Priority Existing Chemical Assessment Report No. 38

Australian Government
Department of Health
National Industrial Chemicals
Notification and Assessment Scheme

Di(methoxyethyl) phthalate

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
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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

2-ME	2-methoxyethanol
4-MP	4-methylpyrazole
ACCC	Australian Competition and Consumer Commission
AICS	Australian Inventory of Chemical Substances
atm	atmosphere
BBP	butylbenzyl phthalate
bw	body weight
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CHAP	Chronic Hazard Advisory Panel
CHIP	Chemical Hazard Information Profile
CIUCUS	Complication of Ingredients Used in Cosmetics in the United States
CosIng	Cosmetic Ingredients and Substances Database
CPSC	Consumer Products Safety Commission
d	day
DBP	dibutyl phthalate, di-n-butyl phthalate
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DINP	diisononyl phthalate
DMEP	di(methoxyethyl) phthalate
DMP	dimethyl phthalate
DnOP	di-n-octyl phthalate
DSL	Domestic Substances List
e.g.	*exempli gratia*, for example
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EGME	ethylene glycol monomethyl ether
EHD	estimated human dose
EPA	Environmental Protection Agency
ESIS	European Chemical Substances Information System
et al.	*et alii*, and others
EU	European Union
g	gram
GD	gestational day
GI	gastrointestinal tract
Hb	haemoglobin
HCT	haematocrit
HI	hazard index
HMW	high molecular weight
HPV	high production volume
hr	hour
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
i.e.	that is
INCI	International Nomenclature Cosmetic Ingredient Directory
INSL3	insulin-like factor 3 (Leydig cell)
IPCS	International Programme on Chemical Safety
ITAP	Initial Targeted Assessment Profile
IUPAC	International Union of Pure and Applied Chemistry
IUR	Inventory Update Report

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
MAA	methoxyacetic acid
MCL	mononuclear cell leukaemia
m-f	male-female
µg	microgram
mg	milligram
µL	microlitre
mL	millilitre
MMEP	monomethoxyethyl phthalate
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
PA	phthalic acid
PEC	Priority Existing Chemical
PND	postnatal day
ppm	parts per million
PVA	polyvinyl acetate
PVC	polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RTECS	Registry of Toxic Effects of Chemical Substances
SA/BW	surface area to body weight ratio
SCCP	Scientific Committee on Consumer Products
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SD	Sprague Dawley (rats)
SPIN	Substances in Preparations in Nordic Countries Database
StAR	Steroidogenic Acute Regulatory protein
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVHC	Substances of Very High Concern
US	United States
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, bis(2-methoxyethyl) ester (CAS No. 117-82-8), also known as di(methoxyethyl) phthalate (DMEP), 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 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 DMEP both directly and through migration and leaching from products;
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from DMEP exposure; and
- overseas regulatory activities including restrictions and review of the use of phthalates, including DMEP, in certain consumer products.

The purpose and scope of this PEC assessment is to determine the health risks to adults and children from the use of DMEP 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 DMEP indicate that DMEP is not manufactured in Australia or imported as a raw material. It is introduced into Australia only in finished products or articles and no information on the importation volume of DMEP is therefore available.

Uses

Information about specific concentrations of DMEP in toys is not available. The information collected by NICNAS indicates that DMEP may be used as a plasticiser (a substance added to make another material softer and more flexible) for toys, including inflatable water products, hoppers, play and exercise balls, at a concentration of up to 40 % (possibly in combination with other phthalates). In children's toys and childcare articles made from polyvinyl chloride (PVC), DMEP is unlikely to be found as the dominant (primary) phthalate plasticiser, as its molecular weight is equivalent to that of the commonly used secondary plasticiser dibutyl phthalate (DBP). Therefore, the chemical may 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). Consequently, the maximum concentration of 40 % in these toy products reported by the Australian industry for DMEP is not likely to be applicable to small mouthable toys made from PVC, where a mixed phthalate plasticiser (e.g. DINP+DMEP) can be assumed to be used at up to 43 %. Based on its physicochemical properties, in a mixed phthalate plasticiser DMEP is assumed to be used at a maximum concentration of 0.5 %.

Cosmetic uses of DMEP were not reported in Australia.

Internationally, DMEP has been reported to be used as a plasticiser in the production of nitrocellulose, acetyl cellulose, polyvinyl acetate (PVA), PVC and polyvinylidene chloride intended for contact with food or drink. DMEP is also used as a solvent and in pesticide products. There is no current overseas information available on the use of DMEP in children's toys and cosmetics.

Health effects

The collective results of all available studies for phthalates assessed by NICNAS to date suggest that DMEP is rapidly and almost completely absorbed following oral administration. The bioavailability of DMEP 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 absorption of inhaled DMEP are limited; therefore, a default bioavailability of 100 % is considered appropriate for the purposes of this assessment.

Following absorption, distribution of DMEP is widespread into tissues, including the placenta, but there is no evidence of accumulation in the body. DMEP is also rapidly metabolised and excreted in the urine, predominantly as metabolites such as monomethoxyethyl phthalate (MMEP), 2-methoxyethanol (2-ME) (also known as ethylene glycol monomethyl ether (EGME)), and methoxyacetic acid (MAA).

DMEP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans. Also, DMEP 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 DMEP in humans.

Toxic effects related to repeated DMEP exposure that are regarded as relevant to a human health risk assessment include haematotoxicity (anaemia), fertility (mediated by testicular toxicity) and developmental toxicity (reduced pup weight and embryolethality, particularly in male rats).

DMEP may alter endocrine function. Although there are uncertainties regarding the exact mechanism by which DMEP affects fertility, foetal metabolism, growth and development in rodents, its alcohol metabolites such as EGME and MAA are well-characterised reproductive and developmental toxicants. In the absence of more detailed information, the reproductive and developmental effects of DMEP are considered comparable between rats and humans if the exposure to DMEP is high and within a critical window of development.

For the systemic and developmental effects, the no observed adverse effect levels (NOAELs) of 33 and 20 mg/kg bw/d are derived for DMEP by applying a factor of three for the lowest observed adverse effect level (LOAEL) to NOAEL extrapolation, respectively.

For fertility-related effects, DMEP and DBP are considered likely to be equally potent taking into account their structural similarities, hazard classifications, and their similar reproductive toxicity profiles (such as reduced testes weight, testicular pathology and sperm abnormalities) observed in rodents, particularly at high doses. On this basis, the NOAEL of 10 mg/kg bw/d derived for the testicular toxicity effects of DBP is used for filling a data gap in this assessment.

Public exposure and health risk

In this assessment, public health risks from modelled DMEP exposure are assessed using a margin of exposure (MOE) approach for the following consumer application only:

- Use by children of toys and childcare articles.

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 of these products. The leaching (migration) rates of DMEP as a component of a mixed phthalate plasticiser (DINP+DMEP) under mouthing conditions are based on those measured in human volunteers for DINP—a common primary plasticiser found in toys. The migration rates of DMEP 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 or quantitative dermal absorption data for DINP or mixed phthalate plasticisers.

Studies conducted overseas indicate 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 DMEP 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 haematological, fertility-related and developmental effects associated with repeated combined handling and mouthing toys containing 0.5 % DMEP and 42.5 % DINP. The risk assessment, comparing the DMEP 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 DMEP for children, derives margins of exposure (MOEs) above 4500 (see Table 7.1) in both typical and worst-case scenarios of toy use, indicating an adequate safety margin or a negligible risk of these adverse health effects in children.

Cumulative risks may arise through exposure to multiple phthalates acting on the same biological targets from a range of sources, such as the simultaneous use of cosmetics and children's toys and childcare articles. The determination of risk from combined exposures to multiple phthalates will take into account any risk mitigation measures recommended in the PEC assessment for each phthalate. The estimated cumulative MOEs for the critical testicular toxicity and developmental effects of phthalates, including DMEP, indicate an adequate safety margin for children's exposure to toys and childcare articles, but support the recommendation to prohibit the cosmetic use of DMEP in Australia (i.e. listing DMEP in Appendix C of the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)).

Recommendations

This section provides the recommendations arising from the assessment of 1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester (CAS No. 117-82-8), also known as di(methoxyethyl) phthalate (DMEP). The recommendation is directed to the appropriate regulatory body with responsibilities for regulating chemicals in consumer products.

Recommendation 1 to the Delegate for Chemicals Scheduling

It is recommended that DMEP be considered for listing in **Appendix C** of the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP)) to limit the potential exposure of the public, including young children, to DMEP from 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 DMEP 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.'
- DMEP represents a hazardous phthalate for reproductive (testicular toxicity) and developmental toxicity (reduced pup weight and teratogenicity), and is considered to have an equal or greater toxicity profile compared with dibutyl phthalate (DBP)—the phthalate of similar molecular weight and structure. DBP also has the same hazard classification as DMEP in HSIS.
- DMEP's alcohol metabolites such as 2-methoxyethanol (2-ME) (also known as ethylene glycol monomethyl ether (EGME)) and methoxyacetic acid (MAA), are well-characterised reproductive and developmental toxicants.
- While there is no current indication of DMEP being used in cosmetics in Australia, DMEP might be considered as a possible substitute for other phthalates that are subject to regulation (e.g. diethylhexyl phthalate (DEHP)), based on its properties, functions and uses. In this case, exposure to DMEP, which is currently low, might increase. Possible substitution of DMEP for hazardous phthalates should be prevented by imposing a similar regulatory framework on all phthalates classified as toxic to reproduction (e.g. DBP, DEHP and DMEP)
- Reproductive toxicity induced by DMEP 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 DMEP is warranted, given the uncertainties regarding the market availability, possibilities for substitution, the severe and irreversible (teratogenic and fertility-based) 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 DMEP, specific circumstances include the following:

- additional information becoming available on the adverse health effects of DMEP;
- DMEP being used in toys and childcare articles at a concentration of >0.5 %;
- additional sources of potentially high public exposure to DMEP 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, bis(2-methoxyethyl) ester (CAS No. 117-82-8), also known as di(methoxyethyl) phthalate (DMEP), 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 DMEP in children's toys, childcare articles and cosmetics.

1.2 Objectives

The objectives of this assessment are to:

- characterise the properties of DMEP;
- determine the use and function of DMEP 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 DMEP from these applications;
- determine any adverse health effects associated with exposure to DMEP;
- characterise the risks to humans posed by exposure to DMEP 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 (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/or 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 and masks, mascara, nail polish.

1.3 Sources of information

Information for this assessment was obtained from various sources including the 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 DMEP) as PECs, importers and manufacturers of DMEP as a raw material for use in children's toys, childcare articles and cosmetics, and importers of finished cosmetic products containing DMEP, were required to apply for assessment and supply information on the use of DMEP in Australia. Unpublished information on the health effects of phthalates (including DMEP) 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 DMEP). Similarly, unpublished information on health effects and exposure to phthalates from migration and leaching from these articles was requested.

1.3.2 Literature review

For this assessment, the following key documents were reviewed:

Assessments by NICNAS:

- Existing Chemical hazard assessment report on bis(2-methoxyethyl) phthalate (DMEP) (NICNAS 2008a);
- *Phthalates Hazard Compendium*—A summary of physicochemical and human health hazard data for 24 ortho-phthalate chemicals (NICNAS 2008b);
- Priority Existing Chemical (PEC) assessment report on diethylhexyl phthalate (DEHP) (NICNAS 2010);
- Priority Existing Chemical (PEC) assessment report on diethyl phthalate (DEP) (NICNAS 2011);
- Priority Existing Chemical (PEC) assessment report on diisononyl phthalate (DINP) (NICNAS 2012);
- Priority Existing Chemical (PEC) assessment report on dibutyl phthalate (DBP) (NICNAS 2013); and
- Priority Existing Chemical (PEC) assessment report on dimethyl phthalate (DMP) (NICNAS 2014).

Assessments by international bodies:

- Chemical Hazard Information Profile (CHIP)—draft report on DMEP by the United States Environmental Protection Agency (US EPA 1985);
- Screening Assessment for the Challenge—human health risk assessment of DMEP by Health Canada (2009);
- Initial Targeted Assessment Profile (ITAP)—reproductive and developmental toxicity assessment of DMEP by the Organisation for Economic Co-operation and Development (OECD 2009);
- Toxicity review of two phthalates and one phthalate alternative for consideration by the Chronic Hazard Advisory Panel (CHAP), including DMEP, by the US Consumer Product Safety Commission staff (US CPSC 2011); and
- Survey of selected phthalates, including DMEP, by the Danish Environmental Protection Agency (Danish EPA 2013).

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 February 2014. 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 by NICNAS during all stages of preparation.

1.5 Applicants

Following the declaration of DMEP as a PEC, one organisation and one company applied for assessment of this chemical.

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. The applicants are as follows:

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

Sigma Aldrich Pty Ltd
12 Anella Avenue
CASTLE HILL NSW 2154

2 Background

2.1 International perspective

DMEP 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 (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 OECD (2004). Transitional phthalates were defined as those produced from alcohols with straight or branched carbon chain lengths of C4–6.

The ester side chain length and the molecular weight of DMEP are considered equivalent to those of DBP (C4) on the basis that the oxygen atom (O) is isoelectronic and isostructural with a methylene unit (CH_2). However, due to the methoxyethylene glycol functional group, DMEP is expected to have an equal or greater reproductive/developmental toxicity profile compared with DBP, due to alcohol metabolites such as 2-methoxyethanol (2-ME) (also known as ethylene glycol monomethyl ether (EGME)) and methoxyacetic acid (MAA) (see Section 6).

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 concentration (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 DMEP. Particular concerns exist when there is the potential for exposure to phthalates for young children from 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 developmental 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 (butylbenzyl phthalate)), and HMW phthalates (DINP, DIDP (diisodecyl phthalate) and DnOP (di-n-octyl phthalate)), for particular uses.

In the European Union (EU), the use of DMEP is banned in all accessible components of toys (at concentrations above the specific classification limit) and in cosmetic products on the basis that DMEP is classified as toxic to reproduction (i.e. Reprotoxic Substances Category 1B—Evidence of effects in animals—with the risk phrase H360Df 'May damage the unborn child. Suspected of damaging fertility.'—CosIng; Danish EPA 2013). Denmark has issued a national ban on the import, sale and use of all phthalates (including DMEP) in toys and childcare articles for children aged 0–3 years if the product contains more than 0.05 % w/w phthalates (Danish EPA 2013). Also, according to Danish EPA (2013), the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) is currently reviewing five phthalates, including DMEP, that are suspected of having endocrine disrupting effects, with the report expected to be released in early 2014.

DMEP is not registered with the European Chemicals Agency (ECHA) at the time of assessment, but is included in the Candidate List of Substances of Very High Concern (SVHC) for authorisation under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals). It is reported to no longer be produced in Europe and it may have already been replaced by alternatives, according to the Danish EPA (2013) and ECPI (2013), although the chemical is currently listed in the Chemical Book <http://www.chemicalbook.com/ProductIndex_EN.aspx>, and offered for sale by 62 suppliers globally.

In the United States of America (USA), DMEP is neither subject to any restrictions for use in children's toys, childcare articles or cosmetics, nor included in the US EPA's Phthalates Action Plan (US EPA 2012a revised). However, DMEP (together with DBP, DEHP, and others) is listed on the US EPA's Universe of Chemicals for potential endocrine disruptor screening and testing (US EPA 2012b). According to the US CPSC (2011), DMEP had not been sold commercially since 1991 with its production/importation volumes significantly decreasing; no surveys were conducted by the US EPA's Inventory Update Report (IUR) after 1998.

In Canada, DMEP is considered to be a high priority for further work following Canada's categorisation of approximately 23000 substances on its Domestic Substances List (DSL) (Health Canada 2008).

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 on 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 DMEP, were identified as currently or potentially in industrial use in Australia. DMEP, 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 use and hazards associated with 24 ortho-phthalates were summarised and compared (NICNAS 2008b).

DMEP 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.

DMEP is not listed in the Poisons Standard (SUSMP).

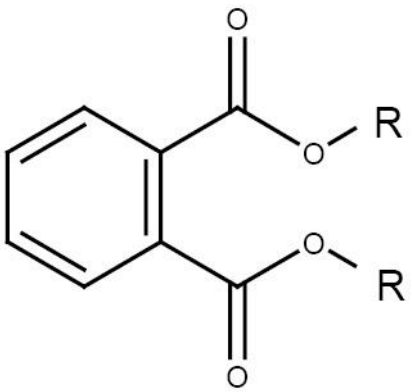
At the time of this PEC assessment, no other restrictions on the introduction (manufacture and/or import) or use of this chemical were identified in Australia. DMEP could, however, be substituted for already regulated phthalates (e.g. DEHP), and hence there is potential for widespread use of DMEP in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

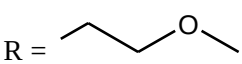
3 Identity and properties

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

3.1 Chemical identity

Chemical name:	1,2-benzenedicarboxylic acid, bis(2-methoxyethyl) ester
CAS No.:	117-82-8
Synonyms:	DMEP
	di(methoxyethyl) phthalate
	di(2-methoxyethyl) phthalate
	bis(methoxyethyl) phthalate
	bis(2-methoxyethyl) phthalate
	bis(methylglycol) phthalate
	dimethyl glycol phthalate
	methyl glycol phthalate
	phthalic acid, bis(2-methoxyethyl) ester
	1,2-benzenedicarboxylic acid, 1,2-bis(2-methoxyethyl) ester
	2-methoxyethyl 2-[(2-methoxyethyl)oxycarbonyl]benzoate (IUPAC)
Molecular formula:	$C_{14}H_{18}O_6$
Molecular weight:	MW 282.29
Purity/impurities:	≥99.5 %
Structural formula:	





3.2 Physical and chemical properties

Table 3.1: Summary of physicochemical properties (adopted from BAuA 2011; ChemIDplus; HSDB 2009)

Properties	Value
Physical state	Colourless oily liquid with slight odour
Boiling point	340 ºC
Freezing / Melting point	−45 ºC to −40 ºC
Density, kg/m^3 (20 ºC)	1160
Vapour pressure, kPa (25 ºC)	3×10^{-5}
Water solubility, g/L (25 ºC)	8.5
Partition co-efficient octanol/water (log K_{ow})	1.11
Henry's Law constant, atm m^3/mol (25 ºC)	2.81×10^{-13}
Flash point	>100 ºC (closed cup); 194 ºC (open cup)

DMEP is miscible with absolute alcohol, but insoluble in mineral oils (ChemIDplus; HSDB 2009).

Conversion factors based on 25 ºC and 1 atmosphere:

DMEP (MW 282.29)
1 ppm = 11.55 mg/m^3
1 mg/m^3 = 0.09 ppm

4 Manufacture, importation and use

4.1 Manufacture and importation

DMEP is introduced into Australia through importation in finished products or articles. There are no data from NICNAS calls for information indicating that the chemical is manufactured in Australia, or imported as a raw material or in mixtures for local formulation and processing.

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

4.2 Uses of DMEP

4.2.1 Uses in Australia

The following Australian industrial uses of DMEP were reported under NICNAS mandatory and/or voluntary calls for information:

- as a plasticiser for imported toys, including inflatable water products, hoppers, play and exercise balls (at a concentration of up to 40 %, possibly in combination with other phthalates).

No cosmetic uses were reported.

In children's toys and childcare articles made from polyvinyl chloride (PVC), DMEP is unlikely to be found as a dominant (primary) phthalate plasticiser, as its molecular weight is equivalent to that of DBP, a commonly used secondary plasticiser. Therefore, the chemical may 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). Consequently, the maximum concentration of 40 % in these toy products reported by the Australian industry for DMEP is not likely to be applicable to PVC small mouthable toys, where a mixed phthalate plasticiser, e.g. DINP+DMEP, is assumed at up to 43 %. Specific concentrations of DMEP in toys used in Australia are not available, and the types of non-PVC articles used as toys (inflatable water products, hoppers, play and exercise balls) in which DMEP is reported to be used are not typical mouthing articles.

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

4.2.2 Uses overseas

Worldwide annual production and/or importation volumes of DMEP were between 10 and 1000 tonnes in the EU with Denmark reporting approximately 70 tonnes per year during 2004–2008 (BAuA 2011; Danish EPA 2013). DMEP is listed as a 'low production volume chemical' under the European Chemical Substances Information System (ESIS). Given DMEP is not currently registered under REACH, the manufactured and/or imported volume should be less than one tonne per year, or there is no intention to market the substance in the EU (BAuA 2011; Danish EPA 2013). The US production/importation volumes of DMEP were between 4.54 and 227 tonnes in the US EPA's IUR surveys conducted every four years from 1990–1998 (US CPSC 2011). Currently, DMEP is listed in the *Chemical Book* and offered for sale by 62 suppliers, including nine Europe- and 12 US-based companies. No further information on the specific volumes of DMEP for either industrial or consumer applications is publicly available.

Internationally, DMEP has been reported to be used as a plasticiser in the production of nitrocellulose, acetyl cellulose, polyvinyl acetate (PVA), PVC and polyvinylidene chloride intended for use in packaging of food or drink; it gives these polymeric materials good light resistance. DMEP is also used as a solvent and in pesticide products (BAuA 2011; Danish EPA 2013; Health Canada 2009; OECD 2009).

The following uses or functions of DMEP have been identified in the:

- Substances in Preparations in Nordic Countries (SPIN) database in: adhesives, binding agents, fillers, construction materials, paints, lacquers, varnishes and process regulators.
- US National Library of Medicine's Haz-Map Database in: solvents, plasticisers (especially for cellulose acetate), moulding compositions, adhesives, laminating cements, and flash bulb lacquers.
- Galleria Chemica in: plasticisers and solvents for cellulose esters.

DMEP is not listed in the following databases:

- European Commission's Cosmetic Ingredients and Substances (CosIng) database;
- Personal Care Products Council's International Nomenclature Cosmetic Ingredient (INCI) dictionary;
- Personal Care Products Council's Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS 2011); and
- US National Library of Medicine's Household Products database.

There is no current information available overseas on the use of DMEP in children's toys and cosmetics.

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 indicates generally 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 physicochemical properties alter with increasing molecular weight and side chain length. As side chain length increases from one to 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 to 52 mPa•s for DINP and up to 190 mPa•s for ditridecyl phthalate (Eastman 2006).

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

Minimal information is available in published literature on the subject of 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, DIBP (diisobutyl phthalate—a possible substitute for DBP), DEHP, DINP and DIDP are likely to be present as traces and/or impurities leaching from plastic materials during production or storage (SCCP 2007). This information relates to use in perfume samples and there is no information available from which to extrapolate from perfumes to other cosmetics.

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

Therefore, while it is clear that phthalates can be considered as substitutable by other phthalates of similar properties, there are likely to be limits on the extent to which dissimilar phthalates can be used. DMEP and DBP have an equivalent molecular weight and structure (see Section 2) and thus DMEP is not likely to substitute for DINP—an HMW phthalate commonly used in PVC toys and childcare articles. DMEP is, however, more likely to substitute for DBP in any of its applications. In the absence of DMEP use data in the children's toys scenario, assumptions need to be made in modelling exposures. In this report, for example, migration or leaching rates reported for DINP are used to undertake an exposure assessment for DMEP as a secondary plasticiser in a mixed phthalate plasticiser (DINP+DMEP) in relation to uses in children's toys and childcare articles.

5 Public exposure

Although DMEP was declared a PEC for assessment of its use in children's toys, childcare articles and cosmetics, there is no evidence to suggest that DMEP is currently used in cosmetic products in Australia. However, there is a potential for DMEP to be used in cosmetics as a substitute for other phthalates (such as DBP) that have similar physical and toxicological properties. It is less likely that phthalates such as DMEP that have a 'carcinogenic, mutagenic, or toxic to reproduction' (CMR) hazard classification would be substituted for safer or less potent phthalates such as DEP—a common cosmetic ingredient. In addition, DMEP is banned in cosmetic products in the EU. Although Llompart et al. (2013) recently reported the detection of DMEP (12.6 µg/g) in 2/26 cosmetic and personal care products available locally in Spain, it is apparent that the chemical was not used intentionally as a cosmetic ingredient, but rather was present as traces and/or impurities. Furthermore, DMEP is not listed as a cosmetic ingredient in the CosIng nor INCI and CIUCUS databases (see Section 4.2).

- 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.

Thus, cosmetic use of DMEP is likely to be rare to non-existent. Consequently, assessment of public exposure to DMEP 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.

Public exposure to DMEP in this report is estimated only for the consumer application in the use of children's toys and childcare articles. Exposure estimates are derived to allow characterisation of the risks associated with this application of DMEP.

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 in exposure assessments; however, modelled data may be used if measured data are not available. The use of Australian data is 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 the 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. It is believed that this approach will 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 representing an average for the target population.

Exposure of children to DMEP from toys and childcare articles was estimated for both oral and dermal routes. Dermal exposure may occur during normal handling and oral exposure may occur through chewing, sucking and biting of these products, regardless of whether the products are intended to be mouthed. Inhalation exposure to DMEP from these products is considered negligible due to the low vapour pressure of the chemical.

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

Oral exposure was modelled by:

- estimating the highest plausible concentration of DMEP 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 DMEP (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 DMEP 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 DMEP is based on the assumption that the chemical completely substitutes for DBP (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 under 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+DMEP) and DMEP 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 hr/d and 2.2 hr/d, 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/mouthing of toys and articles determined by Chen (1998) are regarded as applicable for the typical and worse-case exposure estimates, i.e. 26.03 and 57.93 µg/cm^2/hr, respectively.
- The extractability data for DINP (measured at 43 % w/w of the articles studied by Chen (1998)) are also applicable for a mixed phthalate plasticiser comprising 0.5 % DMEP and 42.5 % DINP, i.e. 43 % of a mixed phthalate consisting of 1.16 % DMEP 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 by the oral route 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, %
BW = Body weight, kg

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

	Total phthalate $D_{int,oral}$ (µg/kg bw/d)	**DMEP[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 DMEP are derived by multiplying the internal doses for total phthalate by the proportion of DMEP (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+DMEP) and DMEP 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/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 hr/d and a reasonable worst-case contact time is 2.2 hr/d.
- Based on the weight of evidence, the mean dermal absorption rate of 0.24 µg/cm^2/hr 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+DMEP) given the lack of available migration rate data 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 % DMEP and 39.9 % DINP, i.e. 40.4 % of a mixed phthalate consisting of 1.24 % DMEP 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 male and female combined.
- The body parts of a child likely to be exposed during toys and childcare articles handling 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/d
R = Dermal absorption rate of the phthalate from toys, µg/cm^2/hr
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 DMEP from dermal exposure to toys and childcare articles in children

	Total phthalate $D_{int,dermal}$ (µg/kg bw/d)	DMEP[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 DMEP are derived by multiplying the internal doses for total phthalate by the proportion of DMEP (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 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

5.4 Biomonitoring data

Biomonitoring 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 2013). There is one study reporting the mean plasma levels of DMEP (male–female: 11.08–10.93 µg/L), which are comparable with those of DEHP (male–female: 11.51–10.67 µg/L), in a cohort of 153 Hong Kong citizens aged 16–63. The reported levels for DBP were 4.41–3.94 µg/L, DEP 2.27–2.16 µg/L, and DMP 2.60–2.65 µg/L (Wan et al. 2013). The authors suggested that 'the illegal and unexpected use of phthalates as food additives in China and the wide applications of phthalates in daily commodities may attribute to these high levels of phthalates', and the data therefore cannot be considered representative of exposures in Australia. It is not possible to determine the relative contribution of different exposure sources or routes directly from population biomonitoring data. Furthermore, biomonitoring data for DMEP exposures in the Australian general population or specific subpopulations are not available. For the purpose of this assessment, modelling is the most suitable approach in estimating DMEP exposures. The assumptions made in the scenarios used to calculate the exposure to DBP (NICNAS 2013) are also considered reasonable and applicable to DMEP on the basis that 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.

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 of the effects observed in animal studies to humans. The hazard characterisation of DMEP is based on the collective results of all available studies through analysing the weight of evidence and deducting 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 DMEP, 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 DMEP, and relevant analogue chemicals published up to February 2014. 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 DMEP. Although the ester side chain length and the molecular weight of DMEP are considered equivalent to those of DBP (C4), DMEP has a methoxyethylene glycol group metabolisable to 2-ME (or EGME) and MAA, and hence DMEP is expected to have equal or greater reproductive/developmental toxicity compared with DBP (see below).

6.1 Toxicokinetics

6.1.1 Absorption

Absorption by the oral route

No data are available on the absorption and bioavailability of orally administered DMEP. The oral bioavailability of the most studied phthalate, DEHP, appears to be higher in young 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 gastrointestinal (GI) tract (Varga & Csáky 1976*) have been suggested as the likely factors causing an increased absorption in young animals. However, for the purposes of this assessment, the bioavailability of DMEP through the oral route is assumed to be 100 % for both adults and children.

Absorption by the dermal route

When being applied to the depilated abdomen of guinea pigs, DMEP showed no evidence of absorption after 24 hours (Eastman Kodak 1985; US CPSC 2011). However, DMEP was reported to be slowly absorbed through human skin in an in vitro study with a steady state absorption rate of 8 µg/cm^2/hr (Eastman Kodak 1991*; US CPSC 2011). In another in vitro study, the steady state absorption rates were 12.8 and 2.4 µg/cm^2/hr for DEP (carbon chain length of 2 or C2) and DBP (C4) respectively (Scott et al. 1987; 1989 Errata). These results combined indicated that the dermal bioavailability of DMEP (~C4) in humans is estimated to be no lower than that of DBP, i.e. 5 % of the applied dose.

Absorption by the inhalation route

Quantitative information on inhalation absorption of DMEP is not available. Inhaled phthalate esters may 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.

6.1.2 Distribution

Intraperitoneal or intravenous injection of ^{14}C-DMEP into pregnant rats on gestational days (GD) 13–14 suggested a rapid transfer of unmetabolised DMEP to the foetus across the placenta (Parkhie et al. 1982; Campbell et al. 1984). Concentration of DMEP and its primary metabolite, monomethoxyethyl phthalate (MMEP), in the placenta was about four times greater than in the foetus, according to Campbell et al. (1984).

Based on the literature review and comparative studies on phthalate kinetics (Albro & Moore 1974; Elsisi et al. 1989; Kluwe 1982; NICNAS 2008b) and findings from the previous NICNAS PEC assessments for DMP and

DEP (LMW), DBP and DEHP (transitional) and DINP (HMW phthalate), distribution of phthalates in general or DMEP in particular is assumed to be widespread into tissues, including the placenta, after exposure with no evidence of accumulation.

6.1.3 Metabolism

Teratogenicity studies by Campbell et al. (1984) and Ritter et al. (1985) indicated that DMEP rapidly undergoes hydrolysis to MMEP and 2-ME (or EGME), followed by oxidation of the latter to MAA. A trace amount of phthalic acid (PA) was also identified from the metabolism of DMEP (Campbell et al. 1984). However, the rat foetus had little or no ability to hydrolyse DMEP to MMEP when compared with the maternal liver and placenta (Campbell et al. 1984).

6.1.4 Elimination and excretion

No data are available on the systemic elimination of DMEP. However, elimination from the placenta and foetus was shown to be rapid with almost 96 % being cleared between 45 minutes and four hours after intraperitoneal injection of 2.49 mmol/kg bw (or 702 mg/kw bw) (Campbell et al. 1984). Overall, it is considered that systemic elimination of DMEP is also rapid, as for other assessed phthalates (DMP, DEP, DBP, DEHP and DINP).

6.2 Acute toxicity

6.2.1 Acute oral and dermal toxicity

The available animal data indicate that DMEP exhibits low acute oral and dermal toxicity.

LD50 oral >2000 mg/kg bw in rats
LD50 dermal >2000 mg/kg bw in guinea pigs
(refer to NICNAS 2008a; RTECS 2012; US CPSC 2011 for further information).

6.2.2 Acute inhalation toxicity

The available animal data provide inadequate evidence concerning the acute inhalation toxicity of DMEP.

Rats survived exposures of 8.1 and 8.9 mg/L/6 hr, but all three rats died when the concentration was increased to 18.4 mg/L/6 hr (RTECS 2012; US EPA 1985).

6.3 Irritation and sensitisation

6.3.1 Skin irritation

The available data suggest that DMEP causes minimal skin irritation in rabbits and guinea pigs (Calley et al. 1966; Eastman Kodak 1985; HSDB 2009; Lawrence et al. 1975; RTECS 2012; refer to NICNAS 2008a; US CPSC 2011 for review).

6.3.2 Eye irritation

The available data suggest that DMEP causes minimal eye irritation in rabbits (Eastman Kodak 1985; HSDB 2009; Lawrence et al. 1975; RTECS 2012; refer to NICNAS 2008a; US CPSC 2011 for review).

6.3.3 Sensitisation

One available study (using standard procedure) in guinea pigs suggested that DMEP is not likely to be a skin sensitiser (Eastman Kodak 1985; refer to NICNAS 2008a; US CPSC 2011 for review).

6.4 Repeated dose toxicity

Mice injected intraperitoneally with DMEP (250 mg/kg bw/d) for six weeks exhibited some degree of weight gain retardation (although body weight was approximately equal in all treatment and control groups when the study ended), and decreased testes weight and testicular atrophy compared to controls. Haematology and relative weights of other organs were unaffected, but acute peritonitis, periportal hepatitis and extramedullary

haematopoiesis in the liver and spleen were found. Calley et al. (1996) considered that acute peritonitis was likely caused by peritoneal irritation due to repeated injections rather than being a direct toxic effect of DMEP.

In rabbits, repeated injections of DMEP (50 mg/kg bw until a minimum total dose level of 350 mg/kg bw) through a vein directly into the heart caused an increase in the respiration rate, but had no significant effect on blood pressure or electrocardiogram or electroencephalogram (Calley et al. 1966).

Following gavage exposure (12 treatments over 16 days) of DMEP (purity 78 %), food consumption and body weight gain, absolute kidney and liver weights, absolute and relative thymus and testes weights and levels of some liver enzymes and creatinine were reduced at 1000 mg/kg bw/d in rats. Atrophy of thymus and testes was also noted, together with moderate to severe histopathological changes in these organs. Decreases in red blood cells, haemoglobin (Hb) and haematocrit (HCT) were observed at both dose levels of 100 and 1000 mg/kg bw/d—being indications of slight anaemia—although changes in red blood cell counts did not reach statistical significance at the low dose. A systemic NOAEL could not be established from this study because the haematological changes were seen at the lowest dose tested (i.e. lowest observed adverse effect level (LOAEL) = 100 mg/kg bw/d) (Eastman Kodak 1985).

Considering that the slight but measurable DMEP-induced anaemia in rats after oral exposure is relevant to a human risk assessment, the NOAEL for systemic effects of DMEP is estimated to be approximately 33 mg/kg bw/d based on a factor of three for LOAEL to NOAEL extrapolation (ECETOC 2003).

6.5 Genotoxicity and carcinogenicity

In bacterial reverse mutation (Ames) tests, DMEP was positive in *Salmonella typhimurium* TA98 without activation, and negative in TA98 with activation, and TA100 with or without activation (NTP 1993).

In vivo, DMEP was positive in a dominant lethal test in mice (intraperitoneal injection of 0, 1.19, 1.79 or 2.38 mL/kg, approximately 1/3, 1/2 or 2/3 of the acute LD50 dose of 3.57 mL/kg). In this study, the apparent mutagenic effects of DMEP and DEHP (0, 12.78, 19.07, 25.56 mL/kg)—that were determined directly from the increased number of early foetal deaths and indirectly by the reduced number of implantations per pregnancy vs controls—were in parallel, particularly at the high doses (Singh et al. 1974). In view of these results and because phthalates including DEHP that show carcinogenic effects in animals are likely to act by a non-mutagenic mechanism (NICNAS 2008b), the measured DMEP positive effects are likely to be related to the findings discussed in Section 6.6 of this report (below), rather than being attributed to genotoxicity.

Studies on the carcinogenicity of DMEP are limited to a report by Lefaux (1968*, cited in Health Canada 2009; HSDB 2009) that states that neither pathological symptoms nor any lesions or anomalies were observed in male rats kept on diets containing 300, 500 or 900 mg/kg DMEP (approximately 15, 25 or 45 mg/kg bw/d) for 24 months. A further five generations of rats were investigated administered 300 mg/kg and three generations with 500 and 900 mg/kg diets. The weight of treated animals and their organs such as liver, kidneys, lungs, heart and brain showed no significant differences from controls. Reproduction was normal. No anomalies were found in parturition or nursing with female rats of various generations. No other information was available.

Across the carcinogenicity data for the 24 ortho-phthalates, mononuclear cell leukaemia (MCL) in rats and hepatocellular neoplasms in rats and mice were the most common tumour types. However, they are not regarded as relevant to humans on the basis that MCL has not been found in other mammalian species and has no direct comparable manifestations in humans; and liver tumours induced by potent phthalates such as DEHP are linked to peroxisome proliferation (NICNAS 2008b). Following DEHP exposure, Leydig cell tumours were also reported in rodents and as Leydig cell micronodules were commonly found in testicular biopsies from men with impaired spermatogenesis and reproductive hormone imbalances, they might originate through developmental toxicity (Holm et al. 2003). In addition, metabolites of DMEP such as EGME and MAA (see Section 6.1) have not been recognised as potential animal or human carcinogens (ECETOC 2005; WHO 2009; ECHA 2010; 2012), although they are associated with the teratogenicity of DMEP (see Section 6.6 of this report).

Overall, on the basis of weight of evidence (whether from carcinogenic mode of action of phthalates in general or metabolites of DMEP), the available data do not provide adequate evidence of carcinogenicity for DMEP in humans.

6.6 Reproductive toxicity

No human studies on reproductive and developmental toxicity are available for DMEP.

6.6.1 Effects related to fertility and sexual development

Rats exposed orally to ≥1000 mg/kg bw/d DMEP showed dose-related reductions in testes weight (Cassidy et al. 1983). The reduction at 1000 mg/kg bw/d was statistically significant after 12 doses over 16 days (Eastman Kodak 1985) but not after 11 consecutive doses (Cassidy et al. 1983). Relative testes weight reduction was also seen following daily injections of DMEP at 250 mg/kg bw/d for a period of 6 weeks (Calley et al. 1966). Atrophy of testes, seminiferous tubules and accessory sex organs, and degenerated sperm were also found at 1000 mg/kg bw/d (Eastman Kodak 1985) as well as increased abnormal sperm at ≥1500 mg/kg bw/d DMEP (Cassidy et al. 1983).

In a dominant lethal test—where male mice after a single intraperitoneal injection of DMEP at 0, 1.19, 1.79 or 2.38 mL/kg were mated with untreated females sequentially over a 12-week period—incidences of pregnancy, implantations per pregnancy and litter sizes were statistically significantly reduced at the high dose, indicating the antifertility effects of DMEP (Singh et al. 1974).

Overall, reproductive toxicity studies of DMEP in animals are limited, non-standard, and unable to provide a reasonable NOAEL for DMEP effects on fertility, testes or sexual development. However, they do support the current classification of DMEP as a Reproductive Toxicant Category 3 with the risk phrase R62 'Possible risk of impaired fertility' in the Hazardous Substances Information System (HSIS, Safe Work Australia).

6.6.2 Other foetal/developmental effects

Maternal administration of DMEP (LOAEL = 291 mg/kg bw/d) by single or repeated intraperitoneal injections within the critical time window (GD 5–15) was shown to cause severe embryo toxicity in rats. It was manifested reproducibly as statistically significant reductions in foetal weight and statistically significant increases in skeletal and/or foetal abnormalities, resorptions and deaths (Campbell et al. 1984; Parkhie et al. 1982; Ritter et al. 1985; Singh et al. 1974). Metabolites of DMEP such as EGME and MAA (but not monoester MMEP) were also highly teratogenic at equivalent molar dosages compared with DMEP. The effects of DMEP and these metabolites were not differentiated clearly from each other in rats (Campbell et al. 1984; Ritter et al. 1985). The equivalence of results for DMEP with EGME and MAA, and the lack of effects for MMEP, indicate that the metabolites, EGME and MAA, are the active species for these effects rather than the phthalate monoester, MMEP. The phthalate monoester is implicated in the reproductive/developmental toxicity of DBP, which causes developmental abnormalities, particularly in the testes, rather than lethality (NICNAS 2013).

Gavage administration of DMEP in dams during GD 5–15 resulted in 100 % embryolethality at 600 mg/kg bw/d; increased skeletal abnormalities, increased foetal resorptions and deaths at ≥180 mg/kg bw/d and reduced pup weight and pup survival from postnatal day (PND) 1–5 at ≥60 mg/kg bw/d, the lowest dose tested. Maternal toxicity evaluated by reduced food consumption and body weight gain was observed at 600 mg/kg bw/d, and therefore the maternal NOAEL was 180 mg/kg bw/d (Krasavage 1991*; Health Canada 2009; OECD 2009).

Overall, teratogenicity studies of DMEP in animals are limited and non-standard. The lowest observed adverse effect level (LOAEL) was at 60 mg/kg bw/d (the lowest dose tested), and therefore a NOAEL for DMEP effects on foetal growth and development could not be determined from these studies. The NOAEL must be below 60 mg/kg bw/d. A NOAEL can be estimated as approximately 20 mg/kg bw/d based on a factor of three for LOAEL (60 mg/kg bw/d) to NOAEL extrapolation (ECETOC 2003). Metabolites of DMEP such as EGME and MAA are well-characterised teratogenic and developmental toxicants (ECETOC 2005; Hays et al. 2000; Health Canada 2009; WHO 2009). Collectively, the available data support the current classification of DMEP as a Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child' in the Hazardous Substances Information System (HSIS, Safe Work Australia).

6.6.3 Determination of NOAELs for fertility-related effects (testicular toxicity)

The available data support the current classifications of DMEP in HSIS (Safe Work Australia):

- Reproductive Toxicant Category 3 with the risk phrase R62 'Possible risk of impaired fertility'.
- Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child'.

Reviews of EGME/MMA (either as a group of glycol ethers or in conjunction with DMEP) by Health Canada (2009), ECETOC (2005), ECHA (2010; 2012), and NICNAS (2008b) also support their current classifications in HSIS:

- Reproductive Toxicant Category 2 with the risk phrase R60 'May impair fertility'.
- Reproductive Toxicant Category 2 with the risk phrase R61 'May cause harm to the unborn child'.

In addition, DMEP and its metabolites EGME/MAA share the same key adverse health effects, including not only fertility (mediated by testicular toxicity) and developmental toxicity (teratogenicity) but also haematotoxic effects (see ECETOC 2005; WHO 2009 for review of EGME/MAA). The World Health Organisation (WHO) (2009), in the Concise International Chemical Assessment Document (CICAD) 67, established no observed adverse effect concentrations (NOAECs) for haematotoxic effects and testicular toxicity of EGME (1.7 mg/m^3 in humans and 32 mg/m^3 in laboratory animals, respectively) based on repeated inhalation exposure. A conversion between the toxicity reference values of NOAEC and NOAEL (for repeated oral/dermal exposure) is not available. However, the relative potency of EGME on these key adverse health effects is considered applicable to DMEP, and hence the NOAEL for the testicular toxicity of DMEP (due to the contribution of EGME) is expected to be greater than 33 mg kg bw/d—the NOAEL for haematotoxicity (see Section 6.4 above).

As previously discussed, DMEP has close structural similarity to the reproductively toxic phthalate, DBP. They have almost identical molecular weights and the oxygen atom (O) in the side chain of DMEP is structurally equivalent to a methylene (CH_2) unit in the side chain of DBP. They also have the same hazard classifications in HSIS. On this basis, DMEP is expected to also show the more subtle testicular effects (reduced testes weight, testicular pathology and sperm abnormalities) associated with DBP. The available data on DMEP do not allow this to be examined because, at the high doses used in the available studies, the more indiscriminate toxicity (testicular atrophy and embryolethality) associated with the EGME metabolite is likely to obscure the histological manifestations of DBP-like toxicity, and lower dose studies and measurements of pre-apical toxicity markers such as StAR (an androgen synthesis gene) and INSL3 (insulin-like factor 3—a foetal Leydig cell product critical for testes descent) have not been reported.

For DBP, the NOAEL for testicular toxicity is 10 mg/kg bw/d (NICNAS 2013). This can be assumed to be relevant also for phthalate monoester-based toxicity of DMEP. The NOAEL for phthalate monoester-based toxicity is therefore lower than that derived from the EGME-mediated toxicity and will be taken forward for risk characterisation.

6.6.4 Mode of action for reproductive/developmental toxicity endpoints and relevance to humans

DMEP showed no oestrogenic activity in a recombinant yeast assay, which is a similar result to those for phthalates in general including DBP and DEHP (Harris et al. 1997). There is a postulated analogy in rats between phthalate-induced testicular damage associated with reduced zinc in testes and DMEP-induced foetal anomalies associated with decreased zinc in the foetus. However, unlike monoester metabolites of DBP and DEHP, the MMEP metabolite of DMEP was not considered an active species for reproductive/developmental toxicity in rodents (Parkhie et al. 1982)

Yonemoto et al. (1984) demonstrated in vitro that the teratogenicity of DMEP was due to MAA (the proximate embryotoxin/teratogen) only because a similar pattern of foetal abnormalities was observed in vivo when dams were injected with 2.49 mM MAA/kg bw on GD 10, and in vitro when 9.5-day rat embryos were cultured with ≥2 mM MAA for 46 hrs, together with no effects seen in cultures of DMEP or any of its other metabolites. Co-administration of EGME with 4-methylpyrazole (4-MP, an alcohol dehydrogenase inhibitor) also provided significant protection against the teratogenic effects of EGME, by inhibiting the oxidation of EGME to MAA (Ritter et al. 1985). Therefore, on an equimolar dosage basis, DMEP was determined to be equally potent to its metabolites EGME and MAA, with their teratogenic effects in rats being strikingly similar (Campbell et al. 1984; Ritter et al. 1985).

An alternate mode of action primarily involves the phthalate monoester. DMEP has been shown to impair fertility (reduced testes weight, testicular atrophy, and sperm abnormalities) and cause foetal abnormalities and death in experimental animals, particularly at high doses, similar to DEHP (the well-studied potent phthalate). Therefore, the plausible mode of action of phthalates involving alterations of endocrine function is considered applicable to DMEP. This is consistent with the inclusion of DMEP (together with DBP, DEHP and others) in the *Universe of Chemicals* list for potential endocrine disruptor screening and testing (US EPA 2012b) and in

the review of five phthalates suspected of having endocrine disrupting effect by SCENIHR (see Section 2.1). Overall, whether considering the mode of action of phthalates in general or of EGME/MAA (see NICNAS 2008b; ECETOC 2005; WHO 2009 for review) there are uncertainties regarding the exact mechanism of DMEP action on fertility, foetal metabolism, growth and development in rodents. In the absence of more detailed information, the mode of action for DMEP on fertility-related and developmental effects is considered comparable between rats and humans if the exposure to DMEP is high and within a critical window of development. In addition, given the severity of harm from exposure to DMEP, these adverse health effects of DMEP observed in animal studies are regarded as relevant to a human risk assessment.

6.7 Summary

The collective results of all available studies for phthalates assessed by NICNAS to date suggest that DMEP 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 by dermal absorption is unlikely to exceed 5 % in humans (adults or children). Data on DMEP absorption by the inhalation 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 DMEP is widespread into tissues, including the placenta, but there is no evidence of accumulation in the body. DMEP is also rapidly metabolised and excreted in the urine, predominantly as metabolites such as MMEP, EGME, and MAA.

DMEP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans. Also, DMEP 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 DMEP in humans.

Toxic effects related to repeated DMEP exposure that are regarded as relevant to a human health risk assessment include haematotoxicity (anaemia), fertility (mediated by testicular toxicity) and developmental toxicity (reduced pup weight and embryolethality, particularly in male rats).

For the systemic and developmental effects, the NOAELs of 33 and 20 mg/kg bw/d are derived for DMEP by applying a factor of three for the LOAEL to NOAEL extrapolation, respectively.

For fertility-related effects, DMEP and DBP are considered likely to be equally potent taking into account their structural similarities, hazard classifications, and similar reproductive toxicity profiles (such as reduced testes weight, testicular pathology and sperm abnormalities) observed in rodents, particularly at high doses. On this basis, the NOAEL of 10 mg/kg bw/d derived for the testicular toxicity effects of DBP is used for filling a data gap in this assessment.

Table 6.1 lists the critical effects for DMEP (including data gap filling from DBP), the specific effects observed and the effect levels selected for risk characterisation.

Table 6.1: Endpoints selected for risk characterisation of DMEP

Toxicity	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) and effects	Species and age at treatment	Reference
Systemic effects (anaemia)	33[a]	100: haematological changes	Rat, Adults	Eastman Kodak 1985
Fertility-related effects (testicular toxicity)	10[b]	50: ↓ testosterone on GD 19	Rat, SD Foetuses	Lehmann et al. 2004; NICNAS 2013
Developmental effects (reduced pup weight)	20[a]	60: ↓ pup weight	Rat, SD Adults	Krasavage 1991*; Health Canada 2009

↓ = decreased; GD = gestational day; NOAEL = no observed adverse effect level; LOAEL = low observed adverse effect level; SD = Sprague Dawley.
[a] Extrapolated from LOAEL.
[b] Read-across from DBP.

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 DMEP exposure through use of toys and childcare articles for children.

7.2 Risk estimates

7.2.1 Estimation of MOE for children from use of toys and childcare articles

Risk estimates take into account the likelihood for adverse effects on haematology 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 DMEP 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 DMEP from use of toys and childcare articles

Toxicity	NOAEL (mg/kg bw/d)	MOE for typical exposure scenario	MOE for worst-case exposure scenario
Systemic effects (anaemia)	33	94000	16000
Fertility-related effects (testicular toxicity)	10	28500	4500
Developmental effects (reduced pup weight)	20	57000	9000

The risk estimates for the toxicity effects of DMEP on haematological and reproductive/developmental systems for both typical and worst-case exposure scenarios for toys used by children derive MOEs ≥4500 (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 DMEP arise mainly from inadequate data and include the:

- absence of Australian-specific data on DMEP 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 DMEP 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 DMEP in children following repeated exposure.

Areas of concern

The risk estimates above do not indicate particular areas of concern from exposure of children to DMEP by handling and mouthing of toys or childcare articles. Concern would arise if DMEP is used as a sole plasticiser in toys under the same conditions as DINP (NICNAS 2012), where the MOE for the worst-case exposure scenario would be 57, i.e. below 100.

It should be noted that DMEP 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 DMEP 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;
- the combination of the two exposure scenarios considered in this assessment.

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

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

There are currently no restrictions on the use of DMEP 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 DMEP content in children's toys.

In Australia, DMEP was identified as being in use, or with the potential for use, in children's toys and childcare articles including inflatable water products, hoppers, play and exercise balls, although these are not typical mouthing articles. One company specified that DMEP content in imported toys for adults and children is up to 40 % (possibly in combination with other phthalates).

8.2 Public health risk standards—cosmetics

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

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

Labelling

There are currently no specific labelling requirements for consumer goods that contain DMEP. 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 DMEP be considered for listing in Appendix C of the Poison's Standard (SUSMP) to limit the potential exposure of the public, including young children, to DMEP from possible use in cosmetics.

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 each of the two endpoints (fertility-related and developmental effects) considered relevant to DMEP 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:

$$MOE_{cumulative} = 1/(1/MOE_1 + 1/MOE_2 + \ldots + 1/MOE_n)$$

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.

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

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

An example of the calculation can be given for combined or additive developmental toxicity (reduced pup weight) of DINP + DMEP in toys and DEP in cosmetics. For this endpoint, DMEP and DINP (NOAEL = 20 and 50 mg/kg bw/d, respectively) are more potent than that of DEP (NOAEL = 197 mg/kg bw/d). Hence, the MOE for DMEP is 113 and DINP (in toys) is 283, compared with 1113 (in toys) and 1021 for DEP (in cosmetics), using the relevant exposure estimates (EHD) for a six-month-old infant (see below):

- $D_{int,\ oral+dermal}$ = 169.93 + 7.04 = 176.97 µg/kg bw/d (Tables 5.1 and 5.2) for the total phthalate (DINP+DMEP) content of 43 % from combined oral and dermal exposure.
- $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/d (Table 5.5 from PEC assessment of DMP, NICNAS 2013) 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:

  MOE cumulative = 1/[(42.5/MOE of DINP + 0.5/MOE of DMEP)/43] or

  1/[(41.5/MOE of DINP + 0.5/MOE of DMEP + 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

  MOE cumulative = NOAEL/EHD.

- For combined scenario:

  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 reproductive/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

Toxicity	Use of multiple phthalates[a] in children's toy and childcare articles (a mixed phthalate plasticiser 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 %		*DMEP 0.5 %*					*DEP 0.5 % (or DMP 0.5 %)*		
Fertility-related	50	283	10	57			270	40	207	117
Developmental	50	283	20	113			278	197	1021	218
	DINP 41.5 %		*DMEP 0.5 %*		*DEHP 1 %*			*DEP 0.5 % (or DMP 0.5 %)*		
Fertility-related	50	283	10	57	4.8	27	223	40	207	108
Developmental	50	283	20	113	46	260	277	197	1021	218

NOAEL = no observed adverse effect level, derived from PEC assessments of DEHP, DEP, DINP and DMEP (NICNAS 2010; 2011; 2012; 2014); MOE = margin of exposure (i.e. NOAEL/EHD) (Section 7.1).

[a] DINP = primary plasticiser; DMEP (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>).

[b] For 'use of toys' scenario, the estimated human dose (EHD) or $D_{int,\ oral+dermal}$ = 169.93+7.04 = 176.97 µg/kg bw/d (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 DMEP)/43] or 1/[(41.5/MOE of DINP + 0.5/MOE of DMEP + 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/Details/F2012L01685/Download>). DBP and DMEP are recommended for exclusion from cosmetic use, similarly to DEHP, based on the NICNAS PEC assessment of DBP and DMEP.

[d] For 'use of cosmetics' scenario, the EHD or $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/d (Table 5.5 from the PEC assessment of DMP, NICNAS 2013) for DEP (or DMP) at 0.5 % from dermal exposure to body lotion.

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