut-offs: concentration ≥5 %: Toxic; R61; R62
  ≥0.5 % concentration <5 %: Toxic; R61.

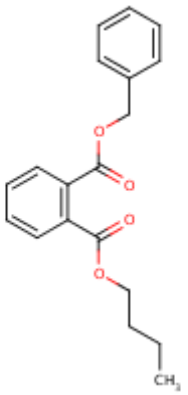
BBP is not listed in the current Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, <http://www.comlaw.gov.au/Details/F2015L00128>).

At the time of this PEC assessment, no other restrictions on the introduction (manufacture and/or import) or use of this chemical were identified in Australia. The chemical BBP could, however, be potentially substituted for already regulated phthalates (e.g. DEHP and DBP), and hence there is potential for widespread use of BBP in a variety of consumer products, including children's toys, childcare articles and cosmetics (see **Section** 4.3).

3 Identity and properties

BBP is listed on the Australian Inventory of Chemical Substances (AICS).

3.1 Chemical identity

Chemical name:	1,2-benzenedicarboxylic acid, butyl phenylmethyl ester
CAS No.:	85-68-7
Synonyms:	BBP butyl benzyl phthalate benzyl butyl phthalate benzyl n-butyl phthalate phthalic acid, benzyl butyl ester 1,2-benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester
Molecular formula:	$C_{19}H_{20}O_4$
Molecular weight (MW):	312.36
Purity:	>98.5 %
Impurities:	<1.0 % dibenzyl phthalate (CAS No. 523-31-9), <0.5 % benzyl benzoate (CAS No. 120-51-4), <0.5 % dibutyl phthalate (CAS No. 84-74-2), <2 ppm α-clorotoluene (CAS No. 100-44-7), <2 ppm α,α-diclorotoluene (CAS No. 98-87-3)
Additives:	<0.5 ppm pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydoxyphenyl) propionate) (CAS No. 6683-19-8)
Structural formula:	

3.2 Physical and chemical properties

Table 3.1: Summary of physicochemical properties (adopted from ChemID*plus*, ECB 2007)

Properties	Value
Physical state	Colourless oily liquid
Boiling point	370 ºC
Melting point	<-35 ºC
Density, kg/m^3 (25 ºC)	1116
Vapour pressure, kPa (25 ºC)	1.10×10^{-6}
Water solubility, g/L (25 ºC)	2.69×10^{-3}
Partition co-efficient octanol/water (log K_{ow})	4.73–4.84
Henry's Law constant, kPa m^3/mol (25 ºC)	1.28×10^{-4}
Flash point	198 ºC

Conversion factors are based on 25 ºC and 1 atmosphere:

BBP (MW 312.36)
1 ppm = 12.78 mg/m^3
1 mg/m^3 = 0.08 ppm

4 Manufacture, importation and use

4.1 Manufacture and importation

BBP is introduced into Australia through importation both in finished products and in mixtures for local formulation and processing. There are no data from NICNAS calls for information that indicate the chemical is manufactured in Australia.

In addition, there is no current information available on the volume of BBP imported for industrial uses.

4.2 Uses of BBP

4.2.1 Uses in Australia

The following Australian industrial uses of BBP were reported under NICNAS mandatory and/or voluntary calls for information (including recent correspondence with the applicants):

- The main use of BBP is in industrial applications such as for manufacturing adhesives (parquetry floors, automotive filters), construction sealants, automotive and marine coatings, road-marking paints and textile printing inks (mostly for T-shirts). It serves as a specialty plasticiser in PVC compounds, vinyl and acrylic lacquers, nitrocellulose lacquers and polyurethane wheels for forklifts. BBP is also used in military-specified topcoats for metal substrates.
- BBP is used as a plasticiser in imported PVC consumer products, including gumboots, toys, play and exercise balls.
- Small quantities of BBP are used for research and analytical purposes.

No cosmetic uses were reported.

In children's toys and childcare articles made from PVC, BBP is unlikely to be found as a dominant (primary) phthalate plasticiser, as its molecular weight is similar to that of DBP, a commonly used secondary plasticiser. Therefore, the chemical might be used as a secondary plasticiser in conjunction with another plasticiser, or occur as a minor contaminant of other phthalates, including DEHP or DINP (see **Section** 4.3). Specific concentrations of BBP in toys used in Australia are not available, and the types of non-PVC articles used as toys (play and exercise balls) in which BBP is reported to be used are not typical mouthing articles.

Given that no data on BBP levels in children's toys found in Australia were provided for the assessment, modelling and overseas data are used to estimate exposure.

4.2.2 Uses overseas

Worldwide annual production and/or import volumes of BBP were 1000–10000 tonnes in the EU (REACH Dossier) and 90000–180000 tonnes in the USA (US EPA Chemical Data Reporting 2012). No further information on the specific volumes of BBP for either industrial or consumer applications is publicly available.

Currently, the chemical is listed in the *Chemical Book* (<http://www.chemicalbook.com>), and offered for sale by 116 suppliers globally, including 61 companies in China, 32 in the US, and nine in Europe. According to VinylPlus (2014), the use of BBP was expected to be phased out in the EU by 21 February 2015 since ECHA received no applications for the REACH authorisation.

The following uses or functions of BBP have been identified in:

- the Personal Care Products Council's International Nomenclature Cosmetic Ingredient (INCI) dictionary: nail polish and enamels;
- the US National Library of Medicine's Household Products database: arts and crafts, auto products, home maintenance products, landscape and yard pastes;
- the REACH BBP Dossier: for manufacturing and formulating substances and preparations; in industrial, professional and consumer coatings for vehicles, electrical batteries, fabrics, textiles, rubber and plastic articles; as well as uses in toys and food packaging; and
- the US National Library of Medicine's Haz-Map Database: as an organic intermediate and a plasticiser for PVC-based flooring products (vinyl floor tiles, vinyl foams and carpet backing), polyvinyl acetate emulsion adhesives, and polyvinyl and cellulose resins.

Although listed in the INCI database, BBP is prohibited for use in cosmetics, including nail polishes, in the EU (CosIng), China and ASEAN countries (see **Section 2.1**). A review of statements/data from the cosmetics industry and Food and Drug Administration (US) by the US Cosmetic Ingredient Review (CIR) Expert Panel indicated that BBP is not currently being used in cosmetic products (Andersen 2011). Consistently, BBP is not found in the Personal Care Products Council's Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS 2011).

- INCI provides a comprehensive international reference of descriptive and technical information about substances that have been identified as potential cosmetic ingredients;
- CosIng is a database of chemicals either known to be in use in cosmetics in the EU or subject to restrictions including prohibition for such use; and
- CIUCUS is the compilations of ingredients that have documented use in cosmetics in the US.

There is no current information available on BBP use in cosmetics overseas.

4.3 Uses of phthalates and possibilities for substitution

Phthalates can be substituted for each other in certain applications. However, given the existing range of phthalate chemicals, there are likely to be limits to substitutability for any particular application. Information on use-patterns of phthalates generally indicates that lower molecular weight phthalates are used as solvents, whilst higher molecular weight phthalates are used as plasticisers (NICNAS 2008b).

The physicochemical factors expected to affect the choice of a specific phthalate for a particular use include viscosity, water solubility and vapour pressure/boiling point. These properties alter with increasing molecular weight and side chain length. As the side-chain length increases (1–13 carbons), phthalates exhibit a number of orders of magnitude increase in the octanol–water partition coefficient (K_{ow}) and a 10-order of magnitude decrease in vapour pressure. Water solubility is also inversely related to molecular weight and side-chain length (NICNAS 2008b). Viscosity varies from 9 mPa·s for DEP, 15 mPa·s for DBP, 52 mPa·s for DINP and up to 190 mPa·s for ditridecyl phthalate (Eastman 2006).

Thus, a HMW phthalate ester (e.g. DINP) will be quite different from a LMW phthalate ester such as DBP. However, the difference in properties between two phthalates of similar molecular weight, such as BBP and DBP, is expected to be much less. To the extent that these are the key considerations, substituting a particular phthalate for another phthalate of similar molecular weight for any given application—for example, substituting BBP for DBP as a cosmetic ingredient—is more probable than substituting a phthalate of a very different molecular weight, such as DINP.

Minimal information is available in the published literature about the substitutability of phthalates. A number of phthalates and their functions are listed in the INCI database, e.g. DMP, DEP, DBP and DEHP, all of which have listed functions as fragrance ingredients, plasticisers and solvents. However, the Scientific Committee on Consumer Products (SCCP) opinion on phthalates in cosmetic products concluded that among the phthalates found in a study of 36 perfumes (Greenpeace International 2005), only DMP (0.3 %) and DEP (up to 2.23 %) are likely to have been deliberately added, while DBP and DEHP are likely to be present as traces and/or impurities leaching from plastic materials used during production or storage (SCCP 2007). This information relates to phthalate use in perfume samples and there is no information available that allows extrapolating from perfumes to other cosmetics.

Among the phthalate plasticisers, DINP is largely used in PVC and PVC/polyvinyl acetate co-polymers due to its high binding affinity, good solvation and the ability to maintain low temperature flexibility. DBP is 'not convenient' as the primary plasticiser for PVC due to its high volatility (although it can be used as a secondary plasticiser) and is normally used for cellulose nitrate (Chanda & Roy 2006).

Therefore, while it is clear that phthalates with similar properties can be substitutable, there are likely to be limits on the extent to which dissimilar phthalates can be used. The chemicals BBP and DBP (which share the same monoester metabolite monobutyl phthalate (MBP)) have a similar molecular weight and structure, and thus BBP is likely to substitute for DBP in any of its applications, but is not likely to substitute for DINP, which is a HMW phthalate commonly used in PVC toys and childcare articles.

Given the lack of data on the use of BBP in children's toys, assumptions need to be made for modelling exposures. In this report, for example, migration or leaching rates reported for DINP are used to undertake an exposure assessment for BBP as a secondary plasticiser in a mixed phthalate plasticiser (DINP+BBP) in relation to uses in children's toys and childcare articles.

5 Public exposure

Although BBP was declared a PEC for assessment of its use in children's toys, childcare articles and cosmetics, there is no evidence to suggest that BBP is currently used in cosmetic products in Australia or overseas (see **Sections** 2.1 and 4.2). However, there is a potential for BBP to be used in cosmetics as a substitute for other phthalates (such as DBP, an already regulated phthalate) that have similar physical and toxicological properties. It is less likely that phthalates that have a carcinogenic, mutagenic, or toxic for reproduction (CMR) hazard classification would be substituted for safer or less potent phthalates such as DEP—a common cosmetic ingredient.

Thus, cosmetic use of BBP is likely to be rare to non-existent. Consequently, assessment of public exposure to BBP from use of cosmetics is not considered in this assessment. It should be emphasised that cosmetic use, were it to occur, may give rise to a significant risk and the restrictions proposed in this report are intended to address this issue.

This report will consider public exposure to BBP only for its use in children's toys and childcare articles. Exposure estimates are derived to allow characterisation of the risks associated with this application of BBP.

5.1 Methodology for assessing exposure

It is acknowledged that there are always uncertainties in deriving exposure estimates. The use of measured data is always preferred; however, modelled data may be used if measured data are not available. Australian data are also preferred. However, if Australian data are not available, overseas data may be used, provided that the scenarios represented by the overseas data are equivalent to Australian exposure scenarios. The uncertainties in the exposure assessment are further discussed in the context of risk characterisation (see **Section** 7).

In this assessment of specific exposure pathways, the 'reasonable worst-case' approach is used, in which estimates are based on worst-case, but plausible, exposure scenarios to consider exposures of all individuals within the target population. In addition, a 'typical' exposure estimate is performed, if information is available to determine a use-pattern that represents an average for the target population.

Children's exposure to BBP from toys and childcare articles was estimated for both oral and dermal routes. Dermal exposure may occur during normal handling and oral exposure through chewing, sucking and biting of these products, regardless of whether the products are intended to be mouthed. Inhalational exposure to BBP from these products is considered negligible due to its low vapour pressure.

Information on the BBP content in toys is insufficient; therefore, the exposure estimate is based on the usage and concentration of an alternative phthalate, DBP, which has a similar molecular weight, higher vapour pressure and lower viscosity than the phthalates typically used in PVC. The chemical DBP is reported to have uses in children's toys and childcare articles in Australia. These estimates are considered valid for BBP because of the possibilities for phthalate substitution as discussed in **Section** 4.3.

Oral exposure was modelled by:

- estimating the highest plausible concentration of BBP as a component of a mixed plasticiser in children's toys and childcare articles in Australia;
- estimating children's mouthing time of toys and childcare articles based on overseas data that are not expected to be markedly different from Australian children's mouthing activities and behaviours;
- estimating the migration rate of the mixed plasticiser from a PVC matrix into saliva based on experimental studies on the extractability of phthalate plasticisers under various mouthing conditions;
- estimating the oral bioavailability of BBP (see **Section** 6.1); and
- using default values for children's body weight and exposed surface area.

Dermal exposure was modelled by:

- estimating the highest plausible concentration of BBP as a component of a mixed plasticiser in children's toys and childcare articles in Australia;
- estimating children's dermal contact time with toys and childcare articles;
- estimating the migration rate of the mixed plasticiser from a PVC matrix through the skin, based on experimental studies; and

- using default values for children's body weight and exposed surface area.

5.2 Exposure estimates for children from use of toys and childcare articles

The calculation of exposures to BBP is based on the assumption that the chemical completely substitutes for DBP (known to be used as a secondary plasticiser) in a mixed phthalate plasticiser at a maximum concentration of 0.5 % w/w. This concentration was determined based on a literature review of analytical studies of toys, as well as the reported maximum DBP level of 0.45 % in children's toys by the Australian industry. The PEC assessment of DBP has a detailed calculation for this scenario, explaining the derivation of all relevant parameters (NICNAS 2013).

5.2.1 Oral exposure

The daily internal oral doses for the reasonable typical and worst-case scenarios for total phthalate content (i.e. a mixed phthalate plasticiser of DINP+BBP) and for BBP alone are calculated using Equation 1 and shown in Table 5.1, based on the following assumptions:

- The exposure estimates are made for a six-month-old infant who has the lowest body weight among the group; that demonstrates the maximum mouthing behaviour with a reasonable typical and worst-case mouthing time of 0.8 hours/day and 2.2 hours/day, respectively (for a review of children's mouthing time studies, refer to the PEC assessment of DINP, NICNAS 2012).
- Based on the weight of evidence, the mean and highest in vivo migration rates of DINP from chewing and/or mouthing of toys and articles determined by Chen (1998) are regarded as applicable for the typical and worse-case exposure estimates for BBP, i.e. 26.03 and 57.93 µg/cm2/hour, respectively.
- The extractability data for DINP (measured at 43 % w/w of the articles by Chen (1998)) are also applicable for a mixed phthalate plasticiser comprising 0.5 % BBP and 42.5 % DINP, i.e. 43 % of a mixed phthalate consisting of 1.16 % BBP and 98.84 % DINP. It is assumed that this mixed phthalate is extracted under mouthing conditions without a change in composition. In addition, the phthalate migration rate from articles appears largely determined by the magnitude of the mechanical force applied to an article and the properties of the PVC grade comprising the article, and less affected by the physicochemical characteristics or concentration of a particular phthalate (NICNAS 2012).
- The child's mean body weight is 7.5 kg based on the 50th percentile value for males and females combined.
- The surface area of a child's open mouth or the surface of an article available for mouthing at any one time is approximately 10 cm^2.
- Phthalate bioavailability from oral exposure is 100 % (**Section** 6.1).

Equation 1 $$D_{int,oral} = \frac{M \times S_{mouth} \times t \times n \times B_{oral}}{BW}$$

Where:

$D_{int,oral}$ = Internal dose by the oral route, µg/kg bw/d
M = Migration rate of the phthalate from toys, µg/cm^2/hr
S_{mouth} = Surface area of a child's open mouth, cm^2
t = Mouthing time, hours
n = Frequency per day
B_{oral} = Bioavailability by the oral route, % (expressed as a decimal)
BW = Body weight, kg

Table 5.1: Estimated daily internal doses for total phthalate content and BBP from oral exposure to toys and childcare articles in children

	Total phthalate $D_{int,oral}$ **(µg/kg bw/d)**	**BBP[a]** $D_{int,oral}$ **(µg/kg bw/d)**
Typical exposure scenario	27.77	0.32

Worst-case exposure scenario	169.93	1.97

[a] Estimates for BBP are derived by multiplying the internal doses for total phthalate by the proportion of BBP (1.16 %) in the mixed phthalate.

5.2.2 Dermal exposure

The daily internal dermal doses for the typical and worst-case scenarios for total phthalate content (i.e. a mixed phthalate plasticiser of DINP+BBP) and for BBP alone are calculated using Equation 2 and shown in Table 5.2, based on the following assumptions:

- The exposure estimates are made for a six-month-old infant who has the highest surface of exposure to body weight ratio, and therefore the combined dermal and oral exposure is expected to be highest for this age group.
- A reasonable typical time the child spends handling toys is 0.8 hours/day and a reasonable worst-case contact time is 2.2 hours/day.
- Based on the weight of evidence, the mean dermal absorption rate of 0.24 μg/cm^2/hour, determined by Deisinger et al. (1998) for DEHP migrating from sheets of PVC film through the rat skin, is regarded as applicable for the mixed plasticiser (DINP+BBP) given the lack of available migration rate data from plasticised PVC or quantitative dermal absorption data for DINP or mixed phthalate plasticisers (for a review of dermal absorption studies, see the PEC assessment of DINP (NICNAS 2012)).
- The *in vivo* dermal absorption rate data for DEHP (measured at 40.4 % w/w of the articles by Deisinger et al. (1998)) are also applicable for a mixed phthalate plasticiser comprising 0.5 % BBP and 39.9 % DINP, i.e. 40.4 % of a mixed phthalate consisting of 1.24 % BBP and 98.76 % DINP. It is assumed that this mixed phthalate migrates from the toys and is absorbed through the skin without a change in composition.
- The child's mean body weight is 7.5 kg based on the 50th percentile value for males and females combined.
- The body parts of a child likely to be exposed while handling toys and childcare articles are the hands and lips, the surface area of which is approximately 100 cm^2.

Equation 2

$$D_{int,dermal} = \frac{R \times S_{dermal} \times t \times n}{BW}$$

Where:

$D_{int,dermal}$ = Internal dose by the dermal route, μg/kg bw/day
R = Dermal absorption rate of the phthalate from toys, μg/cm^2/hour
S_{dermal} = Surface area of a child's hands and lips, cm^2
t = Time of dermal contact, hours
n = Frequency per day
BW = Body weight, kg

Table 5.2: Estimated daily internal doses for total phthalate content and BBP from dermal exposure to toys and childcare articles in children

	Total phthalate $D_{int,dermal}$ **(μg/kg bw/d)**	**BBP[a]** $D_{int,dermal}$ **(μg/kg bw/d)**
Typical exposure scenario	2.56	0.03
Worst-case exposure scenario	7.04	0.09

[a] Estimates for BBP are derived by multiplying the internal doses for total phthalate by the proportion of BBP (1.24 %) in the mixed phthalate.

The combined exposures arising from both oral and dermal contact with children's toys and childcare articles are presented in Table 5.3.

Table 5.3: Estimated total daily internal doses for children

Route of exposure	Typical $D_{int, oral+dermal}$ (µg/kg bw/d)	Worst-case $D_{int, oral+dermal}$ (µg/kg bw/d)
Oral	0.32	1.97
Dermal	0.03	0.09
Combined	0.35	2.06

5.3 Human biomonitoring data

Human biomonitoring (HBM) data for a particular chemical or its metabolites represent exposure to the chemical from all sources and pathways. Population estimates of specific phthalate levels may differ by age, gender, and race/ethnicity (Silva et al. 2004; CDC 2015). The analytical approaches, uncertainty and variability associated with HBM limit their use in exposure and human health risk assessment (Albertini et al. 2006). It is not possible to identify the relative contribution of different exposure sources or routes directly from HBM data. Furthermore, HBM data for BBP exposures in the Australian general population or specific subpopulations are not available. For the purpose of this assessment, modelling is the most suitable approach to estimating BBP exposures. The assumptions made in the scenarios used to calculate exposures to DBP (NICNAS 2013) are also considered reasonable and applicable to BBP, on the basis that the related phthalate DBP is assumed to sometimes be used at a maximum concentration of 0.5 % in children's toys in a mixed phthalate plasticiser with DINP.

However, HBM data can be useful in determining whether the exposures calculated from modelling are within the observed range of exposure and comparable with the integrated exposure of the population. Table 5.4 summarises representative international HBM investigations in recent years, which provide exposure estimates for BBP (vs DBP), as determined from their urinary metabolite concentrations, MBzP and MBP, respectively.

Generally, the biomonitoring levels of MBzP are lower than those of MBP, possibly because of the lesser likelihood of BBP being present in various products compared with DBP, as well as MBP being a common metabolite of both BBP and DBP. Children had higher urinary levels of MBzP and MBP than mothers or total females (see **Table 5.4**). Based on the analysis of the National Health and Nutrition Examination Survey (NHANES) 2001–2002 through 2009–2010 (a large, nationally representative sample of the US population), Zota et al. (2014) noted pronounced temporal trends in phthalate exposure. Urinary metabolite concentrations of DEHP, DBP and BBP declined approximately 20–50 %, whereas urinary metabolite concentrations of diisobutyl phthalate (DiBP) and DINP increased by more than 100 %, which provides an evidence for the occurrence of substitutions between phthalates.

There are a number of studies that use HBM data to estimate daily BBP (vs DBP) intakes for mothers and children, expressed in an ascending order of medians followed by 95th percentile or P95 values. They include, but are not limited to:

- BBP 0.23–1.30 µg/kg bw/day vs DBP 1.82–5.86 µg/kg bw/day (465 German children aged 8–10 years; Kasper-Sonnenberg et al. 2014);
- BBP 0.42–1.73 µg/kg bw/day vs DBP 2.38–7.25 µg/kg bw/day (52 Belgian children aged 1–12 years; Dewalque et al. 2014);
- BBP 0.42–2.57 µg/kg bw/day vs DBP 4.07–14.9 µg/kg bw/day (creatinine-based), and BBP 0.77–4.48 µg/kg bw/day vs DBP 7.61–30.50 µg/kg bw/day (volume-based model) (239 children aged 2–14 years; Koch et al. 2007; Wittassek et al. 2011);
- BBP 0.50–2.47 µg/kg bw/day vs DBP 0.84–2.33 µg/kg bw/day (214 mothers of male infants exhibiting reduced anogenital distance (AGD); Marsee et al. 2006);
- BBP 0.70–3.40 µg/kg bw/day vs DBP 0.90–3.50 µg/kg bw/day (742 US children aged 6–11 years from NHANES 2005–2008; Christensen et al. 2014).

Overall, there is close agreement between the calculated exposures from use of BBP in children's toys and childcare articles through modelling (Table 5.3) and the BBP intake estimates from HBM data. This substantiates that the assumptions made in the scenarios used to calculate the exposures are reasonable and applicable to BBP, despite variations in children's ages and sources of exposure. The biomonitoring results are

considered consistent with the basis of the exposure modelling for BBP, as they indicate that the general exposure of children (corresponding to means and medians) can be several times lower than the highest individual exposures, which can arise from specifically high exposure scenarios (corresponding to P95 values). The modelled worst-case exposure scenario considered in this assessment is thus applicable to highly exposed individuals among the population of children.

Table 5.4: Biomonitoring data for urinary MBzP vs MBP metabolites (µg/g creatinine for adjusted values, otherwise specified as unadjusted, µg/L urine)

Study	Population (sample size, age)	Mean		Median		95th Percentile	
		MBzP	MBP	MBzP	MBP	MBzP	MBP
Kasper-Sonnenberg et al. 2012	Germany Duisburg 2006–08 /Mothers (103, 29–49 years)	6.60[a]	32.80[a]	6.30[a]	30.90[a]	24.50[a]	139.00[a]
	Germany Duisburg 2006–08 /Children (104, 6–8 years)	12.50[a]	48.10[a]	11.70[a]	54.20[a]	62.90[a]	148.00[a]
Saravanabhavan et al. 2013	Canada /Females CHMS 2007–09 (1604, 6–49 years)	14.20	30.70	13.10	27.70	75.20	127.90
	Canada /Children CHMS 2007–09 (1034, 6–11 years)	32.40	50.80	31.60	45.90	147.30	213.40
Larsson et al. 2014	Sweden /Mothers (95, <45 years)	12.07	59.36	10.83	58.49	74.16	161.19
	Sweden /Children (97, 6–11 years)	22.49	86.83	22.37	83.24	96.58	236.58
Den Hond et al. 2015	European values 2011–12 /Mothers (1800, 24–52 years)	4.50	23.90	NR	NR	17.70[b]	66.20[b]
	European values 2011–12 /Children (1816, 5–11 years)	7.10	34.80	NR	NR	27.80[b]	95.50[b]
CDC 2015 updated tables	US NHANES 2007–08 /Females (1310, ≥6 years)	8.07	23.10	8.37	22.80	48.30	89.80
	US NHANES 2007–08 /Children (389, 6–11 years)	19.00	33.10	20.70	34.20	118.00	109.00
	US NHANES 2009–10 /Females (1350, ≥6 years)	7.29	17.80	6.90	17.60	38.80	70.60
	US NHANES 2009–10 /Children (415, 6–11 years)	15.10	28.30	14.60	26.70	92.20	130.00
	US NHANES 2011–12 /Females (1229, ≥6 years)	5.87	9.81	5.65	10.30	28.70	44.80
	US NHANES 2011–12 /Children (395, 6–11 years)	12.50	15.90	11.90	17.70	81.00	73.30

a = unadjusted values; b = 90th percentile or P90 values; CHMS = Canadian Health Measures Survey; NHANES = National Health and Nutrition Examination Survey; NR = not reported.

6 Human health hazard characterisation

This section provides a brief overview of the main features of the toxicological data, identifies the critical toxicity endpoints and the NOAELs, and discusses the relevance to humans of the effects observed in animal studies. The hazard characterisation of BBP is based on the collective results of all available studies through analysing the weight of evidence and deducing conclusions drawn from previous national and international reviews.

Given that there is limited information available from human studies on the potential health effects associated with exposure to BBP, the hazard profile is based principally on animal data. In addition, for those toxicological endpoints where the data are incomplete or unavailable, information from structurally similar chemicals was used to examine the potential toxicity. The assessment information was obtained from NICNAS assessment reports, international reviews and journal articles on BBP, and relevant analogue chemicals, published up to April 2015. References marked with an asterisk (*) were not reviewed, but were quoted as secondary citations from the key documents listed in **Section** 1.3 of this report.

The NICNAS *Phthalates hazard compendium* (NICNAS 2008b) contains a comparative analysis of toxicity endpoints across 24 ortho-phthalates, including BBP. Structurally, BBP is an asymmetrical diester, consisting of a benzyl ring and a butyl group on side chains. The chemical BBP belongs to the transitional C4–6 phthalate group and shares a monoester metabolite, monobutyl phthalate (MBP), with DBP—a known potent antiandrogenic phthalate (NICNAS 2013).

6.1 Toxicokinetics

6.1.1 Absorption

Absorption from oral exposure

Orally administered BBP is readily absorbed and hydrolysed both in the gastrointestinal (GI) tract and the liver, based on excretion data in animal and human studies (Anderson et al. 2001; Eigenberg et al. 1986; Nativelle et al. 1999; WHO 1999).

The absorption can become saturated and limited at high doses or after repeated dosing. In rats, total urinary recovery of the chemical decreased from 56 % at 150 mg/kg bw/day to 30 % at 1500 mg/kg bw/day after three consecutive doses (Nativelle et al. 1999). Twenty-four hours after single doses, faecal excretion increased with the increasing dose, from 13–19 % at 2–200 mg/kg to 57 % at 2000 mg/kg (with concomitant decreases in urinary excretion from 61–74 % to 16 %) (Eigenberg et al. 1986). In beagle dogs dosed at 5000 mg/kg, the absorption was only up to 10 % based on the recovery of unchanged BBP in the faeces of 88–91 % and in the urine of 4 %; this could be also attributable to pharmacokinetic differences between species (ECB 2007; Erickson 1965*; NTP-CERHR 2003). In human volunteers, the urinary monoester metabolites of BBP represented 67–84 % (on a molar basis) of the administered doses of 0.253–0.506 mg/kg bw/day (Anderson et al. 2001).

The chemical BBP is also excreted in the bile (as monoesters) and undergoes enterohepatic recirculation, which could result in extended bioavailability (Eigenberg et al. 1986). No information on the total excretion via all routes and/or the extent of faecal excretion (whether as the result of biliary elimination or incomplete absorption) is available. In addition, there is limited information available comparing the oral absorption and bioavailability of BBP between adult and immature animals, or between animals and humans. The oral bioavailability of the most studied phthalate, DEHP, appears to be higher in young rats compared with adult rats (Sjoberg et al. 1986). The higher proportion of intestinal tissue in relation to body weight (Younoszai & Ranshaw 1973) and the relatively higher blood flow through the GI tract (Varga & Csáky 1976*) have been suggested as the likely factors causing an increased absorption in young animals. For the purposes of this assessment, the bioavailability of BBP via the oral route is assumed to be 100 % for both adults and children.

Absorption from dermal exposure

BBP is considered to be slowly absorbed through the skin, given that the excretion following a single occlusive application to male rat skin was relatively constant over seven days at 3–6 % of the applied dose (30–40 mg/kg over 5–8 mg/cm^2) (Elsisi et al. 1989). Although BBP—probably due to its higher molecular weight—was less absorbed than DBP, it had a higher cumulative tissue concentration of ~5 % (cf. 3 % for DBP) of the applied dose (Elsisi et al. 1989).

Considering this limited information, the EBC (2007) worst-case estimate of 5 % is used for the dermal bioavailability of BBP in humans.

Absorption from inhalational exposure

Quantitative information on inhalational absorption of BBP is not available. Inhaled phthalate esters will not be subject to first-pass metabolism in the liver and so a significant inhaled proportion is likely to be available systemically. On this basis, a default bioavailability of 100 % is considered appropriate for this route of exposure.

6.1.2 Distribution

When a single dose of ^{14}C-BBP was applied to the skin of male rats, very little radioactivity was detected in the tissues seven days after exposure. The observed distribution of radioactivity ranged from 4.6 % in muscle, 0.17 % in adipose tissue, and down to <0.5 % being the summation of dose found in the brain, lung, liver, spleen, small intestine, kidney, testis, spinal cord and blood (Elsisi et al. 1989). In humans, BBP metabolites were found in foetal serum, breast milk and semen (Lashley et al. 2004; Main et al. 2006; Rozati et al. 2002).

Based on review of the literature and comparative studies on phthalate kinetics (ECB 2007; Eigenberg et al. 1986; Elsisi et al. 1989; Kluwe 1982; NICNAS 2008b) and findings from the previous NICNAS PEC assessments for DMP (LMW), DBP and DEHP (transitional) and DINP (HMW phthalate) (see **Section** 1.3), phthalates in general or BBP in particular are assumed to be distributed widely into the tissues, including the placenta, after exposure. The metabolites have short half-lives and there is no evidence of accumulation.

6.1.3 Metabolism

Following oral exposure, BBP is rapidly metabolised by intestinal and hepatic esterases to monoesters (monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP)), which are absorbed, further metabolised and glucuronidated for excretion (ECB 2007; IARC 1999; NTP-CERHR 2003; WHO 1999).

In rat studies, urinary ^{14}C was found as 10–42 % monoesters and 2–21 % monoester-glucuronide conjugates at a dose of 2–2000 mg/kg. The ratio of monoesters MBP:MBzP was 3:1 (44 % vs 16 % after single doses or 34 % vs 12 % after three consecutive doses) (Eigenberg et al. 1986; Nataville et al. 1999). Hippuric acid (the main metabolite of benzoic acid) was another major metabolite of BBP, while phthalic acid, benzoic acid and a ω-oxidised metabolite of MBP were recovered in small quantities (Nataville et al. 1999).

In contrast, MBzP was the predominant metabolite of the ingested BBP in humans with an excretion fraction of 67–78 %, compared with MBP at only 6%, on a molar basis. Therefore, MBzP was suggested to be used as a biomarker for measuring human exposure to BBP (Anderson et al. 2001).

Consistently, Takahara et al (2014) has recently demonstrated the *in vitro* hydrolysis pattern of BBP in mammalian liver microsomes that MBzP>MBP for humans and dogs, and MBP>MBzP for monkeys, rats and mice.

6.1.4 Elimination and excretion

Elimination of intact BBP and its metabolites after oral exposure is rapid and almost complete (84–93 % in 24 hours), based on excretion data in animal and human studies (Anderson et al. 2001; Eigenberg et al. 1986; Nativelle et al. 1999; WHO 1999). In rats, low doses are excreted mainly in the urine while at high doses the chemical is also excreted in faeces. Monoester metabolites may be excreted in the bile, reabsorbed and ultimately eliminated in the urine (Eigenberg et al. 1986).

The rate of excretion after dermal exposure was much slower, possibly due to the rate-limiting nature of dermal absorption. Urine was the major route of excretion (Elsisi et al. 1989).

6.2 Acute toxicity

6.2.1 Acute oral and dermal toxicity

The available animal data indicate that BBP has low acute oral and dermal toxicity with median lethal doses as follows:

LD50 oral >2000 mg/kg bw in rats, mice, and guinea pigs.
LD50 dermal >2000 mg/kg bw in rats, mice, and rabbits.

Target organs include the haematological and central nervous systems (refer to ChemID*plus*, NICNAS 2008a; REACH; WHO 1999 for review).

6.2.2 Acute inhalational toxicity

The available animal data provide inadequate evidence concerning the acute inhalational toxicity of BBP.

Four male rats survived after being exposed for six hours to a saturated atmosphere of BBP vapour (doses not specified) with three-day observation (REACH).

6.3 Irritation and sensitisation

6.3.1 Skin irritation

The available data suggest that BBP causes minimal skin irritation in rabbits and humans.

A 24-hour application of undiluted BBP showed no irritant effects on intact or abraded skin of six albino rabbits. It was not irritating in 200 human volunteers in a repeated-dose patch test (refer to ECB 2007; NICNAS 2008a; REACH for study details).

6.3.2 Eye irritation

The available data suggest that BBP causes minimal eye irritation in rabbits.

A 24-hour application of undiluted BBP showed a slight irritant effect to the eyes of six albino rabbits, but this subsided within 48 hours (refer to ECB 2007; NICNAS 2008a; REACH for study details).

6.3.3 Sensitisation

The available data suggest that BBP is not likely to be a skin sensitiser in humans.

The chemical BBP had a slight skin sensitising effect in an old study in rabbits. It was negative in various tests for sensitising potential in mice and guinea pigs, including a reliable guinea pig maximisation test (GPMT) registered under REACH. Antibody formation tests in mice showed equivocal results for BBP. When assayed with bovine serum albumin, BBP did not form the hapten-protein complexes necessary for inducing immune hypersensitivity. No sensitisation was reported with BBP in two human patch tests (refer to ECB 2007; NICNAS 2008a for study details).

Epidemiological studies were inconclusive for skin or respiratory sensitising effects of BBP. For associations between indoor dust concentrations of BBP and allergic symptoms, BBP was found associated with rhinitis and eczema (but not with asthma) in a Swedish nested case-control study; however, this was not replicated in Bulgarian children (Bornehag et al. 2004; Kolarik et al. 2008; US CPSC 2010). The differences between median concentrations of BBP in dust among cases of allergic children and healthy controls in the Bornehag study were considered small (0.15 vs 0.12 mg/g dust, measured from 175 vs 177 cases, respectively) (ECB 2007). There were reports of significantly higher BBP indoor intakes among sensitised children with atopic dermatitis or asthma than the non-sensitised ones, although a direct association between BBP exposure and the case subjects was inconclusive (Beko et al. 2015; Hsu et al. 2012).

In one study, the child's risk of asthma was associated with urinary concentrations of a BBP metabolite (MBzP) in mothers (300 pregnant Columbian women; Whyatt et al. 2014). In other studies, the asthma risk was not associated with urinary MBzP concentrations in children (623 Norwegian children aged 10 years or 440 Danish children aged 3–5 years; Bertelsen et al. 2013; Callesen et al. 2014). Among the National Health and Nutrition Examination Survey (NHANES) 2005–2006 participants, MBzP was not found to be correlated with asthma in children of 6–17 years (n = 779), although it was positively associated with allergic symptoms in adults (n = 1596) (Hoppin et al. 2013). Results for an association between prenatal exposure to MBzP and the risk of developing eczema in early childhood were also inconsistent (Just et al. 2012; Gascon et al. 2015). Gascon et al. (2015) observed a moderate increased risk of wheeze and asthma in children from birth to seven years of age per doubling of exposure (measured as maternal urinary MBzP during the first and third trimesters of pregnancy), whilst Beko et al. (2015) reported no significant associations between MBzP in urine and allergic sensitisation, in a cohort of 3–5 years old Danish children (200 cases with asthma, rhinoconjunctivitis or atopic dermatitis vs 300 healthy controls).

6.4 Repeated dose toxicity

The repeated dose toxicity of BBP in laboratory animals has been well investigated. Key studies identified by international reviews are briefly summarised below (refer to ECB 2007; NICNAS 2008a; NTP-CERHR 2003; WHO 1999 for review).

6.4.1 Repeated dose oral and dermal toxicity

Key oral studies were primarily in rats and used dose ranges suitable for characterising dose-response effects of BBP. The reported effects in mice and dogs consisted of decreases in body weight observed at relatively higher doses than the effects in the rat (ECB 2007; WHO 1999).

In short-term studies, dietary treatment of male Fischer 344 (F344) rats with BBP for 14 days significantly increased relative liver and kidney weights at ≥312 mg/kg bw/day (the lowest dose tested), while total body, thymus, testis, epididymis, prostate and seminal vesicle weights were reduced at 1250–2500 mg/kg bw/day. Histological evaluation showed dose-dependent atrophy of the testes, prostates and seminal vesicles and necrosis of the epididymal epithelium at these high doses. The chemical BBP at ≥1250 mg/kg bw/day also reduced bone marrow cellularity in a dose-related manner (Agarwal et al. 1985; ECB 2007).

In 90-day feeding studies (10/sex/group), Wistar rats received BBP doses of 0, 151, 381, or 960 mg/kg bw/day; and Sprague-Dawley (SD) rats doses of 0, 188, 375, 750, 1125, or 1500 mg/kg bw/day. For Wistar rats, the NOAEL was 151 mg/kg bw/day and the LOAEL 381 mg/kg bw/day, based on increased kidney weight, decreased urinary pH, histopathological changes in the pancreas, and gross pathological changes in the liver. At 960 mg/kg bw/day, body weight decreased, liver weight increased and slight anaemia was observed. For less sensitive SD rats, the NOAEL was 375 mg/kg bw/day, based on increases in kidney (male) and liver (female) weights at ≥750 mg/kg bw/day. No histopathological changes in the liver, pancreas or testes were reported (Hammond et al. 1987; ECB 2007).

In a 26-week dietary study with male F344 rats (0, 30, 60, 180, 550, 1660 mg/kg bw/day), observations included increased haemoglobin (Hb) and relative liver weight at ≥550 mg/kg bw/day, decreased body, testis and epididymis weights and sperm concentrations, together with histopathological changes in reproductive organs and kidneys, at 1660 mg/kg bw/day. Thus, the NOAEL for systemic toxicity was 180 mg/kg bw/day (NTP 1997; ECB 2007).

Overall, the NOAEL of 151 mg/kg bw/day from the 90-day oral study in Wistar rats (identified by ECB 2007) is considered most appropriate for risk characterisation because it is based on histopathological changes, rather than on organ and/or body weight changes or slight haematological changes, at the higher doses.

International reviews of the earlier literature indicated that there is evidence of BBP-induced peroxisome proliferation in the liver of both male and female rats after repeated oral exposure (ECB 2007; WHO 1999). Its potency was lower than that for longer chain and/or branched phthalate esters such as DEHP, based on the 21-day feeding study (Barber et al. 1987). From a recent two-generation reproductive study, histopathological lesions in the liver were also found consistent with hepatomegaly (hepatocyte hypertrophy) due to induction of peroxisome proliferation from exposure to BBP (Tyl et al. 2004).

There was only one poorly reported dermal study available (Statsek 1974*; cited in ECB 2007), and thus no NOAEL value is derived for repeated dermal exposure to BBP.

6.4.2 Repeated dose inhalational toxicity

Data on the toxicity of BBP following repeated inhalational exposure were limited to two 4-week and one 13-week studies, all conducted in SD rats (refer to ECB 2007; NICNAS 2008a; WHO 1999 for review).

Collectively, the lowest observed adverse effect concentration (LOAEC) for decreased body weight was 526 mg/m^3. Atrophy of spleen and testes was seen at 2100 mg/m^3 in the short-term studies (Hammond et al. 1987; Monsanto 1981*; cited in ECB 2007). In the 13-week study (0, 51, 218, 789 mg/m^3), significant increases in kidney and liver weight in both sexes and marked decreases in serum glucose in males were seen at 789 mg/m^3. At 218 mg/m^3, although there was a significant increase in kidney weight in male rats, it was reported at interim sacrifice only. No dose-related histopathological changes were observed in any group. Therefore, the no observed adverse effect concentration (NOAEC) was determined as 218 mg/m^3 (Monsanto 1982*; cited in ECB 2007).

6.5 Genotoxicity and carcinogenicity

The genotoxicity and carcinogenicity of BBP have been well investigated and reviewed (ECB 2007; IARC 1999; NICNAS 2008a; WHO 1999). The National Toxicology Program (NTP) conducted genotoxicity and long-term carcinogenicity studies for BBP and presented a Testing Status summary (<http://ntp.niehs.nih.gov/testing/status/agents/ts-10422-e.html>).

6.5.1 Genotoxicity

The chemical BBP was negative in bacterial reverse mutation assays (Kozumbo et al. 1982; Monsanto 1976*; NTP 1997; Zeiger et al. 1982).

In vitro, BBP did not increase gene mutations in mouse lymphoma cells (Monsanto 1976*; Myhr & Caspary 1991*; NTP 1997). It did not induce sister chromatid exchanges or chromosome aberrations in Chinese hamster ovary cells (Galloway et al. 1987*). Morphological cell transformation was detected with BBP in Syrian hamster embryo cells (le Boeuf et al. 1996*), but not in mouse Balb/3T3 cells (Monsanto 1985*; Barber et al. 2000).

In vivo, there was no induction of micronucleus in rats or mice (Ashby et al. 1997*; NTP Testing Status of BBP). Following a single intraperitoneal injection of 1250–5000 mg/kg bw BBP in one study (NTP 1997), bone marrow tests for sister chromatid exchanges showed a weak positive response, while tests for chromosomal aberrations gave conflicting results (i.e. a positive trend observation at 17 hours, but negative at 36 hours post injection). Sex-linked recessive lethal mutations were not seen in *Drosophila melanogaster* (Valencia et al. 1985*), nor dominant lethal mutations in mice (Bishop et al. 1987* (abstract only)),

On the basis of available data, BBP is not considered likely to be a mutagen in humans.

6.5.2 Carcinogenicity

The chemical BBP was tested for carcinogenicity in rats (three studies) and in mice (one study) via oral route only. For rats, a feed-restricted protocol (NTP 1995*) was also used, where the animals were fed BBP-containing diet in amounts that restricted mean body weights to approximately 85 % of the mean ad libitum control body weights (i.e. standard protocol; NTP 1982; 1997).

There is no evidence of carcinogenicity for BBP in mice based on a two-year standard dietary study (NTP 1982).

In female rats, mononuclear cell leukaemia (MCL) was observed; however, the increased incidence was either within the historic control range, similar to incidences found in the control groups, or not replicated in later studies in which a higher concentration was tested (NTP 1982; 1995*; 1997; ECB 2007). In addition, MCL is not regarded as relevant to humans on the basis that MCL has not been found in other mammalian species and has no directly comparable manifestations in humans (NICNAS 2008b).

There were marginal increases (~4 %) in pancreatic adenomas (observed in a standard protocol only; NTP 1997), and in bladder papillomas (in both standard and feed-restricted protocols; NTP 1995*; 1997). There was also a non-significant increase in bladder carcinomas at 1200 mg/kg bw/day after 32 months of dietary restriction (NTP 1995*), but not in any of the two-year standard or feed-restricted protocol (NTP 1995*; 1997). In male rats, an increased incidence of benign pancreatic tumours (adenomas) was seen after conventional dosing, but not after dietary restriction for either 24 or 36 months (NTP 1995*; 1997). At two years, increased incidences of focal pancreatic hyperplasia in male rats and of bladder transitional-cell hyperplasia in female rats, compared with the controls, were also reported (NTP 1997).

In separate short-term studies in rats, treatment of BBP for seven days was shown to inhibit mammary DNA adduct formation and mammary carcinogenesis, that was induced by prior administration of 7,12-dimethylbenz[a]anthracene (Singletary et al. 1997). Prenatal, neonatal, or prepubertal exposure to BBP was found to induce modifications in gene expression, either associated with mammary gland maturation or with an increased susceptibility to carcinogenesis (Moral et al. 2007; 2011). However, these results are considered preliminary.

Overall, IARC (1999) and ECB (2007) considered that on the weight of evidence, the available data do not provide adequate evidence of carcinogenicity for BBP in humans.

6.6 Reproductive toxicity

The reproductive and developmental toxicity of BBP, and its monoester metabolites MBP and MBzP, have been well characterised and reviewed (ECB 2007; NICNAS 2008a; NTP-CERHR 2003; US CPSC 2010; WHO 1999).

6.6.1 Effects on fertility and reproductive organs

Impaired fertility has been reported after oral exposure to BBP, particularly at doses causing systemic toxicity, in a number of animal studies (including two out of three well-conducted multi-generation studies). The

mechanism of toxicity involves overt effects on the male reproductive system (e.g. reduced testis and accessory organ weight, increased testicular pathology and sperm abnormality).

Pregnancy rates were significantly reduced when unexposed female rats were mated to male rats administered BBP at 2200 mg/kg bw/day for 10 weeks or 1650 mg/kg bw/day for 26 weeks in the diet (NTP 1997; ECB 2007). Reduced sex organ weights and degenerative changes in the testes, epididymides and/or seminiferous tubules were noted at ≥1250 mg/kg bw/day (Agarwal et al. 1985; Hammond et al. 1987; NTP 1997). Dose-dependent reductions in spermatozoal concentration were seen from BBP doses as low as 200 mg/kg bw/day in the absence of systemic toxicity. Concentrations were 87 %, 70 % and 0.1 % of control at 20, 200, and 2200 mg/kg bw/day, respectively (NTP 1997). Since the reduction of 30 % in the sperm count at 200 mg/kg bw/day (10-week exposure) was not replicated at 550 mg/kg bw/day (26-week exposure), interpretation of this result should be viewed accordingly (NTP 1997; NTP-CERHR 2003).

In another study, 4-week administration of BBP (500 mg/kg bw/day) was shown to decrease sperm count and sperm motility, along with increased liver weight, decreased body weight, and no change in food consumption (Kwack et al. 2009).

In an OECD 421 reproductive toxicity screening protocol, BBP at 1000 mg/kg bw/day had adverse effects on body weight gain and food consumption, on testis and epididymis weight, spermatogenesis, time to conception, pregnancy rate, postimplantation survival, litter size and weight, but it had no effects on ovaries. Testicular degeneration along with significantly increased Leydig cell hyperplasia and cellular debris was seen (Piersma et al. 1995).

Results from multi-generation reproductive toxicity studies were similar although the reproductive capacity was unaffected in the F0 parental generation.

Dietary administration of BBP to SD rats (30/sex/dose) for two offspring generations, one litter per generation, resulted in adult F1 (but not F0) reproductive toxicity. At 750 mg/kg bw/day, together with systemic toxicity (such as reduced body weights, increased liver weights with histopathological evidence of peroxisome proliferation), F1 parents showed reductions in mating and fertility indices, in implantation sites, total and live pups per litter at birth, sperm motility and concentrations, as well as showing male reproductive tract malformations and both gross and histopathological lesions in testes, epididymides, and prostates. Reproductive organ weights (testis, epididymis, prostate, seminal vesicle, ovary and uterus) were significantly reduced in the F1 generation at 750 mg/kg bw/day. There were dose-dependent increases in epididymis and testis histopathological changes (3–4 and 15–23 vs 2–3/28 F1 controls, at 250 and 750 mg/kg bw/day, respectively) and fluid-filled uterus (1 and 3 vs 0/30 F1 controls, at 250 and 750 mg/kg bw/day, respectively) (Tyl et al. 2004).

In another two-generation study in SD rats (24/sex/dose), F1 animals with perinatal exposure to a gavage dose of 400 mg/kg bw/day showed reduced fertility index, delayed preputial separation, and small size of testes and epididymides. There were histopathological findings of diffuse atrophy of seminiferous tubules and hyperplasia of Leydig cells in the testes (statistically significant at 400 mg/kg bw/day), and of decreased spermatozoa and residual germ cells in the epididymal lumina, together with autopsy findings of dose-dependent softening of the testes at ≥100 mg/kg bw/day, i.e. doses lower than those inducing effects on kidney and liver (≥200 mg/kg bw/day) (Aso et al. 2005).

Although no dose-related changes in either F0 or F1 reproductive performance of SD rats (25/sex/dose) were observed in a two-generation reproductive study conducted by Nagao et al. (2000), the characteristic effects of BBP on reproductive organs were reported at 500 mg/kg bw/day. These included reduced sex organ weights (testis, epididymis, prostate, and seminal vesicle in adult F1 male rats, as well as ovary in F0 and F1 female rats) with increased incidences of histopathological changes (seminiferous tubular atrophy and germinal epithelial loss), and decreased numbers of spermatogonia and spermatocytes in the epididymis.

A one-generation study (OECD TG 415) showed no effects on implantation, fertility or fecundity in Wistar rats at the highest dose tested of 418–446 (m-f) mg/kg bw/day (Monsanto 1993*; NTP-CERHR 2003).

In earlier animal studies, testicular atrophy was noted after a 14-day gavage exposure at ≥480 mg/kg bw/day (1/6 animals) for SD rats, and at 1600 mg/kg bw/day for Wistar rats. Atrophic changes of the testes in SD rats after a 4-day exposure were reported for BBP at ≥800 mg/kg bw/day (3/6 animals). Similar effects were seen for MBP at 855 mg/kg bw/day, and MBzP at 985 mg/kg bw/day (Lake et al. 1978*; ECB 2007).

In a dominant lethal test—where male mice after subcutaneous injections of BBP at doses up to 3200–4560 mg/kg bw/day on days 1, 5, and 10 were mated for 4-day intervals sequentially to three untreated females—no damage to fertility or foetal deaths were observed in either strain of mice (B6C3F1 or CD-1) (Bishop et al. 1987* (abstract only); ECB 2007; NTP-CERHR 2003). No effects on the testes of mice or dogs were observed after three months of dietary exposure to BBP at 3750 mg/kg bw/day or 1852 mg/kg bw/day, respectively (Hammond et al. 1987). Sensitivities of the reproductive system to BBP exposure might be different between species as seen for repeated dose toxicity. However, the limited available information and different study designs precluded a conclusive comparison.

In human studies, statistically significantly higher levels of mixed phthalate esters (including BBP) were identified in the semen samples of 21 infertile men, compared with 32 fertile men (Rozati et al. 2002). Non-significantly higher MBzP was reported in the urine samples of 56 couples requiring assisted reproduction, compared with 56 control couples (Tranfo et al. 2012). Urinary MBP and MBzP levels were higher in the subjects with ≥1.5 mL semen volume (n = 39) than in those <1.5 mL (n = 2) (Toshima et al. 2012). There was a dose-response relationship between MBP and MBzP and low sperm concentration in a cohort of 168–463 male partners of subfertile couples (Duty et al. 2003; Hauser et al. 2006). Although not statistically significant, MBP and MBzP were reported to be associated with an overall trend in the decline of sperm motion parameters, analysed from another subfertile cohort of 187 subjects (Duty et al. 2004). In contrast, there was no clear pattern of association between urinary MBP or MBzP, collected from 234 young Swedish men, with any of the reproductive biomarkers (i.e. semen volume, sperm concentration, motility or reproductive hormones) (Jonsson et al. 2005). The null associations were also found with MBP and MBzP, collected from 268 men attending an infertility clinic and having normal semen volumes. Among the measured semen quality parameters and reproductive hormone levels, MBP was significantly associated only with computer-aided semen analysis (CASA) parameters, which were used to measure sperm progression, sperm vigour, and swimming pattern (Jurewicz et al. 2013).

Overall, human studies are limited by questions concerning small sample sizes, the reliability of single spot urine/semen samples, and other confounding factors such as the measured presence of other phthalates and monoester metabolites. However, there is sufficient evidence in appropriate animal studies that BBP causes testicular toxicity and/or fertility, and these are more marked after perinatal exposure (i.e. F1 generation). Testicular toxicity induced by BBP is manifested reproducibly as statistically significant reductions in testis weights, testicular and accessory sex organ atrophy, as well as dose-dependent decreases in spermatozoal concentration. Although the deleterious effects of BBP on the testes and/or fertility were sometimes observed at the higher or the same dose levels as other toxic effects, they are not considered secondary non-specific consequences of the systemic toxicity (ECB 2007; NTP-CERHR 2003). On this basis, the current classification of BBP as a Reproductive Toxicant Category 3 with the risk phrase R62 ‘Possible risk of impaired fertility’ in HSIS (Safe Work Australia) is supported.

6.6.2 Effects on development

The developmental toxicity of BBP, and its monoester metabolites MBP and MBzP, has been sufficiently explored in both rats and mice, in a wide range of study designs.

Embryo-foetal toxicity and teratogenicity

In well-conducted NTP studies, BBP was shown to cause marked maternal and developmental/foetal effects following dietary exposure of dams during GD 6–15. For SD rats, an increased percentage of foetuses with variations and malformations (per litter) were observed at maternally toxic doses of ≥1100 mg/kg bw/day, together with increased resorptions per litter (40 % vs 4 % in controls), increased malformed foetuses per litter (53 % vs 2%), and decreased average foetal body weight per litter (20 %) at 1640 mg/kg bw/day. The maternal and developmental NOAELs were 420 mg/kg bw/day (NTP 1989*). For CD-1 mice, at 910 mg/kg bw/day, where maternal effects were limited to a 15 % reduction in body weight gain, increases in non-live implants per litter (resorptions plus late foetal deaths, 15 % vs 8 % in controls) and in malformed foetuses per litter (14 % vs 4 %) were observed. At maternally toxic doses of ≥2330 mg/kg bw/day, prenatal mortalities and foetal malformations were significantly increased (93 % vs 8 % and 89 % vs 4 % in controls, respectively); also, average foetal weight per litter was reduced by 17 %. The maternal and developmental NOAELs were 182 mg/kg bw/day (NTP 1990*). Given the wide dose spacing in mice (182, 910, 2330 mg/kg bw/day) compared with rats (420, 1100, 1640 mg/kg bw/day), it is not possible to compare sensitivity between the two species quantitatively (NTP-CERHR 2003).

Ema and colleagues reported embryolethality (or prenatal mortality) and teratogenicity associated with BBP in a series of dietary and gavage studies with Wistar rats. Following GD 7–15 exposure, high maternal lethality and 100 % resorption of implanted embryos in all surviving dams (6/10) were observed at 1000 mg/kg bw/day. Increased embryo-foetal deaths, increased foetal malformations, and decreased foetal weight were found at 750 mg/kg bw/day, along with reductions in maternal body weight gain and food consumption (Ema et al. 1992a). The maternal and developmental NOAELs were 500 mg/kg bw/day, comparable to those for SD rats.

The dose and exposure time dependency of BBP prenatal effects were also examined in Wistar rats. Dams given BBP for an extended exposure period (i.e. GD 0–20) had reduced foetal weight (by sex per litter) at ≥654 mg/kg bw/day, and live litter size at ≥375 mg/kg bw/day, resulting in a developmental NOAEL of 185 mg/kg bw/day (Ema et al. 1990; NTP-CERHR 2003). Complete resorption was observed in dams given BBP at 974 mg/kg bw/day after GD 0–20 or 0–11 exposure, and higher postimplantation loss was found after GD 0–7 or 7–16, but not after GD 16–20 exposure (Ema et al. 1992b; 1992c). Although no increase in postimplantation loss was found in dams after GD 11–20 exposure, marked teratogenicity was detected in the foetuses (Ema et al. 1992b). While food consumption was decreased in treated animals, absence of complete resorptions and slightly increased postimplantation loss were found in pair-fed controls, which received the same amount of diet and had comparable reductions in maternal adjusted weight gain (i.e. body weight gain excluding gravid uterus). Therefore, the embryotoxic and teratogenic effects in the BBP group were considered related to treatment rather than to the maternal malnutrition from decreased food consumption (Ema et al. 1991; Ema et al 1992b; ECB 2007; NTP-CERHR 2003).

In a study evaluating the effects of BBP (at 974 mg/kg bw/day) during early pregnancy (GD 0–7, 0–9, and 0–11 exposures), postimplantation loss on day 11 was markedly higher than that in the control and pair-fed groups. Regardless of the day of sacrifice (7, 9, or 11), uterine and ovarian weights and plasma progesterone levels, except for the ovarian weight on day 7, were significantly lower than those in the control and pair-fed groups (Ema et al. 1994). In another study using GD 0–8 exposure and evaluating the pregnancy outcome on GD 20, BBP significantly increased postimplantation loss in females having implantations at ≥750 mg/kg bw/day, and significantly increased preimplantation loss in females successfully mated at 1000 mg/kg bw/day. Applying the same dose and time exposure regime in pseudopregnant rats (induced decidual cell response on days 0–8 of pseudopregnancy), BBP at 750 mg/kg bw/day significantly decreased uterine decidual growth (Ema et al. 1998). Taken together, it was suggested that the early embryonic loss due to the BBP may be mediated via the reduction in plasma progesterone levels (an impairment of luteal function) and, at least in part, via the suppression of uterine decidualisation (an impairment of uterine function) (Ema et al. 1994; Ema et al. 1998).

In similar prenatal study design as for BBP (see Ema et al. 1992a), the monoester metabolites of BBP (MBP and MBzP) and a related phthalate (DBP, for which MBP is the active metabolite), following GD 7–15 exposure via gavage, induced developmental toxicity effects (including resorption, postimplantation loss or embryo-foetal death, foetal malformation, and decreased foetal weight), comparable to BBP (Ema et al. 1995a; 1995b; 1996a). In addition, there were similarities in the time dependence of gestational exposure (GD 7–9, 10–12, and 13–15) on the manifestation of foetal toxicity and on the spectrum of foetal malformations between these compounds, leading to a conclusion that both metabolites may have similar mechanisms of action, and hence may contribute to the developmental toxicity of the parent compounds BBP and DBP (Ema et al. 1995b; 1996b; 1996c; NTP-CERHR 2003). Observed malformations included deformity of the vertebral column and ribs (frequently after treatment on GD 7–9), and cleft palate and fusion of sternebrae (predominantly after treatment on GD 13–15) (Ema et al. 1995b; 1996b; 1996c). Dilation of the renal pelvis was also observed following both MBP and MBzP treatment (Ema et al. 1995a; 1996b).

Comparative embryotoxicity of BBP and its metabolites was evaluated both *in vivo* and *in vitro*. After a single gavage dose, both OF1 mice (GD 8) and SD rats (GD 10) were susceptible to the toxic effects of BBP, although the incidence of external malformations and embryonic deaths was far greater in mice than in rats. The chemicals MBP and MBzP were embryolethal and teratogenic in mice (in the absence of maternal toxicity) at ≥0.9–1.8 mmol/kg, while no significant developmentally toxic effects were observed in rats at ≤5.4 mmol/kg (maternally toxic doses). In both mice and rats, MBzP tended to be more maternally toxic than MBP, as evidenced by a higher incidence of mortality and a decrease in body weight gain at the high doses. In contrast, MBzP was less embryolethal than MBP in mice, causing 47 % vs 82% post-implantation loss at 5.4 mmol/kg. However, 46-hour cultures of GD 8 mouse embryos did not appear intrinsically more sensitive to MBP or MBzP than cultures of GD 10 rat embryos. Collectively, the authors concluded that the species' sensitivity to BBP, MBP and MBzP observed *in vivo* during early organogenesis might be due to maternal metabolic and pharmacokinetic factors (Saillenfait et al. 2003).

Effects on birth weight, offspring development and sexual differentiation

In a low-dose exposure study, male rats exposed to BBP (at a single dose level of 1000 µg/L drinking water during foetal and neonatal life until PND 22) showed statistically significant reductions in mean testicular size (5–13 %) and in mean daily sperm production (10–20 %) in adulthood (PND 90–95), without any recorded changes in body, kidney or ventral prostate weight. The effects on sperm were found to be proportionately similar to the decrease in testis weight (relative to body or kidney weight). Based on water consumption (mL/48-h), nominal intakes of BBP were estimated as 0.126, 0.274, and 0.366 mg/kg bw/day on PND1–2, 10–11, and 20–21, respectively. They were presumed to be an overestimate of actual exposure levels because the calculations take no account of spillage, adsorption, or instability of BBP in drinking water (Sharpe et al. 1995).

However, none of these effects were reproducible in BBP pups following similar treatment, at doses up to 0.674 mg/kg bw/day, in four subsequent studies by other laboratories (Ashby et al. 1997*; Bayer AG 1998*; TNO 1998a*; 1998b*). Therefore, ECB (2007) judged that exposure of dams to low doses of BBP during gestation and lactation caused no impairment to the development of reproductive system in their male offspring.

In addition to reproducing the foetotoxic effects previously reported (such as increased resorptions, reduced foetal weights, increased skeletal anomalies), Piersma et al. (2000) observed adverse effects of BBP on foetal testis weight in the presence of retarded testicular descent in Harlan Cpb-WU rats (examined on GD 21). Foetotoxicity appeared more sensitive after long exposure (GD 5–20) than short exposure (GD 5–16). On the basis of critical effect doses (CEDs) derived from a fitted dose-response model (using ten dose groups between 270 and 2100 mg/kg bw/day, together with the benchmark approach vs the NOAEL approach), the developmental effects of BBP generally occurred at lower levels than the maternal effects. Except for foetal weight where its CED of 415 mg/kg bw/day was in the range of CEDs for increases in maternal liver and kidney weights, the other four foetotoxic indicators were associated with CEDs in the range of 95–280 mg/kg bw/day for long exposure.

Ema and colleagues reported increased incidences of undescended testes in GD 21 foetuses of dams given BBP (≥500 mg/kg bw/day) or the metabolite MBzP (≥250 mg/kg bw/day) during late pregnancy (GD 15–17). In male (but not female) foetuses, decreases in anogenital distance (AGD) and in the ratio of AGD to cube root of body weight were also observed at the above doses for BBP and MBzP (Ema & Miyawaki 2002; Ema et al. 2003).

BBP (together with DBP and DEHP) at 500 mg/kg bw/day significantly reduced AGD in male foetuses following in utero exposure from GD 12–19. The results for BBP were in agreement with the Ema and Miyawaki study reported above, although limited data were presented from this study (Liu et al. 2005).

Gestational exposure (GD 15–18) to the metabolite MBP (1000 mg/kg bw/day) was reported to induce transabdominal ascent of the foetal testes prenatally (in GD 20 foetuses), while causing either bilateral or unilateral cryptorchidism (84.6 % vs 0 % in controls) postnatally (in PND 30–40 offspring) (Imajima et al. 1997). The findings were confirmed in a later similar study at lower doses between 492–922 mg/kg bw/day, where MBP was reported to significantly increase transabdominal testicular ascent in GD 19 foetuses, and cause bilateral or unilateral undescended testes (54.5 %) in adult rats on PND 60. Gene expression of insulin-like hormone 3 (insl3), a foetal Leydig cell product critical for testicular descent, was significantly decreased in the MBP-treated testes (Shono et al., 2005).

In a study using a range of phthalates in rats (Gray et al. 2000), after perinatal exposure (GD 14 – PND 3, claimed as the period of sexual differentiation) to DEHP and BBP (750 mg/kg bw/day), male offspring showed shortened AGDs (~30 %) and reduced paired testis weights (~35 %) on PND 2. Males in the DEHP and BBP groups displayed female-like areolas/nipples on PND 13 (87 % and 70 % vs 0 % in controls, respectively), as well as reproductive tract malformations at 3–4 months of age (82% and 84% vs 0 % in controls, respectively). They included cleft phallus, hypospadias, undescended testes, and agenesis/atrophy of testes, epididymides, ventral prostates, seminal vesicles and/or bulbourethral glands. Therefore, DEHP and BBP were considered equivalently potent in altering male sexual differentiation, and producing male reproductive tract malformations; these appeared to be characteristic of an androgenic disturbance during the critical window of development (Foster 2006; Gray et al. 2006). Although pup weight reductions at birth (15 %) were seen in both sexes after DEHP or BBP treatment, they were reversible at weaning (PND 28) or later in life (Gray et al. 2000). This profile of androgen-dependent malformations from DEHP and BBP exposure was almost identical to that for DBP seen from a range of studies (Mylchreest et al. 1998; 2000; Wolf et al. 1999; see Foster 2006; NICNAS 2013 for review).

In a recent study, albino pregnant rats were treated by gavage with DBP (2, 10, 50 mg/kg bw/day) or BBP (4, 20, 100 mg/kg bw/day) from GD 14 to parturition. Maternal body weight gain was significantly lower in all treated groups, compared to controls. Male pup weights on PND 1 and PND 21were decreased (DBP ≥10 mg/kg bw/day vs BBP ≥4 mg/kg bw/day). On PND 75 (adulthood), there were reductions in body weight (BBP ≥20 mg/kg bw/day), kidney weight, reproductive organ weight (epididymis and prostate, but not testis), as well as decreases in sperm quality and serum testosterone concentration (BBP at 100 mg/kg bw/day). The chemical DBP showed similar effects on F1 adult male rats; however, only at the highest dose tested (50 mg/kg bw/day) (Ahmad et al. 2014). The lack of testis weight effects and the LOAELs from this study were considered inconsistent with those reported from other well-conducted studies, and thus this study is not included in the derivation of NOAEL for risk assessment of BBP.

In the following three multi-generation reproductive studies, compatible findings concerning the pup weight, the antiandrogenic effects and testicular toxicity (discussed above) of BBP were reported. In particular, the effects on birth weight and AGD were seen in the absence of maternal toxicity in two out of three studies.

After oral administration in SD rats, BBP caused a decrease in serum testosterone concentration (F0 and adult F1 at 500 mg/kg bw/day). While an increase in follicle-stimulating hormone (FSH, a regulator of components of the seminiferous tubules via Sertoli cells) was observed in F0 (≥100 mg/kg bw/day), a decrease was observed in F1 weaning male rats (500 mg/kg bw/day). At 500 mg/kg bw/day, AGD at birth was decreased in male pups and increased in female pups; preputial separation was delayed and macroscopic and microscopic changes of the testes were seen after puberty. Female reproductive tract development was less susceptible. Birth weights in both sexes were reduced (≥100 mg/kg bw/day), with the decrease at 500 mg/kg bw/day sustained throughout the study (from weaning on PND 21 until 13 weeks of age). Therefore, the NOAEL was determined to be 20 mg/kg bw/day for developmental effects, as well as for maternal effects, based on increases in kidney weight of both sexes at 100 mg/kg bw/day (Nagao et al. 2000).

In the study of Tyl et al. (2004), the developmental NOAEL was 50 mg/kg bw/day (based on reduced AGD in a dose-dependent manner at ≥250 mg/kg bw/day in F1 and F2 males), while the maternal NOAEL was 250 mg/kg bw/day (based on reduced body weights (F1) and increased liver (F0) and kidney (F0 and F1) weights of both sexes at 750 mg/kg bw/day). Other signs of offspring toxicity at 750 mg/kg bw/day included retention of nipples and/or areolae on PND 11–13 and reproductive system malformations (males, F1 and F2), delayed puberty (males-females, F1), and reduced pup weights (per litter) during lactation (F1 and F2).

In a two-generation reproductive study by Aso et al. (2005), the developmental effects reported at the maternal NOAEL of 100 mg/kg bw/day were reduced AGD in males, increased AGD in females, and decreased birth weight in males (F1) and in both males and females (F2). At 400 mg/kg bw/day, delayed preputial separation and pup weight reduction were reported.

Taken together, the lowest LOAEL is 100 mg/kg bw/day, based on reduced birth weight in both sexes (Aso et al. 2005; Nagao et al. 2000), while the highest NOAEL selected for risk characterisation in this review will be 50 mg/kg bw/day from the Tyl et al. (2004) study.

Overall, there are sufficient reports of BBP-induced developmental toxicity, including prenatal, neonatal and postnatal endpoints. They commonly included resorption, postimplantation loss or embryo-foetal death, foetal malformation, teratogenicity, decreased foetal weight and birth weight. For reproductive development, females seem less susceptible than males to the adverse effects of BBP. In males, there were reports of reduced foetal testosterone levels, altered neonatal AGDs and infant areolae (see **Section** 6.6.3 for mode of action below), delayed puberty, and after puberty there were decreases in testosterone, impaired sexual differentiation and malformed reproductive organs (including hypospadias and cryptorchidism), and altered reproductive functions (including increased testicular pathology, sperm abnormality, and reduced fertility in F1 generation, see **Section** 6.6.1).

These are clear results in appropriate animal studies, where effects have been observed in the absence of marked maternal toxicity (mainly reduced body weight gain accompanied by a decreased food consumption), or at around the same dose levels as other toxic effects (mainly increased kidney and/or liver weight). The findings are not considered secondary non-specific consequences of the maternal toxic effects. On this basis, the current classification of BBP as a Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child' in HSIS (Safe Work Australia) is supported.

Developmental effects of BBP in humans

In human studies, maternal urinary concentrations of monoethyl phthalate (MEP), monoisobutyl phthalate (MiBP), MBP, and MBzP were found inversely related to AGI (AGI = ratio of AGD to body weight), analysed from 85 mother-son pairs. The corresponding odds ratios were 4.7, 9.1, 10.2, and 3.8, respectively. Association between MBzP and AGD was of borderline significance ($p = 0.055$) (Swan et al. 2005). This study was criticised by McEwen & Renner (2006) from Cosmetic Toiletry and Fragrance Associations of America and Europe. They were of an opinion that AGD is likely to be proportional to infant body length (or height) rather than weight, and that maternal phthalate urinary concentrations were not normalised for urine volume.

Swan subsequently replicated and extended the study. In a cohort of 106 mother-son pairs, MBzP was no longer associated with AGI or AGD (Swan 2008). Similar results were reported by Huang et al. (2009) and Suzuki et al. (2012).

There was no association between phthalate monoester levels in the breast milk (including monoethylhexyl phthalate (MEHP), MBP and MBzP) and cryptorchidism in a Danish-Finnish cohort (62 cryptorchid vs 68 healthy boys). For levels of reproductive hormones measured in the serum of 96 boys three months of age with and without cryptorchidism, MBP showed positive correlations with sex hormone-binding globulin (SHBG) and luteinizing hormone (LH): free testosterone ratio (a measure of Leydig cell function), and negative correlation with free testosterone. There was a tendency, although not reaching statistical significance, toward an increase in inhibin B (a measure of Sertoli cell function) with increasing concentration of MEHP and MBzP (Main et al. 2006).

In a multi-ethnic cohort of 352 mother-infant pairs in New York City, maternal urinary MBzP concentrations were found to be positively correlated with birth length and infant head circumference, but not with birth weight or gestational age (Wolff et al. 2008). The extent to which these associated parameters were related to maternal anthropometry was not known.

Meeker et al. (2009) reported a positive association between maternal urinary MBP and MBzP with preterm birth in a Mexican birth cohort (30 cases of preterm vs 30 controls). In contrast, MBP and MBzP were not associated with preterm birth or any of the maternal sex hormones (e.g. oestradiol, progesterone, or SHBG), measured from 106 pregnant women in Northern Puerto Rico (Johns et al. 2015).

Urinary levels of phthalate metabolites (including MEHP, MBP and MBzP) were not associated with age at pubertal onset, serum testosterone concentrations or presence of pubertal gynaecomastia, based on a Copenhagen puberty study of 555 healthy boys aged 6.07–19.83 years (Mieritz et al. 2012).

In a cohort of 295 volunteer men recruited from Massachusetts General Hospital, MBzP was found associated with a decrease (10 %) in FSH. However, the authors indicated that it was unclear whether the association presented a physiological relevance as the hormone concentration did not change in an expected pattern (Duty et al. 2005).

Overall, the human data on the developmental effects of BBP are limited and provide insufficient evidence for risk characterisation.

6.6.3 Mode of action for reproductive and developmental endpoints and relevance to humans

Historically, human health impacts associated with phthalates have been linked most strongly to reproductive effects. The majority of data on the mode of action for phthalates in inducing reproductive effects comprise studies of C4–6 or transitional phthalates such as DEHP, DBP, and to a lesser extent, BBP. These studies support the characterisation of transitional phthalates as antiandrogens, involving alterations of steroidogenesis and gene expression critical for development of the reproductive system, particularly in male rats (reviewed by Foster 2006; Howdeshell et al. 2008a; Kay et al. 2014; NICNAS 2010; 2013).

Available mechanistic studies for BBP (including those in parallel with DEHP and DBP) are discussed below.

After exposure to DEHP (750 mg/kg/day), DBP (1000 mg/kg bw/day) or BBP (1000 mg/kg bw/day) in utero during sexual differentiation (GD 14–18), rat foetal testes showed a significant decrease in both ex vivo testosterone production and insl3 gene expression. This concurrent inhibition was noted to happen only with the three studied phthalates, and not with known androgen receptor (AR) antagonists and/or inhibitors of foetal testosterone (such as vinclozolin, prochloraz and linuron) (Wilson et al. 2004).

During in utero exposure from GD 14–18, although acting by different mechanisms, two “antiandrogens” linuron (75 mg/kg bw/day) and BBP (500 mg/kg bw/day) were shown to decrease testosterone production and

alter reproductive development of male foetuses in a dose-additive fashion. Changes to neonatal AGD and infant areolae relating to BBP were found significantly correlated with adult AGD, nipple retention, reduced reproductive organ weights and malformations. Therefore, AGD and areolae measurements were considered useful biomarkers of antiandrogenic action, and they may not 'necessarily be transient and in many cases are reflective of permanent changes in adult phenotype or physiology' (Hotchkiss et al. 2004). As a consequence, after prenatal exposure to this binary mixture, the characteristic spectrum of androgen-dependent malformations was observed in the adult male rat, while such malformations were nearly absent with either linuron or BBP alone at this dose level. Externally, they included cleft prepuce, cleft phallus, hypospadias, exposed penile bone, vaginal pouch, and incomplete preputial separation; and internally they included undescended-ectopic or fluid filled testes, agenesis of epididymides, prostates, and seminal vesicles. Unlike the effects of BBP on androgen-dependent tissues, gubernacular agenesis (mediated by insl3) was not enhanced by the co-administration, although linuron did induce undescended, free-floating testes and cryptorchidism (mediated by both testosterone and insl3) (Hotchkiss et al. 2004; Wilson et al. 2004).

In a similar study design, a mixture of seven antiandrogenic chemicals with diverse structures (DEHP, DBP, BBP, procymidone, vinclozolin, prochloraz, and linuron) was found to alter the androgen signalling pathway via diverse mechanisms, disrupting male reproductive tract differentiation and inducing malformations (hypospadias or epididymal agenesis) in a cumulative, dose-additive manner (Rider et al. 2008).

Howdeshell et al. (2008b) reported a cumulative, dose-additive inhibition of foetal testicular testosterone production (following GD 8–18 exposure) from a mixture of five phthalate esters of the same C4–6 carbon chain length (i.e. BBP, DEHP, DBP, DiBP (300 mg/kg bw/day per chemical), and dipentyl phthalate (DPP, 100 mg/kg bw/day)), confirming a hypothesis that they act via a similar mechanism of action. The mixture ratio was selected such that each phthalate would contribute equally, in terms of potency, to the testosterone reduction. Comparing individual dose-response effects of the phthalates indicated that BBP, DBP, and DiBP were of equivalent potency to DEHP at reducing foetal testosterone, whereas DPP was three times as potent as DEHP.

The findings were later reviewed and confirmed with more studies using both binary mixtures (e.g. DBP+BBP, DBP+DEHP, etc.) and multi-component mixtures (e.g. seven chemicals above plus DiBP, DPP, and diisoheptyl phthalate (DiHP)). According to the authors, increasing the number of chemicals allowed for the use of lower concentrations of individual chemicals, and hence increasing the certainty around their mode of action (i.e. to ascertain that the chemicals act on a common target), given that the chemicals present below their NOAELs can contribute to mixture toxicity in a cumulative, dose-additive manner when the chemicals are in combined (Rider et al. 2010).

By using a fixed-ratio mixture of nine phthalates (BBP, DEHP, DBP, DiBP, DPP, DiHP, diheptyl-, dihexyl-, and dicyclohexyl phthalate) corresponding to their relative potencies, Hannas et al. (2011) reported a similar observation that the phthalates reduced foetal testosterone production in a dose-dependent manner best predicted by dose addition, following in utero exposure of rats on GD 14–18. In the second study, by comparing the sensitivity of the affected genes to testosterone production, Hannas et al. (2012) found that the antiandrogenic phthalates (i.e. those reduced testosterone production) act through a similar mode of action in the foetal testes, due to the consistency in dose-related reduction of expression of a subset of genes involved in steroid transport and synthesis.

Overall, exposure of rats to BBP has been shown to impair fertility (reduce testis and accessory organ weight, increased testicular pathology and sperm abnormality) (see **Section** 6.6.1), reduce foetal testosterone, disrupt male reproductive tract differentiation, and produce prenatal and postnatal malformations (including hypospadias and cryptorchidism) (see **Section** 6.6.2 and 6.6.3). The chemical BBP also induced downregulation of insl3 gene expression, which is critical for gubernacular development and testicular descent. The observed effects were consistent with those of DEHP and BBP (the well-studied potent phthalates), supporting the mode of antiandrogenic action that involves alterations of steroidogenesis and gene expression critical for male reproductive development. This is consistent with the inclusion of BBP (together with DBP, DEHP and others) in the endocrine disruptor priority lists for further evaluation, screening and testing (EC 2015; US EPA 2012b) (see **Section** 2.1).

Therefore, although the cellular and molecular mechanisms remain uncertain, this plausible mode of action for phthalates is considered comparable between rats and humans if the exposure to antiandrogenic phthalates, including BBP, is high and within a critical window of human development. In addition, given the severity of

harm from exposure to BBP, the adverse effects of BBP on fertility and development observed in animal studies are regarded as relevant to a human risk assessment.

6.7 Non-reproductive effects

Several human studies suggest some statistical correlations between urinary MBzP (either alone or in combination with metabolites of other antiandrogenic phthalates such as DEHP) and possible adverse changes such as:

- increased pre-pregnancy body mass index (BMI) (382 New York City women with an average maternal age of 24; Wolff et al. 2008);
- increased biomarker levels of inflammation and/or oxidative stress during pregnancy (130 cases of preterm birth vs 352 controls; Ferguson et al. 2011; 2015);
- increased risk of diabetes (2350 women aged 20–79 years participating in the US National Health and Nutrition Examination Survey (NHANES) 2001–2008; James-Todd et al. 2012);
- increased insulin resistance and waist circumference (1443 adult men from NHANES 1999–2002; Stahlhut et al. 2007);
- increased body mass index (BMI) and waist circumference (4369 adult men aged 20–59 from NHANES 1999–2002; Hatch et al. 2010);
- decreased Orientation and Quality of Alertness scores on the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) for neurodevelopment in girls (but not boys) within five days of birth (205 mother-child pairs; Engel et al. 2009);
- increased scores in the clinical range for withdrawn and internalising behaviours at age three (277 mother-child pairs; Whyatt et al. 2012);
- decreased overall intelligence quotient (IQ) at age three and perceptual reasoning at age seven; the association appeared stronger among boys than girls (328 mother-child pairs; Factor-Litvak et al. 2014).

Overall, these findings are preliminary and provide insufficient evidence for risk characterisation. Furthermore, there were reports of null associations (Sun et al. 2014; Swan et al. 2010; Teitelbaum et al. 2012), resulting in questions concerning the repeatability and reproducibility of the epidemiological results; however, they are not examined in this review.

6.8 Summary

BBP is rapidly and almost completely absorbed following oral administration. The bioavailability by the oral route is assessed as 100 % for both adults and children. Bioavailability from dermal absorption is unlikely to exceed 5 % of the applied dose in humans. Data on BBP absorption by the inhalational route are limited; therefore, a default bioavailability of 100 % is considered appropriate for this route for the purposes of this assessment.

Following absorption, distribution of BBP is widespread into tissues, including the placenta, but there is no evidence of accumulation in the body. The chemical BBP is also rapidly metabolised and excreted in the urine, predominantly as metabolites such as MBzP and MBP monoesters.

The chemical BBP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans. In addition, BBP is not expected to be an eye or skin irritant, or have skin sensitising potential in humans.

Based on the weight of evidence, the available data do not support a mutagenic, genotoxic or carcinogenic potential for BBP in humans.

Toxic effects related to repeated BBP exposure that are regarded as relevant to a human health risk assessment include systemic toxicity (increased liver and/or kidney weight), fertility (mediated by testicular toxicity) and developmental toxicity (antiandrogenic effects, reduced birth weight, embryolethality and teratogenicity, particularly in male rats).

The available data indicate that BBP, as well as DEHP and DBP, are antiandrogens with the mode of action that involves alterations of steroidogenesis and gene expression critical for the male reproductive development. Although there are uncertainties regarding the exact mechanism by which BBP affects fertility, foetal hormonal levels, and growth and development in rodents, this plausible mode of action for phthalates is considered comparable between rats and humans if the exposure to antiandrogenic phthalates, including BBP, is high and within a critical window of human development.

For the systemic effects, the NOAEL of 151 mg/kg bw/day from the 90-day oral study, based on histopathological changes in the pancreas and gross pathological changes in the liver of Wistar rats, is considered most appropriate for risk characterisation.

For fertility-related and developmental effects, the highest NOAEL of 50 mg/kg bw/day is selected from the collective results of the three multi-generation studies, based on reduced birth weight in both sexes at 100 mg/kg bw/day.

Table 6.1 lists the critical effects for BBP, the specific effects observed and the effect levels selected for risk characterisation.

Table 6.1: Endpoints selected for risk characterisation of BBP

Toxicity	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day) and effects	Species and age at treatment	Reference
Systemic effects (kidney and liver)	151	381: ↑ kidney weight, histopathological changes in the pancreas, gross pathological changes in the liver	Rat, Adults	Hammond et al. 1987; ECB 2007
Developmental effects (reduced birth weight)	50[a]	100: ↓ birth weight in both sexes	Rat, Adults	Aso et al. 2005; Nagao et al. 2000; Tyl et al. 2004

↓ = decreased; ↑ = increased; BBP = butylbenzyl phthalate; NOAEL = no observed adverse effect level; LOAEL = low observed adverse effect level.

On the basis of mode of action studies (**Section** 6.6.3), BBP is expected to be equivalent to DBP in reducing foetal testosterone. However, the foetal hormonal change has not been well characterised at the high doses used in the available studies for BBP. Given MBP is a common metabolite of both BBP and DBP and occurs as a major monoester metabolite in rodents, the NOAEL of 10 mg/kg bw/day for foetal testosterone reduction derived from the DBP PEC assessment (NICNAS 2013) is considered relevant to the MBP-based toxicity of BBP. This NOAEL will be taken forward for cumulative risk assessment.

7 Human health risk characterisation

7.1 Methodology

A margin-of-exposure (MOE) methodology is frequently used in international assessments to characterise risks to human health associated with exposure to chemicals (ECB 2003). The risk characterisation is conducted by comparing quantitative information on exposure to the NOAEL and deriving a MOE as follows:

- Identifying critical health effect(s);
- Identifying the most appropriate/reliable NOAEL (if available) for the critical health effect(s);
- Where appropriate, comparing the measured or estimated human dose or exposure (EHD) to provide a MOE: MOE = NOAEL/EHD; and
- Characterising risk, by evaluating whether the MOE indicates a concern for the human population under consideration.

The MOE provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgement is required. Such judgments are usually made on a case-by-case basis and should take into account uncertainties arising in the risk assessment process, such as the completeness and quality of the data, the nature and severity of effect(s) and intra/interspecies variability.

In this assessment, the MOE methodology is used to characterise the public health risks from BBP exposure through use of toys and childcare articles for children.

7.2 Risk estimates for children from use of toys and childcare articles

Risk estimates take into account the likelihood for adverse effects on kidney and/or liver and reproduction/development at future life stages related to long-term exposure through repeated handling and mouthing of toys. Table 7.1 provides the MOE calculated from the internal BBP dose in children (see Table 5.3) and the dose at which no adverse effect is observed for the critical health endpoints in laboratory animals, i.e. the NOAEL (see Table 6.1).

Table 7.1: Calculated MOE in children for the critical health effects of BBP from use of toys and childcare articles

Toxicity	NOAEL (mg/kg bw/day)	MOE for typical exposure scenario Typical $D_{int, oral+dermal}$ (0.35 µg/kg bw/d)	MOE for worst-case exposure scenario Worst-case $D_{int, oral+dermal}$ (2.06 µg/kg bw/d)
Systemic effects (kidney and liver)	151	431000	73000
Developmental effects (reduced birth weight)	50[a]	142000	24000

$D_{int, oral+dermal}$ = Estimated daily internal dose by oral and dermal routes of exposure.

The risk estimates for the toxicity effects of BBP on systemic and reproductive/developmental systems for both typical and worst-case exposure scenarios for toys used by children derive MOEs ≥24000 (Table 7.1) and hence indicate a low risk of these adverse health effects under these conditions of exposure.

An MOE of greater than 100 in risk characterisation is usually regarded as an indication of low concern as it encompasses the conservative default uncertainty factors of 10 each for intraspecies and interspecies variability (ECETOC 2003; IPCS 1994).

Uncertainties in the risk estimate

Uncertainties in any risk characterisation process arise from inadequate information, assumptions made during the process and variability in experimental conditions. The uncertainties inherent in the characterisation of risk for BBP arise mainly from inadequate data and include the:

- absence of Australian-specific data on BBP content in toys and childcare articles;
- absence of Australian-specific data on children's mouthing behaviours;
- absence of specific information on the migration rate of BBP from plastic matrices through the skin;
- significance of the observed toxicity in animals, particularly the reproductive/developmental effects, to the human population; and
- lack of adequate epidemiological studies for determining the health effects of BBP in children following repeated exposure.

Areas of concern

The risk estimates above do not indicate particular areas of concern from exposure of children to BBP by handling and mouthing of toys or childcare articles. If BBP is used as a sole plasticiser in toys under the same conditions as DINP (NICNAS 2012), the MOE for the worst-case exposure scenario would be 283, which is still above 100.

It should be noted that BBP is not found in toys in isolation, but generally with other primary and secondary plasticisers such as DINP, DBP or DEHP (at maximum 1 %; ACCC 2011). The estimation of cumulative risks is discussed in Appendix A. This takes into consideration the combined exposures to BBP together with multiple phthalates acting on the same biological targets as follows:

- using children's toys and childcare articles containing DINP and DEHP;
- using cosmetics containing DEP or DMP; and
- the combination of the two exposure scenarios considered in this assessment.

Based on its properties, functions and uses, BBP may be considered as a possible substitute for other phthalates (e.g. DBP or DEHP). In this case, exposure to BBP, which is currently low, may increase. Possible substitution of BBP for hazardous phthalates should be prevented by imposing a similar regulatory measure on all phthalates classified as toxic to reproduction.

8 Public health risk management

This section discusses current regulatory controls and risk management measures in Australia for protection of the public from the adverse health risks of BBP.

8.1 Public health risk standards—children's toys and childcare articles

There are currently no restrictions on the use of BBP in children's toys and childcare articles in Australia. The Australian/New Zealand Standard AS/NZS ISO 8124 *Safety of toys* does not specify any labelling or testing requirements for BBP content in children's toys.

In Australia, BBP was identified as being in use, or with the potential for use, in children's toys and childcare articles including toys, play and exercise balls, although these are not typical mouthing articles.

8.2 Public health risk standards—cosmetics

There are currently no restrictions on the use of BBP in cosmetics in Australia.

There is no available information indicating that BBP is used in cosmetics in Australia.

Labelling

There are currently no specific labelling requirements for consumer goods that contain BBP. However, disclosure of the presence of cosmetic ingredients is required on the packaging or on the product itself for cosmetics and toiletries in accordance with the Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations 1991. This legislation prescribes the mandatory standard for cosmetics and toiletries—ingredients labelling, which sets out the standards, the supplier and retailer responsibilities, and the Australian Competition & Consumer Commission (ACCC)'s role in enforcing cosmetic and toiletries ingredients labelling (ACCC 2008).

8.3 Recommendation

It is recommended that BBP be considered for listing in Schedule 10/Appendix C of the Poisons Standard (SUSMP) to limit the potential exposure of the public, including young children, to BBP from possible use in cosmetics (refer to the **Recommendation** section of this report).

Appendix A: Cumulative risk estimates from combined exposures to multiple phthalates

Cumulative risks can arise due to combined exposures from use of cosmetics and/or use of children's toys and childcare articles containing multiple phthalates acting on the same biological targets, through simultaneous exposures or from multiple sources.

The determination of risk from combined exposures to multiple phthalates will take into account any risk mitigation measures recommended in the individual PEC assessments for each phthalate. The cumulative risk estimates will be then considered to determine if further risk mitigation measures are required for a particular phthalate of concern.

The cumulative risk calculation is undertaken according to the WHO/IPCS Framework for risk assessment of combined exposure to multiple chemicals (Meek et al. 2011). The assumption is made that phthalates operate by a similar mode of action for developmental effects considered relevant to BBP without antagonising or synergising each other's effects. Accordingly, dose additivity with adjustment for the potency of each of the phthalates (Tier 1 of the framework) was used. Under Tier 1 of the framework, the hazard index (HI), which is the ratio of the exposure (EHD) to the toxicity reference value (e.g. NOAEL) for each of the chemicals, can be added and a cumulative MOE determined. It should be noted that the hazard index for an individual chemical calculated in this way is the inverse of the MOE (i.e. HI = 1/MOE, refer to **Section** 7.1 Methodology). Equations for calculating the cumulative MOE are provided in *Appendix 4 Mixture risk assessment methodology—evaluating the health risk due to exposure to mixtures of chemicals* in the Sixth Framework Programme of the Health and Environment Integrated Methodology and Toolbox for Scenario Development (HEIMTSA) (Sarigiannis et al. 2010). This includes a number of different equations for determining cumulative risks; the choice of the most appropriate equation depends on the available input data. For the current calculations, the equation used is:

$$\text{MOE cumulative} = 1/(1/\text{MOE}_1 + 1/\text{MOE}_2 + \ldots + 1/\text{MOE}_n)$$

The cumulative risk calculations are undertaken for the following scenarios (Table A.1):

- The combined exposure to a mixed phthalate plasticiser (DINP 42.5 % + BBP 0.5 %) in toys and DEP 0.5 % (or DMP 0.5 %) in cosmetics.
- The combined exposure to a mixed phthalate plasticiser (DINP 41.5 % + BBP 0.5 % + DEHP 1 %) in toys and DEP 0.5 % (or DMP 0.5 %) in cosmetics.

Given the cumulative effects of phthalates on developmental toxicity (reduced testosterone and reduced birth or pup weight) are best predicted by dose addition model (Hannas et al. 2011; Howdeshell et al. 2008b; Rider et al. 2010), the calculations for toys using Equation A.1 are based on the MOE for each phthalate as a primary plasticiser, regardless of whether it is actually used in this way. Hence, the MOE for DEHP and BBP (each calculated at 43 % in toys) is 27 and 57 for reduced testosterone endpoint, respectively. For the reduced birth weight endpoint, both DINP and BBP share the same NOAEL (50 mg/kg bw/day) and are more potent than DEP (NOAEL = 197 mg/kg bw/day). Hence, the MOE for DINP or BBP (in toys) is 283, compared with 1113 (in toys) and 1021 (in cosmetics) for DEP, using the relevant exposure estimates or daily internal doses (D_{int}) for a six-month-old infant (see below).

- $D_{int,\ oral+dermal}$ = 169.93 + 7.04 = 176.97 µg/kg bw/day (Tables 5.1 and 5.2) for the total phthalate content of 43 % from combined oral and dermal exposure.
- $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/day (Table 5.5 from PEC assessment of DMP, NICNAS 2014) for DEP or DMP at 0.5 % from dermal exposure to body lotion.

The relevant cumulative MOEs are calculated from the equations:

- For 'use of toys' scenario:

Equation A.1 MOE cumulative = 1/[(42.5/MOE of DINP + 0.5/MOE of BBP)/43] or

1/[(41.5/MOE of DINP + 0.5/MOE of BBP + 1/MOE of DEHP)/43].

- For ‘use of cosmetics’ scenario:

  DEP and DMP are currently allowed to be used in body lotion at maximum 0.5 % in Australia (SUSMP) and they share the same NOAEL, hence

  Equation A.2 MOE cumulative = NOAEL/EHD.

- For combined scenario:

  Equation A.3 MOE cumulative = 1/[1/MOE of a mixed phthalate plasticiser (in toys) + 1/MOE of DEP or DMP (in cosmetics)].

The estimated cumulative MOEs for the critical developmental effects indicate an adequate safety margin for children (Table A.1). These MOEs are specifically calculated for a six-month-old infant, the youngest age that demonstrates the maximum mouthing behaviour, because newborn babies are unlikely to use teethers or childcare articles, while the MOEs for older babies (e.g. 12-month-old infants) are expected to be higher, based on their lower surface area to body weight (SA/BW) ratio (DMP PEC Report Table 5.5, NICNAS 2014).

Table A.1: Calculated cumulative risks (MOE) in children (6-month-old) for the critical health effects of phthalates from combined exposures

Developmental Toxicity	Use of multiple phthalates[a] in children's toy and childcare articles (each phthalate calculated at maximum 43 %[b])							Use of DEP[c] (or DMP[c]) in body lotion (at maximum 0.5 %[d])		Cumulative MOE (Combined scenarios)
	NOAEL	MOE	NOAEL	MOE	NOAEL	MOE	Cumulative MOE	NOAEL	MOE	
	DINP 42.5 %		*BBP 0.5 %*					*DEP 0.5 % (or DMP 0.5 %)*		
Reduced testosterone	50	283	10	57			270	40	207	117
Reduced birth weight	50	283	50	283			283	197	1021	221
	DINP 41.5 %		*BBP 0.5 %*		*DEHP 1 %*			*DEP 0.5 % (or DMP 0.5 %)*		
Reduced testosterone	50	283	10	57	4.8	27	223	40	207	108
Reduced birth weight	50	283	50	283	46	260	282	197	1021	221

NOAEL = no observed adverse effect level, derived from PEC assessments of DEHP, DEP, DINP and BBP (NICNAS 2010; 2011; 2012; 2015); MOE = margin of exposure (i.e. NOAEL/EHD) (Section 7.1).

[a] DINP = primary plasticiser; BBP (as for DBP) = secondary plasticisers with the concentration assumed at maximum 0.5 %; DEHP at >1 % is banned from use in plastic products intended to be placed in the mouth by children aged ≤36 months (ACCC 2011 <http://www.productsafety.gov.au>). The calculations for toys are based on the MOE for each phthalate as a primary plasticiser, regardless of whether it is actually used in this way.

[b] For 'use of toys' scenario, the estimated human dose (EHD) or daily internal dose $D_{int,\ oral+dermal}$ = 169.93+7.04 = 176.97 µg/kg bw/day (Tables 5.1 and 5.2) for the total phthalate content of 43 % from combined oral and dermal exposure. Cumulative MOE = 1/[(42.5/MOE of DINP + 0.5/MOE of BBP)/43] or 1/[(41.5/MOE of DINP + 0.5/MOE of BBP + 1/MOE of DEHP)/43].

[c] DEP and DMP at >0.5 % are excluded from use in body lotion; DEHP is excluded from cosmetic use (SUSMP <http://www.comlaw.gov.au/Series/F2015L00128>). BBP are recommended for exclusion from cosmetic use, similarly to DEHP and DBP, based on the NICNAS PEC assessment of BBP.

[d] For 'use of cosmetics' scenario, the EHD or $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/day (Table 5.5 from the PEC assessment of DMP, NICNAS 2014) for DMP or DEP at 0.5 % from dermal exposure to body lotion.

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