Priority Existing Chemical Assessment Report No. 37

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

Dimethyl 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 in conjunction with the Australian Government Department of the Environment, which carries out the environmental assessment for NICNAS.

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.

This priority existing chemical report has been prepared by 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 PEC 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. Hard copies are available (free) by contacting NICNAS at:

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

Contents

Acronyms and glossary

ACCC	Australian Competition and Consumer Commission
AGD	anogenital distance
AGI	anogenital index
AICS	Australian Inventory of Chemical Substances
BBP	butylbenzyl phthalate
bw	body weight
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
cf.	*confer*, compare
CHMS	Canadian Health Measures Survey
CIR	Cosmetic Ingredient Review
COLIPA	European Cosmetic Toiletry and Perfumery Association (Cosmetics Europe)
CosIng	Cosmetic Ingredients and Substances Database
CPSC	Consumer Products Safety Commission
CSTEE	Scientific Committee on Toxicity, Ecotoxicity and the Environment
d	day
DBP	dibutyl phthalate, di-n-butyl phthalate
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DINP	diisononyl phthalate
DMP	dimethyl phthalate
DNA	deoxyribonucleic acid
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
EHD	estimated human dose
ESIS	European Chemical Substances Information System
et al.	*et alii*, and others
etc.	*et cetera*, and so forth, and so on
EU	European Union
F0	parental generation
F1	first filial/offspring generation
F2	second filial/offspring generation
g	gram
GD	gestational day
GI	gastrointestinal
Hb	haemoglobin
HCT	haematocrit
hER	human oestrogen receptor
HMW	high molecular weight
HPV	high production volume
hr	hour
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
i.e.	that is
ICCA	International Council of Chemical Associations
IGHRC	Interdepartmental Group on Health Risks from Chemicals

INCI	International Nomenclature Cosmetic Ingredient Directory
IPCS	International Programme on Chemical Safety
IUCLID	International Uniform ChemicaL Information Database
kg	kilogram
L	litre
LD50	median lethal dose
LH	luteinizing hormone
LMW	low molecular weight
LOAEL	lowest observed adverse effect level
LOD	limit of detection
m^3	cubic metre
MAMA	Methods Advancement for Milk Analysis study
MEHP	monoethylhexyl phthalate
MEP	monoethyl phthalate
m-f	male-female
µg	microgram
mg	milligram
MIBP	monoisobutyl phthalate
mL	millilitre
MMP	monomethyl phthalate
mo	month
MoBa	Mother and Child cohort
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
PVC	polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SA/BW	surface area to body weight ratio
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SD	Sprague Dawley (rats)
SPIN	Substances in Preparations in Nordic Countries Database
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVHC	Substances of Very High Concern
TWA	time weighted average
US EPA	United States Environmental Protection Agency
USA	United States of America
vs	*versus*, against
w/w	weight/weight
WHO	World Health Organization
yr	year

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

Dimethyl phthalate (DMP) (CAS No. 131-11-3) was declared as 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, including DMP, as solvents and plasticisers in industrial and consumer products;
- consumer products such as soft plastic articles and cosmetics being potentially significant sources of repeated and long-term exposure of the public to DMP through migration and leaching from products;
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from DMP exposure; and
- current overseas activities including reassessment and review of the use of phthalates, including DMP, 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 DMP 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 DMP suggest that the total volume of DMP imported annually to Australia for industrial uses is in the range of 1000–2000 tonnes. In 2006, the amount of DMP reported for uses in children's toys, childcare articles and cosmetics with the potential widespread public exposure was 10 tonnes or less. For cosmetic applications, DMP is imported as a raw material (or in mixtures) for local formulation (60 % of imported volume) and in finished (ready-to-use) products (40 % of imported volume). Manufacture of DMP in Australia as a raw material was not reported.

Uses

The information collected by NICNAS indicates that uses of DMP in Australia are mainly as solvents in the mining industry for mineral recovery, in the manufacture of adhesives, fibreglass, automotive plastics, surface coatings, and in various textile wet processing products, with a small proportion in children's toys and cosmetics. Concentrations of DMP in domestic detergents, cosmetics, perfumes and personal care products are highly variable and range from 0.00004 % to 34 % (in combination with its analogue diethyl phthalate (DEP)). In polyvinyl chloride (PVC) children's toys and childcare articles, DMP—a low molecular weight (LMW) phthalate—is not found as the dominant phthalate plasticiser, but may be used in conjunction with another plasticiser as a secondary plasticiser or occur as a minor contaminant of other phthalates, including diethylhexyl phthalate (DEHP) or diisononyl phthalate (DINP). Specific concentrations of DMP in children's toys are not available. Based on its physicochemical properties, DMP is assumed to be used in a mixed phthalate plasticiser at a maximum concentration of 0.5 %.

International sources report that DMP is used as a fragrance ingredient in cosmetics, domestic and personal care products, as a solvent and plasticiser for cellulose acetate compositions, and in insect repellents, lacquers, paints, plastics and rubbers.

Health effects

DMP is rapidly and almost completely absorbed following oral administration. The bioavailability via the oral route is assessed to be 100 % for both adults and children. Bioavailability via dermal absorption is not likely to exceed 10 % in humans. Data on DMP absorption via the inhalation route are limited; a default bioavailability of 100 % is considered appropriate for this route.

Tissue distribution of DMP is widespread including to breast milk and the placenta, but there is no evidence of accumulation. DMP is also rapidly metabolised and excreted, predominantly as a metabolite, monomethyl phthalate (MMP), via the urine.

DMP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans or to have eye or skin irritation, or skin sensitising potential in humans.

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

Toxic effects related to repeated DMP exposure that are regarded as relevant to a human health risk assessment include those in the liver and in the reproductive system, particularly in male rats. Similar effects are observed in rodents exposed to the structurally related phthalate, DEP, at comparable doses (NICNAS 2011).

There is insufficient information to examine the mode of action of DMP on male reproductive tract development and sexual function. Collectively considering the in vitro and in vivo findings with LMW phthalates (refer to NICNAS 2011 for DEP), the assessed transitional (DEHP, NICNAS 2010) and high molecular weight (HMW) phthalates (DINP, NICNAS 2012), it appears that direct binding to oestrogen or androgen receptors is not the likely mode of action for phthalates to mediate their effects on testes and testicular hormones. The available human data are limited and do not provide sufficient evidence for a causal relationship between exposure to DMP or DEP and possible adverse health effects. There are also uncertainties regarding the exact mechanism of DMP or DEP action on developmental and fertility-related parameters in rodents, although the mechanism appears to involve alterations of endocrine function. In the absence of more detailed information, the mode of action for DMP (read-across from a structurally related phthalate) and DEP effects on testosterone production, pup weight and onset of development are considered to be parallel in rats and humans if the exposure to DMP or DEP is high and within a critical window of development.

Therefore, for the systemic organ effects, by applying the LMW phthalate category approach and read-across from DEP data, a no observed adverse effect level (NOAEL) of 150 mg/kg bw/d is derived for DMP based on increased liver weight at 750 mg/kg bw/d (Brown et al. 1978).

Similarly, evaluations of the potential toxicity of DMP and DEP to the male rat reproductive system have consistently found no effect on testis weight or testis atrophy at oral doses of ≤1000 mg/kg bw/d. Both also did not alter sexual differentiation such as decreased anogenital distance (AGD), increased nipple retention or testicular pathology at ≤750 mg/kg bw/d, as commonly noted with C4–6 transitional phthalates. However, reduced testosterone in the testes and/or in serum have been reported with DMP and DEP as well as with the transitional (DEHP) and HMW (DINP) phthalates of various potencies. For DEP, the increased incidence of abnormal and tailless sperm in the parental (F0) and first offspring (F1) generations (which did not affect fertility outcomes) was statistically significant and dose-dependent. Reduced pup weight and developmental delay were also observed with DEP and certain other phthalates (e.g. DEP at ~1000 mg/kg bw/d cf. DINP at ~100 mg/kg bw/d). On the basis of read-cross and trend analysis of the assessed phthalate data, a two-generation dietary study in rats by Fujii et al. (2005) is considered appropriate for filling data gaps by identifying a NOAEL of 40 mg/kg bw/d and 197 mg/kg bw/d based on the fertility-related and developmental effects of DMP at higher doses, respectively.

Public exposure and health risk

In this assessment, public health risks from modelled DMP exposure are assessed using a margin of exposure (MOE) approach for two exposure scenarios:

1. Use of toys and childcare articles by children; and
2. Use of cosmetic products by the general population.

The scenario involving children's use of toys considered routes of exposure including 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 DMP as a component of a mixed phthalate plasticiser (DINP+DMP) under mouthing conditions are based on those measured in human volunteers for DINP—a common primary plasticiser found in toys. The migration rates of DMP from plasticised PVC through the human skin are estimated using the rates of DEHP (another common primary plasticiser) migrating from PVC film through the rat skin given the lack of 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 of toys is low for DMP given the low acute toxicity of the chemical, its low skin and eye irritation potential and the absence of skin sensitising potential.

The long-term health risks for children include potential liver and reproductive and/or developmental effects associated with repeated combined handling and mouthing of toys containing 0.5 % DMP and 42.5 % DINP. The risk assessment, comparing the DMP dose at which there is no observed adverse effect on target organs and/or systems in experimental animals (the 'no observed adverse effect level', or NOAEL) with the estimated human dose (EHD) of DMP for children, derives margins of exposure (MOEs) above 10000 in both typical and worst-case scenarios of toy use, indicating an adequate safety margin or a low risk of these adverse health effects in children.

For the scenario involving the use of cosmetics, the main route of exposure is through dermal contact. Inhalation exposure is also possible from application of aerosol products. Current information does not indicate use of phthalates in products most prone to incidental oral ingestion such as toothpastes, mouthwashes or lipsticks. In the absence of specific Australian data, a reasonable worst-case exposure scenario of daily use of multiple cosmetic products is derived from reported European use patterns.

The risk of adverse acute effects for consumers exposed to DMP through cosmetics is low given the low acute toxicity of the chemical, its low skin and eye irritation potential and the absence of skin sensitising potential.

Assessment of the long-term health risks for DMP through repeated use, especially of leave-on cosmetic products, derives MOEs above 100, indicating a low risk of the potential liver and reproductive toxicity in the general population from simultaneous use of multiple cosmetic products containing DMP at the current reported or likely levels.

As body lotion could be applied repeatedly on large areas of the body of infants or young children, the risk from use of body lotions containing DMP is also evaluated for the three different age groups of children (newborn, six and 12 months). Using the conservative NOAEL of 40 mg/kg bw/d for reproductive effects of DMP, the MOEs calculated are also found to be above 100 for these subgroups of the population indicating a low risk at the current reported or likely levels in Australia.

Cumulative risks due to combined exposures can arise 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 PEC assessment for each phthalate. The estimated cumulative MOEs for the critical reproductive effects of phthalates including DMP indicate an adequate safety margin in children and are supportive of the current prohibition of the use of DMP at >0.5 % in body lotion (SUSMP).

Recommendations

No recommendation to amend the existing regulatory controls is required based on the findings of this assessment. Current risk management measures are considered adequate to protect the Australian population from use of DMP in children's toys, childcare articles and cosmetics provided that all requirements are met under the poisons legislation as adopted by the relevant state or territory.

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 DMP, specific circumstances include the following:

- additional information becoming available on the adverse health effects of DMP;
- additional information or events that change the assumptions in estimating the exposures and risks of DMP in this assessment; or
- additional sources of public exposure to DMP giving rise to similar levels as those found in the cosmetic use scenario 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 commit an offence under this Act.

1 Introduction

1.1 Declaration

Dimethyl phthalate (DMP) (CAS No. 131-11-3) was one of nine phthalate chemicals declared as 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 DMP in children's toys, childcare articles and cosmetics.

1.2 Objectives

The objectives of this assessment are to:

- characterise the properties of DMP;
- determine the use and function of DMP 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 DMP from these applications;
- determine any adverse health effects associated with exposure to DMP;
- characterise the risks to humans posed by exposure to DMP 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 as defined below:

- 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, 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 the 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 on the importation and/or manufacture of phthalates as raw materials and information on products imported or manufactured containing phthalates were requested from industry in Australia.

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

Assessments by international bodies:

- Toxicity profile for dimethyl phthalate by BIBRA Information Services Ltd (BIBRA 1994)
- International Uniform ChemicaL Information Database (IUCLID) dataset on dimethyl phthalate by the European Chemicals Bureau (ECB 2000)
- Annual review of cosmetic ingredient safety assessments–2002/2003 by the Cosmetic Ingredient Review Expert Panel (CIR 2005)
- Opinion on phthalates in cosmetic products by the Scientific Committee on Consumer Products (SCCP 2007)
- Toxicity review for dimethyl phthalate by the US Consumer Product Safety Commission (US CPSC 2011)

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 September 2013.

All references, except those marked with an asterisk (*), were reviewed for the purposes of this assessment. Those references marked with an asterisk were not reviewed but 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 DMP as a PEC, one organisation and four companies 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 correction and variation stages of the PEC consultation process. The applicants are as follows:

Drom International Pty Ltd
Suite 2, 1 Maitland Place
BAULKHAM HILLS NSW 2153

International Flavours & Fragrances Australia Pty Ltd
310 Dandenong–Frankston Road
DANDENONG VIC 3175

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

Sigma Aldrich Pty Ltd
12 Anella Avenue
CASTLE HILL NSW 2154

Symrise Pty Ltd
168 South Creek Road
DEE WHY NSW 2099

2 Background

2.1 International perspective

Dimethyl phthalate (DMP) 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 Organisation for Economic Co-operation and Development (OECD 2004). Transitional phthalates were defined as those produced from alcohols with straight or branched carbon chain lengths of C4–6.

On the basis of the ester side chain length, DMP is considered a LMW phthalate (as is diethyl phthalate (DEP)) (NICNAS 2011).

The physicochemical properties of phthalates that impart usefulness as plasticisers also permit their migration and leaching from polymer matrices. Some phthalates such as DEHP (diethylhexyl phthalate) and DINP (diisononyl phthalate) 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 DMP. Particular concerns exist when there is the potential for exposure of young children from toys and childcare articles or for prolonged exposure of general population through cosmetic uses.

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 (dibutyl phthalate) and BBP (butylbenzyl phthalate)), and HMW phthalates (DINP, DIDP (diisodecyl phthalate) and DnOP (di-n-octyl phthalate)), for particular uses.

There are no regulations in the European Union (EU) that restrict the use of DMP in children's toys and childcare articles. However, regulatory action has been taken in 1999–2001 in several EU countries (e.g. Austria, Denmark, France, Germany, Italy, Sweden, etc.) and non-EU countries (e.g. Norway) to prohibit the use of all phthalate plasticisers, including DMP, in toys and childcare articles intended to be placed in the mouth by children under the age of three (Greenpeace International 2003). This general prohibition is a risk management decision based on the precautionary principle and risk assessments of selected phthalates (DEHP, DBP, BBP, DINP, DIDP, DnOP) present in soft polyvinyl chloride (PVC) toys and childcare articles conducted by the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) (VKM 2005).

There are no restrictions on the use of DMP in cosmetics in the EU. However, as for other unregulated or unrestricted cosmetic ingredients, the manufacturer has obligations to ensure the products are safe for use by consumers. It is noted that the EU Scientific Committee on Consumer Products (SCCP) has calculated the margin of safety or risk of 'unintentional exposure' for the consumer based on trace levels of DMP found in perfumes and other cosmetics (2982 mg/kg or 0.3 %, Greenpeace International 2005) and the no observed adverse effect level (NOAEL) for maternal toxicity in rats (600 mg/kg bw/d, intraperitoneal, Peters & Cook 1973). In this report, it was stated by the European Cosmetic Toiletry and Perfumery Association (or COLIPA; now called Cosmetics Europe) that DMP was not used intentionally as a cosmetic ingredient, but rather is present as traces and/or impurities that may leach unintentionally into perfumes and other cosmetics through contact of the finished products or raw materials with plastic material (containers, pipes, pumps) during production or storage (SCCP 2007).

DMP has been registered with the European Chemicals Agency (ECHA) in the tonnage band of 10000–100000 tonnes a year under REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) and is not included in the Candidate List of Substances of Very High Concern (SVHC) for authorisation.

Regulatory information on DMP from the United States of America (USA) is as follows:

- DMP (together with DEP) is on the US Environmental Protection Agency's list of 'potentially toxic inerts/high priority for testing' because they are considered structurally similar to chemicals known to be toxic and/or there are data suggesting a basis for concern about the toxicity of the chemical (US EPA 1989).
- DMP (together with DEP) is listed in the LMW Phthalate Esters Category for a screening-level hazard characterisation under the US EPA HPV Challenge Program (US EPA 2010).
- DMP is neither subject to any restrictions for use in toys, childcare articles nor included in the US EPA's Phthalates Action Plan (US EPA 2012 revised).
- No warnings or restrictions were identified for use of DMP in cosmetics.

In Canada, DMP (similarly to DEP) is considered to be a MODERATE priority for further work following Canada's categorization 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 developmental and reproductive 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 from industry in 2004 and 2006, one terephthalate and 24 ortho-phthalates, including DMP, were identified as currently or potentially in industrial use in Australia. DMP, 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 public and industry 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).

DMP is currently listed in:

- the Hazardous Substances Information System (HSIS) (Safe Work Australia) with a time weighted average (TWA) exposure standard of 5 mg/m^3. This hazard is associated with atmospheric contaminants in the occupational environment only. The liquid form does not present the same hazard in the absence of further processing, which can cause aerosol formation or other atmospheric release. The HSIS does not include a human health hazard classification for DMP.
- the Poisons Standard (the Standard for Uniform Scheduling of Medicines and Poisons (SUSMP)) under Appendix C, which excludes the use of DMP 'in sunscreens, personal insect repellents or body lotion preparations for human use except in preparations containing 0.5 per cent or less of DMP'. This decision was based on concerns about the potential reproductive/developmental toxicity of short chain or low molecular weight phthalates including DMP and DEP in late gestation or during puberty, when applied to large areas of the body.

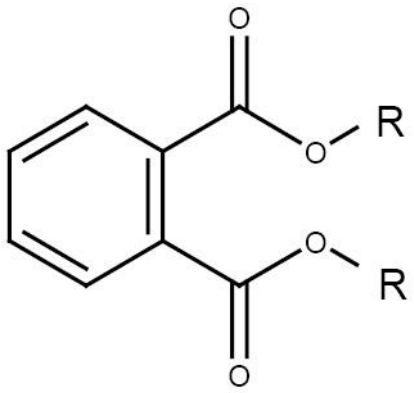
At the time of this PEC assessment, no other restrictions on the introduction (manufacture and/or import) or use of this chemical were identified in Australia.

3 Identity and properties

Dimethyl phthalate (DMP) is listed on the Australian Inventory of Chemical Substances (AICS).

3.1 Chemical identity

Chemical name:	1,2-benzenedicarboxylic acid, dimethyl ester
CAS No.:	131-11-3
Synonyms:	DMP
	dimethyl phthalate
	phthalate, dimethyl
	phthalic acid, dimethyl ester
	dimethyl benzene-1,2-dicarboxylate
	dimethyl 1,2-benzenedicarboxylate
	1,2-benzenedicarboxylic acid, 1,2-dimethyl ester
Molecular formula:	$C_{10}H_{10}O_4$
Molecular weight:	MW 194.19
Purity/impurities:	≥99 % (cosmetics grade)
Structural formula:	



R = CH_3

3.2 Physical and chemical properties

Table 3.1: Summary of physicochemical properties (adopted from ChemIDplus; HSDB 2012)

Properties	Value
Physical state	Pale yellow or colourless oily liquid with slight aromatic odour
Boiling point	284 ºC
Melting point	5.5 ºC
Density, kg/m3 (20 ºC)	1190
Vapour pressure, kPa (20 ºC)	4×10^{-4}
Water solubility, g/L (25 ºC)	4.3
Partition co-efficient octanol/water (log Kow)	1.60
Henry's Law constant, atm m3/mol (25 ºC)	1.97×10^{-13}
Flash point	146 ºC (closed cup)

DMP is miscible with common organic solvents, e.g. alcohols, ketones, esters, ethers and chloroform. It is slightly soluble in some types of mineral oils and insoluble in petroleum ether and paraffin hydrocarbons (ChemIDplus; HSDB 2012; NTP 1995).

Conversion factors based 25 ºC and 1 atmosphere:

DMP (MW 194.19)
1 ppm = 7.94 mg/m^3
1 mg/m^3 = 0.13 ppm

4 Manufacture, importation and use

4.1 Manufacture and importation

DMP is introduced into Australia through importation both in finished (ready-to-use) products and as a raw material or in mixtures for local formulation and processing. There are no data from NICNAS calls for information indicating the chemical is manufactured in Australia.

The total volume of DMP imported to Australia for industrial uses was in the range of 1000–2000 tonnes each year between 1999–2004, according to calls for information on phthalates. About 50 % of this volume was used for mineral separation in the mining industry. In 2006, the amount of DMP reported for uses in children's toys, childcare articles and cosmetics with the potential widespread public exposure was not more than 10 tonnes a year. The ratio of imported volume of DMP as a raw material (or in mixtures) to finished product is approximately 60:40. No further information on the specific volume of DMP for these uses is publicly available.

4.2 Uses of DMP

4.2.1 Uses in Australia

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

- mainly as solvents in the mining industry for mineral recovery and separation, in the manufacture of adhesives, fibreglass, plastic putty hardeners, automotive plastics, insulation and surface coatings or paints, in various textile wet processing products.
- as cosmetic ingredients or in fragrance bases for domestic detergents, cosmetics, perfumes and personal care products. Concentrations of DMP (in combination with its analogue DEP) in these products are highly variable and range from 0.00004 % to 34 % in unspecified products.
- as plasticisers for toys and childcare articles, including inflatable water products, hoppers, play and exercise balls.

DMP is also imported for distribution to various institutions and laboratories for biotechnological and pharmaceutical research.

Table 4.1 provides a list of different types of cosmetics marketed in Australia and overseas along with the range of DMP concentrations. Cosmetic products are divided into rinse-off (i.e. intended to be removed after application on the skin, the hair or the mucous membranes) and leave-on (i.e. intended to stay in prolonged contact with the skin, the hair or the mucous membranes) (European Commission's Cosmetics Glossary, available at http://ec.europa.eu/consumers/sectors/cosmetics/glossary/index_en.htm).

Table 4.1: Cosmetic uses and concentrations of DMP reported by the Australian industry (NICNAS calls for information 2004 & 2006) and Cosmetic Ingredient Review Expert Panel (CIR 2005)

Cosmetic products	Concentrations (%) reported in Australia	Concentrations (%) reported overseas
Leave-on		
Hair spray (aerosol fixative)		0.00002–2
Hair tonic, dressing, etc.		>0.1–5
Wave set		>0.1–1
Hair preparation (non-colouring)		>0.1–1
Blusher		0.00008
Face powder		0.00008
Foundation		0.005
Deodorant (underarm)		0.2
Aftershave lotion		0.2
Unspecified cosmetics/personal care products	0.001–34[a]	
Rinse-off		
Bath soaps and detergent		0.004
Hand wash	0.00004–0.000044	
Shampoo (non-colouring)		0.00002
Hair rinse		>0.1–1
Hair conditioner		>0.1–1

[a] in combination with an analogue DEP.

No data on the DMP levels in children's toys found in Australia were provided for the assessment, therefore modelling assumptions and overseas data are used in the exposure estimations.

4.2.2 Uses overseas

Worldwide annual production and/or import volumes of DMP were reported to be around 345 tonnes in Nordic countries in 2010 (SPIN), 4500–22700 tonnes in the US in 2005 (US EPA 2010), and 10000–100000 tonnes in the EU (REACH Dossier, ECHA). DMP was found on a number of high production volume (HPV) lists managed by the International Council of Chemical Associations (ICCA), OECD and US EPA, but specific annual volumes of chemical production, import or export were not identified (Galleria Chemica).

The following international uses or functions of DMP have been identified through the:

- European Commission's Cosmetic Ingredients and Substances (CosIng) Database: film forming, masking, plasticisers, solvents.
- Personal Care Products Council's International Nomenclature Cosmetic Ingredient (INCI) Dictionary: fragrance ingredients, plasticisers, solvents.
- REACH Dossier: a wide variety of industrial uses including dispersive indoor/outdoor uses, consumer and professional uses of adhesives, coatings, paints and inks, as well as uses in plasticisers, cosmetics and personal care products.
- Substances in Preparations in Nordic Countries (SPIN) Database: softeners, cleaning/washing agents, colouring agents, fillers, paints, lacquers, varnishes and process regulators.

- US National Library of Medicine's Household Products Database: in liquid hardeners for home maintenance.
- Galleria Chemica: solvents and plasticisers for cellulose acetate and cellulose acetate-butyrate compositions, in insect repellents, lacquers, plastics and rubbers.

In cosmetic uses, DMP was measured in concentrations as high as 2982 mg/kg or 0.3 % in one perfume and between 0.1 and 1.9 mg/kg (or 0.0002 %) in the other 18 perfumes (Greenpeace International 2005). These were considered as traces and/or impurities that may leach unintentionally into perfumes by COLIPA (SCCP 2007). In a range of products marketed in northwest Spain, the maximum concentration of DMP was measured at 0.0025 % and it was found in 9/70 commercial perfumes designed to be used by men, women, children or babies (cf. the DEP maximum level of 3.16 %; found in 57/70 products) (Sanchez-Prado et al. 2011). Perez-Fernandez et al. (2013) also detected DMP in 3/15 perfumes marketed in Madrid, Spain at up to 0.12 % (1207 ± 43 mg/L) and DEP in 10/15 perfumes at 0.3 % (3115 ± 167 mg/L). Therefore, it appears that DMP is not as widely used in perfumery as is DEP. According to CIR (2005), DMP was commonly used as an ingredient in some hair preparations (non-colouring) and hair sprays (aerosol fixatives) with the maximum concentration of 2 %.

In PVC children's toys and childcare articles, DMP as a LMW phthalate is not found as the dominant phthalate plasticiser, but may be used in conjunction with another plasticiser as a secondary plasticiser or occur as a minor contaminant of other phthalates, including DEHP or DINP (see below). Specific concentrations of DMP in toys are not available, and the types of non-PVC articles (inflatable water products, hoppers, play and exercise balls) in which DMP is reported to be used are not typical mouthing articles.

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 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 to 52 mPa • s for DINP and up to 190 mPa • s for ditridecyl phthalate (Eastman 2006).

Thus, a HMW phthalate ester (e.g. DINP) will be quite different from a LMW phthalate ester such as DEP. However, the difference in properties between two phthalates of similar molecular weight, such as DMP 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 DMP for DEP as a cosmetic ingredient—is more probable than substitution for a phthalate of very different molecular weight, such as DINP.

Little information is available in open 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 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 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. DMP and DEP are also used in cellulose nitrate systems (Chanda & Roy 2006).

Therefore, while it is clear that phthalates can be considered to be substitutable by other phthalates of similar properties, there are likely to be limits on the extent to which dissimilar phthalates can be used. DMP is a LMW phthalate and thus it is not likely to substitute for DINP—a HMW phthalate commonly used in PVC toys and childcare articles. In the absence of DMP use data in the two scenarios considered, assumptions may need to be made. In this report, for example, migration or leaching rates reported for DINP are used to undertake an exposure assessment for DMP as a secondary plasticiser in a mixed phthalate plasticiser (DINP+DMP) in relation to uses in children's toys and childcare articles.

5 Public exposure

Public exposure to DMP is estimated for each of the following consumer applications only:

- use in children's toys and childcare articles; and
- use in cosmetics.

Exposure estimates are derived to allow characterisation of the risks associated with these applications of DMP.

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 fundamentally address 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.

5.1.1 Model for exposure of children

Exposure of children to DMP 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 DMP from these products is considered negligible due to the chemical's low vapour pressure.

Information on the DMP content in toys is insufficient, and therefore the exposure estimate is based on the usage and concentration of an alternative phthalate, DBP, which has a low molecular weight (<250 Da), 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 DMP because of the possibility of substitution, as discussed in Section 4.3.

Oral exposure was modelled by:

- estimating the highest plausible concentration of DMP 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 which are not expected to be markedly different from Australian children's mouthing activities and behaviours;
- estimating the migration rate of the mixed plasticiser from PVC matrix into saliva based on experimental studies on the extractability of phthalate plasticisers under various mouthing conditions;
- estimating the oral bioavailability of DMP (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 DMP 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.

5.1.2 Model for exposure of the general population

Exposure of the general population to DMP from cosmetics was estimated for both dermal and inhalation routes. Dermal exposure may occur through using creams or liquid products. Inhalation exposure may occur through breathing overspray from application of aerosol products, although the respirable fraction of DMP

particles may be very low (CIR 2005). Due to the low vapour pressure of DMP, inhalation exposure from using creams or liquid products is considered negligible.

Frequent incidental oral exposure to phthalates from use of cosmetics and personal care products is unlikely to occur and would involve very small amount of phthalates. Available information does not indicate use of phthalates in oral hygiene products that are likely to be subject to inadvertent ingestion, such as toothpastes and mouthwashes, or lipsticks. Therefore, the potential for public exposure via this route is considered negligible and is not further characterised.

While it is known that DMP is used in cosmetic and personal care products in Australia, information on the DMP levels in these products is insufficient. Accordingly, the exposure estimate is based on the usage and concentration of an alternative phthalate, in this case DEP, which is commonly reported in cosmetic products in Australia. These estimates are considered valid for DMP, at least in individual products, because of the possibility of substitution, as discussed in Section 4.3.

Dermal exposure was modelled by:

- estimating the highest plausible concentration of DMP in cosmetic products for dermal application in Australia;
- using default values for the amount of the cosmetic product applied daily and frequency of application based on overseas use patterns, which are not expected to be markedly different from Australian usage; and
- estimating the dermal bioavailability of DMP (see Section 6.1).

Inhalation exposure was modelled by:

- estimating the highest plausible concentration of DMP in spray cosmetic products in Australia;
- using default values for the amount of the cosmetic product applied daily and frequency of application based on overseas use patterns, which are not expected to be markedly different from Australian usage;
- using default values for the inhalation rate and other parameters related to spraying application of cosmetics;
- estimating the inhalation bioavailability of DMP (see Section 6.1).

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

The calculation of exposures to DMP 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 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 DEP has a detailed calculation under this scenario explaining the derivation of all relevant parameters (NICNAS 2011).

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+DMP) and DMP 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 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, see 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 $\mu g/cm^2/hr$, respectively.
- The extractability data for DINP (measured at 43 % w/w of the articles by Chen (1998)) are also applicable for a mixed phthalate plasticiser comprising 0.5 % DMP and 42.5 % DINP, i.e. 43 % of a mixed phthalate consisting of 1.16 % DMP 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 male and female 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 via 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 via 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, hr
n = Frequency per day
B_{oral} = Bioavailability via the oral route, %
BW = Body weight, kg

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

	Total phthalate $D_{int,oral}$ (μg/kg bw/d)	**DMP[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 DMP are derived by multiplying the internal doses for total phthalate by the proportion of DMP (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+DMP) and DMP 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+DMP) given the lack of 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 % DMP and 39.9 % DINP, i.e. 40.4 % of a mixed phthalate consisting of 1.24 % DMP 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, 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 via 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, hr
n = Frequency per day
BW = Body weight, kg

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

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

5.3 Exposure estimates for the general population from use of cosmetics

5.3.1 Dermal exposure in adults—deterministic approach

The calculation of exposures to DMP is based on the assumption that the chemical completely substitutes for DEP (a common cosmetic ingredient), at least in individual cosmetic products, e.g. body lotion and perfume. Thus, the estimates are based on the reported DEP levels by the Australian industry and on the overseas data (where the Australian information is absent) for the DMP usage and levels in different product types. Not all product types have been included in the calculation of worst-case exposure, as some of the cosmetic and personal care products have interchangeable uses (e.g. hand wash and bar soap), and hence only product types with the higher concentration have been used in these categories.

The daily internal dermal doses for the cosmetic use scenario for DMP are calculated using Equation 3 and shown in Table 5.4 based on the following assumptions:

- Default values for the typical use pattern of various cosmetic products are selected from either the European Chemicals Bureau's *Technical guidance document on risk assessment, part 1* (ECB 2003) or the Scientific Committee on Consumer Safety's *Notes of guidance for the testing of cosmetic substances and their safety evaluation*, 8th revision (SCCS 2012).

- The adult's mean body weight is 70 kg based on lifetime average male and female combined (enHealth 2012).
- Phthalate bioavailability via the dermal route is 10 % (Section 6.1). This is considered to better reflect the absorption over an extended period of use as compared with the absorption rate.

Equation 3

$$D_{int,dermal} = \frac{A \times n \times C \times B_{dermal} \times RF}{BW}$$

Where:

$D_{int,dermal}$ = Internal dose via the dermal route, µg/kg bw/d
A = Amount of cosmetic product applied daily, µg/event
n = Frequency of application per day, events/d
C = Concentration of phthalate in the product, %
B_{dermal} = Bioavailability via the dermal route, %
RF = Retention factor
BW = Body weight, kg

Table 5.4: Typical use pattern and estimated daily internal doses from dermal exposure ($D_{int,dermal}$) to multiple cosmetics and personal care products in adults

Product type	A × n [a] (µg/d)	RF[a]	C[b] (% w/w)	$D_{int,dermal}$ (µg/kg bw/d)
Leave-on				
Hair spray/styling product	4.00E+06#	0.1	2.00[c]	11.43
Antiperspirant/Deodorant (roll-on)	1.50E+06#	1	1.13	24.21
Cologne/Aftershave/Splash	2.40E+06	1	0.97	33.26
Nail polish	1.07E+05	1	25.00	38.27
Face cream/Moisturiser	1.54E+06#	1	0.42	9.24
Body lotion	7.82E+06#	1	0.25	27.93
Perfume spray	3.19E+06[d]	1	2.50	113.84
Rinse-off				
Soap bar	4.80E+06	0.01	0.15	0.10
Shower product	1.00E+07	0.01	0.48	0.69
Shampoo	1.05E+07#	0.01	0.05	0.07
Hair conditioner	3.92E+06#	0.01	1.00[c]	0.56
Shaving products (cream, gel, stick, lather)	2.00E+06	0.01	0.005	0.0014

[a] Typical values for use levels of cosmetics are adopted from the deterministic estimates by ECB (2003) and those with number signs (#) are from the probabilistic estimates by SCCS (2012). A = amount of cosmetic product applied daily (µg/event) and n = frequency of application (events/d) are presented as a product of the two parameters. RF = retention factor.

[b] Concentrations of DMP are derived from the highest reported DEP levels by the Australian industry because of the possibility of substitution of similar phthalates (see PEC assessment of DEP, NICNAS 2011).

[c] Concentration of DMP are based on overseas data (CIR 2005).

[d] Typical values for perfume (toilet water): A = 7.50E+05 µg/event and n = 5 events/d (ECB 2003), and assuming 85 % of the spray amount lands on the skin (Bremmer et al. 2006).

For the worst-case scenario estimation under these assumptions, if a person were a user of all the cosmetic products listed in Table 5.4 simultaneously, the internal dose from dermal exposure is determined to be 259.60 µg/kg bw/d.

5.3.2 Dermal exposure in adults—probabilistic approach

The internal dermal exposures calculated using Equation 3 are frequently referred to as point estimates from a deterministic approach, i.e. using single values to represent each exposure variable to produce a single exposure estimate.

An alternative method used in the exposure calculations is a probabilistic modelling approach, which uses the distribution around each variable as inputs, rather than single values, to generate an exposure distribution. Calculations therefore account for all the possible values of a variable in relation to the probability of each value occurring, generating a range of exposure estimates (WHO 2005).

In the case of the internal exposure estimates for DMP, the probabilistic approach was not conducted since implementing this distribution-based approach requires data obtained from a large sample size (IGHRC 2004). However, the use levels (amount and frequency of use) for certain cosmetic products (Table 5.4) were based on the recently available distribution data (90th percentile) from actual monitoring of the use of some cosmetic products by 44100 households and 18057 individual consumers in five European countries (Hall et al. 2007; SCCS 2012). These probabilistic values are considered more realistic estimates of exposure than those calculated using single point values based upon extreme exposure scenarios. Therefore, the internal dermal dose estimates for DMP are semi-probabilistic.

5.3.3 Dermal exposure in children or infants—deterministic approach

There are no data available on children's cosmetic use pattern by age or dermal absorption or dermal bioavailability differences between adults and children.

Using the exposure model developed for phthalates assessment by NICNAS (see PEC assessment of DEHP, NICNAS 2010), the quantity of whole body product applied to a child can be estimated from the ratio of body surface area of the child relative to the adult. The systemic dose depends on the body weight of the child, and therefore the systemic dose for any products (used similarly in adults and children) will vary according to the ratio of surface area to body weight (SA/BW) given that skin permeability is the same for both adults and children. An estimate of the magnitude of the difference can be made using data issued by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) on the margin of safety calculation for children (SCCP 2006). For children aged 0–10 years, the difference in SA/BW ratio is: 2.3-fold at birth, 1.8-fold at six months, 1.6-fold at 12 months, 1.5-fold at five years, and 1.3-fold at 10 years.

Assuming that phthalates of similar molecular weight can be substituted for one another, one type of cosmetic product that could contain DMP and that is used on children or infants is body lotion or cream. The maximum concentration of DMP in body lotion is 0.25 %. The daily internal dermal doses for children up to 12 months solely using this type of product are shown in Table 5.5, using the SA/BW ratio correction for the point estimates of product amount and frequency of use (A = 7.50E+06 µg/event and n = 2 events/d) from general population as described in ECB (2003). These are considered more appropriate for children than the probabilistic data derived specifically for adult activities. These calculations and assumptions were previously used in DEHP and DEP PEC assessments conducted by NICNAS (2010; 2011).

Table 5.5: Estimated daily internal doses from dermal exposure ($D_{int,dermal}$) to body lotion in children or infants

Infant age	Adult $D_{int,dermal}$ (µg/kg bw/d)	Surface area/ body weight ratio	$D_{int,dermal}$ (µg/kg bw/d)
Newborn	53.57	2.3	123.21
6 months	53.57	1.8	96.43
12 months	53.57	1.6	85.71

5.3.4 Inhalation exposure in adults

Inhalation exposure to DMP from cosmetic and personal care products can occur through incidentally breathing spray aerosols such as antiperspirant body sprays and/or perfume sprays.

The daily internal inhalation doses for DMP from use of these products are calculated using Equation 4 and shown in Table 5.6 based on the following assumptions:

- Default values for the typical use pattern of antiperspirant/deodorant and perfume sprays are selected from the European Chemicals Bureau's *Technical guidance document on risk assessment, part 1* (ECB 2003).
- The room volume is 2 m^3 to represent the air immediately surrounding the user (ECB 2003).
- The adult's mean body weight is 70 kg based on lifetime average value for male and female combined (enHealth 2012).
- The adult's inhalation rate is 20 m^3/d based on the 95th percentile value for male and female combined (enHealth 2012).
- Exposure time is 0.0022 day or 3.17 minutes, consisting of 10 seconds for actual spraying of the product and a further three minutes of exposure after spraying (Bremmer et al. 2006).
- Phthalate bioavailability via the inhalation route is 100 % (Section 6.1).

Equation 4

$$D_{int,inh} = \frac{A \times n \times C \times B_{inh} \times IR_{air} \times t}{BW \times V_{room}}$$

Where:

$D_{int,inh}$ = Internal dose via the inhalation route, µg/kg bw/d
A = Amount of cosmetic product applied daily, µg/event
n = Frequency of application per day, events/d
C = Concentration of phthalate in the product, %
B_{inh} = Bioavailability via the inhalation route, %
IR_{air} = Inhalation rate of person, m^3/d
t = Time of contact, d
BW = Body weight, kg
V_{room} = Room volume, m^3

Table 5.6: Estimated daily internal doses from inhalation exposure ($D_{int,inh}$) to spray cosmetics in adults

Product type	A × n [a] (µg/d)	C [b] (% w/w)	$D_{int,inh}$ (µg/kg bw/d)
Antiperspirant/deodorant (spray)	9.00E+06	0.37	10.47
Perfume spray	3.75E+06	2.50	29.48

[a] Typical values for use levels of cosmetics are adopted from the deterministic estimates by ECB (2003). A = amount of cosmetic product applied daily (µg/event) and n = frequency of application (events/d) are presented as a product of the two parameters.

[b] Concentrations of DMP are derived from the highest reported DEP levels by the Australian industry because of the possibility of substitution of similar phthalates (see PEC assessment of DEP, NICNAS 2011).

It is considered likely that only one of these two types of products listed in Table 5.6 would be used by an individual on a single day. Therefore, the internal dose from inhalation exposure is determined to be 29.48 µg/kg bw/d.

Overall, for the worst-case scenario estimation under these assumptions, the combined exposures for adults arising from both dermal and inhalation contact with cosmetics are presented in Table 5.7.

Table 5.7: Estimated total internal doses for adults

Route of exposure	$D_{int, dermal+inh}$ (µg/kg bw/d)
Dermal	259.60
Inhalation	29.48
Combined	289.08

5.4 Biomonitoring data

There have been some attempts to use biomonitoring data to estimate exposure to phthalates, including DMP, as a result of the use of cosmetic and personal care products. However, DMP is ubiquitous and it is difficult to assess DMP exposure specifically through these products unless there is available information on their actual phthalate content and use levels. For example, one US study (Sathyanarayana et al. 2008) monitored the presence of nine phthalate metabolites in the urine of 163 infants in relation to their mother's reported use of five types of baby care products within 24 hours of urine collection. The urine measurements were not used to determine internal doses. No information was available on the phthalate content of the products used in the study (tested or manufacturer-reported) and exposure information was derived from self-reporting by the mothers, which did not include reporting on the amount and frequency of use. However, the study reported that there were associations between use of infant lotion with increased infant urine concentrations of monomethyl phthalate (MMP) and monoethyl phthalate (MEP) (DMP and DEP metabolites, respectively), and between the use of infant shampoo with MMP. These associations were strongest in infants younger than eight months. These findings support the exposure modelling approach for DMP above.

Biomonitoring data for a particular chemical or its metabolites represent exposure to the chemical from all sources and pathways. Toxicokinetic data demonstrate that DMP is rapidly excreted and does not appear to accumulate in tissues (Section 6.1), so single urine measurements may approximate the individual daily intake. However, population estimates of specific phthalate levels may differ by age, gender, and race/ethnicity (Silva et al., 2004; CDC 2013). The analytical approaches, uncertainty and variability associated with biomonitoring data limit their use in exposure and human health risk assessments (Albertini et al. 2006). It is not possible to determine the relative contribution of different exposure sources or routes directly from population biomonitoring data. For the purpose of this assessment, modelling is the most suitable approach.

Biomonitoring data, however, can be useful in determining whether the exposures calculated through modelling are within the observed range of exposure and comparable with the integrated exposure of the population. Biomonitoring data for the Australian general population or specific subpopulations are not available. Table 5.8 summarises representative international biomonitoring investigations that provide exposure estimates for DMP (vs DEP) as determined from their urinary metabolite concentrations, MMP and MEP respectively. The biomonitoring levels of MMP were lower than those of MEP because of the lesser likelihood of DMP being present in various products compared with DEP. Based on the analysis of the National Health and Nutrition Examination Survey (NHANES) 2001–02 through 2009–10, the *Fourth National Report on Human Exposure to Environmental Chemicals* (CDC 2013 revised) indicated that, although the detection frequency was less than 60 % in recent NHANES survey periods, the overall population urinary levels of MMP generally did not vary. In modelling for the cosmetic use scenario, especially where DMP is assumed to completely substitute for DEP, the use levels of DMP for individual cosmetic products and hence the exposure estimates from use of a particular cosmetic product are not expected to be different from those of DEP.

The available conversion of biomonitoring measurements (µg/L urine or µg/g creatinine) to internal doses (µg/kg bw/d) for DMP is limited. However, the close agreement between the calculated exposures through modelling for DEP (NICNAS 2011) and the internal exposure doses derived by Wormuth et al. (2006) from urine measurements of MEP metabolites (especially the maximum or the 95th percentile values) substantiates that the assumptions made in the scenarios used to calculate the exposures are reasonable and applicable to both DEP and DMP. Based on the data in Table 5.8, the internal doses of DMP will be less than those calculated for DEP.

Similarly to DEP, the calculated reasonable worst-case DMP exposure to cosmetic and personal care products is greater than the biomonitoring data of the DMP metabolite due to the worst-case assumptions used. However,

the estimates for use of a single cosmetic product such as body lotion both in adults and in infants are within the 95th percentile range of the biomonitoring studies for DEP. This indicates that the worst-case exposure scenarios considered in this assessment are applicable for highly exposed individuals or a subset of the population. The results of biomonitoring studies are also consistent with the basis of the exposure modelling for DMP, as they indicate that the general population exposure is much lower than the individual exposure which can arise from these specific high exposure scenarios.

As seen in Table 5.8, there is a wide range between the measure of central tendency (mean or median) and the 95th percentile values indicating that some members of the population have been exposed to much higher DMP levels than the population average. For example, the 95th percentile biomonitoring value reported for cosmetic use in infants of 2–28 months is 228.3 µg/g creatinine, compared with 1.6 µg/g creatinine for the median (Sathyanarayana et al. 2008). Also, in NHANES 2001-02, the group of children aged 6–11 years is reported to have higher levels of DMP exposure compared with the general population (CDC 2013).

Table 5.8: Biomonitoring data of urinary MMP vs MEP metabolites (µg/g creatinine for adjusted values, otherwise specified as unadjusted, µg/L urine)

Study	Population (sample size, age)	Mean		Median		95th Percentile	
		MMP	MEP	MMP	MEP	MMP	MEP
Duty et al. 2005	Boston /Male partners of subfertile couples (337–338, 20–54 yr)	4.5[a]	179[a]	4.8[a]	154[a]	32.1[a]	2030[a]
Swan et al. 2005	Los Angeles /Pregnant women (85, >18 yr)			0.7[a]	128.4[a]		
Jaddoe et al. 2006	Netherlands Generation R /Pregnant women (100, 18–41 yr)	7.7	465.8				
Ye et al. 2009	Norway MoBa /Pregnant women (10 × 11, 15–53 yr)	2.6	405.9				
Hauser et al. 2007	Boston /Male partners of subfertile couples (379, 36.3 ± 5.4 yr)	3.6[a]	171[a]	4.0[a]	154[a]	29.1[a]	2030[a]
Itoh et al. 2007	Japan /Adults—1 Child (36, 4–70 yr)			33[a]	18[a]		
Hogberg et al. 2008	Sweden /Breastfeeding women (38, 23–39 yr)	2.5	101	1.9	39	12[b]	862[b]
Sathyanarayana et al. 2008	US/Infants (163, 2–28 mo)	4.4	178.2	1.6	60.9	228.3[b]	4481[b]
Wirth et al. 2008	Michigan /Male partners of subfertile couples (45, 23–48 yr)	1.1[a]	121.9[a]	2.4[a]	108[a]	14.7[a]	1180[a]
Hines et al. 2009	US EPA MAMA 2004–05/Women (30; 3–4 mo postpartum)			4.9	113	6.4	2444
Ying et al. 2011	China/Adults (40, 21–49 yr)	16.4	22.5	9.7	17		
	India/Adults (22, 21–49 yr)	8.6	132	5.8	120		

Kasper-Sonnenberg et al. 2012	Germany Duisburg 2006-08/Children (105, 6–8 yr)	4.9[a]	39.1[a]	3.8[a]	33.6[a]	46.3[a]	391[a]
	Germany Duisburg 2006-08/Mothers (104, 29–49 yr)	1.3[a]	50.5[a]	1.2[a]	53.8[a]	21.3[a]	265[a]
Dirtu et al. 2013	Belgium 2009–11 /Adult, obese (152, 18–84 yr)			12	80		
	Belgium 2012 /Adult, lean (43, 19–59 yr)			8	50		
Saravanabhavan et al. 2013	Canada/ CHMS 2007–09 (1034, 6–11 yr)	LOD	39.7	LOD	33	LOD	212.8
CDC 2013 revised	US NHANES 2001–02 /Children (393, 6–11 yr)	1.65	64.0	2.32	53.6	13.2	556
	US NHANES 2003–04 /Children (342, 6–11 yr)	2.22	66.6	1.88	57.4	16.2	474
	US NHANES 2009–10 /Children (415, 6–11 yr)	2.77	45.9	2.85	39.0	20.5	296

[a] unadjusted values; [b] maximum values; mo = month; yr = year; CHMS = Canadian Health Measures Survey; LOD = limit of detection; MAMA = Methods Advancement for Milk Analysis study; MoBa = Mother and Child cohort; NHANES = National Health and Nutrition Examination Survey.

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 DMP is therefore based on the collective results of all available studies through analysing the weight of evidence and deductive 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 DMP, 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 phthalates was used to examine the potential toxicity. In particular, information on DEP, a phthalate of similar molecular weight, physicochemical properties and reactivity, was considered to be representative of DMP for many endpoints. The assessment information was obtained from NICNAS assessment reports, international reviews and journal articles on relevant phthalates published up to September 2013. References marked with an asterisk (*) were not reviewed but were quoted as secondary citations from the key documents listed in Section 1.3 Sources of information.

The NICNAS Phthalates Hazard Compendium (NICNAS 2008b) contains a comparative analysis of toxicity endpoints across 24 ortho-phthalates, including DMP. DMP has a straight carbon chain length of ≤3 and therefore is considered a LMW phthalate (refer to Section 2 for definition).

6.1 Toxicokinetics

6.1.1 Absorption

Absorption via the oral route

Orally administered DMP is readily and extensively absorbed after being metabolised from the gastrointestinal (GI) tract. This is based on the urinary excretion data in rats and an in vitro absorption study (Albro and Moore 1974; White et al. 1980*).

No information is available concerning differences in absorption and bioavailability of orally administered DMP between adult and immature animals, or between animals and humans. The oral bioavailability of the most studied phthalate, DEHP, appears to be higher in young than mature rats (Sjoberg et al. 1986). The higher proportion of intestinal tissue in relation to body weight (Younoszai & Ranshaw 1973) and the relatively higher blood flow through the GI tract (Varga & Csaky 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 DMP via the oral route is assumed to be 100 % for both adults and children.

Absorption via the dermal route

When phthalates were applied to male rat skin at 5–8 mg/cm^2 under occlusion, the cumulative percentage dose excreted in the urine and faeces over seven days was greatest for DEP (~50–60 % of the applied ^{14}C) and intermediate for DMP (20–40 %) (Elsisi et al. 1989). Given that the excretion rate of DMP is relatively constant at 6–7.5 % of the applied dose over seven days, DMP is considered to be slowly absorbed through the skin. In vitro studies reported that dermal absorption of DMP through rat skin was about 10–20 times higher than through human skin, with the steady state absorption rates of 410 vs 39.5 µg/cm^2/hr (Scott et al. 1987; 1989 Errata) or maximum absorption rates of 51 vs 2.5 µg/cm^2/hr (Hilton et al. 1994), respectively. These may reflect differences in species, vehicle effects and/or study designs. Scott et al. (1987; 1989 Errata) also reported that although having comparable rates of absorption (410 vs 413 µg/cm^2/hr) through rat skin, the in vitro absorption rate of DMP was three times higher than that of DEP (39.5 vs 12.8 µg/cm^2/hr) through human skin.

Overall, based on the cumulative absorption of 20–40 % for DMP through rat skin and the higher permeability rate of DMP vs DEP through human skin, the dermal bioavailability of DMP in humans is estimated to be no lower than that of DEP, i.e. 10 %.

Absorption via the inhalation route

Quantitative information on inhalation absorption of DMP is not available.

A significant positive correlation between personal air and urine measurements was reported for DEP in cohorts of pregnant women in New York, indicating absorption of DEP through the lungs (Adibi et al. 2003; 2008). In rats, about 90 % of radiolabelled DEHP from aerosol exposure was found equally distributed in the urine and faeces within 72 hours (General Motors 1982a*;b*). 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. Taking all into consideration, the bioavailability of DMP via the inhalation route is considered no lower than that of DEP or DEHP, i.e. 100 %.

6.1.2 Distribution

When a single dose of DMP was applied to male rat skin, very little radioactivity was detected in the tissues seven days after exposure. The amounts of radioactivity ranged from 0.6 % in muscle, and 0.3 % in adipose tissue to <0.5 % of the dose for the summation of the percentage dose found in the brain, lung, liver, small intestine, kidney, testis, spinal cord and blood (Elsisi et al. 1989).

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 DEP (LMW), DEHP (transitional) and DINP (HMW), distribution of phthalates in general or DMP in particular (as determined from urinary metabolites) is assumed to be widespread into tissues, including breast milk and the placenta (Mortensen et al. 2005; Mose et al. 2007) after exposure, with no evidence of accumulation.

6.1.3 Metabolism

Rat urinary metabolites of orally administered DMP comprised mainly monomethyl phthalate (MMP, 77.5 %) and minor amounts of phthalic acid (PA, 14.4 %) and intact DMP (8.1 %) (Albro and Moore 1974). In vitro, DMP was also rapidly metabolised and almost disappeared two hours after incubation with rat liver or kidney homogenates (Kaneshima et al. 1978). Comparing the hydrolysis of a range of phthalates by both hepatic and intestinal preparations from the rat, ferret, baboon and human, Lake et al. (1977*) suggested a species similarity in the phthalate metabolism and that with decreasing chain length the hydrolysis rate increased. Intestinal esterases may play a key role in hydrolysing phthalate diesters to their corresponding monoesters during absorption (Lake et al. 1977*; White et al. 1980*).

The in vitro DMP-hydrolytic activity of whole rat skin was found to be only about 1.5 % that of the liver (Kozumbo et al. 1982; Kozumbo & Rubin 1991), which may explain the slow dermal absorption of DMP in vivo.

6.1.4 Elimination and excretion

Elimination of intact DMP and its metabolites after oral and intraperitoneal exposure was rapid and almost complete (100 % and 97 % respectively) based on the analyses of 24-hr urinary data (Albro & Moore 1974; Kozumbo & Rubin 1991). Excretion after dermal exposure was at a much slower rate, possibly due to the rate-limiting nature of dermal absorption. Urine was considered the major route of excretion for a number of phthalates, especially for those with carbon chain lengths of ≤4 (Elsisi et al. 1989).

6.2 Acute toxicity

6.2.1 Acute oral and dermal toxicity

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

LD50 oral >2000 mg/kg bw in rats, rabbits, guinea pigs, chicks and mice.
LD50 dermal >2000 mg/kg bw in rats, rabbits and guinea pigs.
(Krauskopf 1973; refer to NICNAS 2008a; 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 DMP.

Rats survived an exposure to saturated vapour or aerosol of 10.4 mg/L/6 hr and cats to a mist of 2.0 mg/L/6.5 hr, but one of two cats died when the concentration was increased to 10.1 mg/L/6.5 hr (Levinskas 1973*; BIBRA 1994; REACH Dossier).

6.3 Irritation and sensitisation

6.3.1 Skin irritation

The available data suggest that DMP causes minimal skin irritation in rabbits, guinea pigs and mice (Dow Chemical 1946*; Draize et al. 1948; Dupont 1970*; Lehman 1955; NTP 1995; refer to NICNAS 2008a; US CPSC 2011 for review).

In humans, irritation was observed in 3/190 subjects (and equivocal results in another six subjects) following closed patch tests with 0.5 % DMP in a cream base (Takenaka et al. 1970*). No irritation was observed in 10 subjects following an application of 50 % DMP in ethanol onto the perspiring face (Frosch & Kligman 1977).

6.3.2 Eye irritation

The available data suggest that DMP causes minimal eye irritation in rabbits (Carpenter & Smyth 1946*; Draize et al. 1944; Lawrence et al. 1975; Liggett 1988*; refer to NICNAS 2008a; US CPSC 2011 for review).

McLaughlin (1946*) reported that human contact with undiluted DMP produced corneal epithelial damage, which following medical treatment healed within 48 hours, with no loss of vision.

6.3.3 Sensitisation

The available data suggest that DMP is not likely to be a skin sensitiser. In rabbits, DMP was not an active sensitiser (Draize et al. 1948; Lehman 1955). In humans, minimal allergic patch test reactions were observed with 5 % DMP over a six-year period (Kanerva et al. 1999) and with a mixture of 2 % DMP, 2 % DEP and 2 % DBP (in petrolatum) among a large population of dermatitis patients (1/1532 patients) (Schulsinger & Mollgaard 1980*). An uncommon case of spectacle frame dermatitis was noted in a 71-year-old woman who showed positive patch tests to 5 % DMP, 5 % DEP or 5 % DBP (Oliwiecki et al. 1991).

6.4 Repeated dose toxicity

The repeated dose toxicity of DMP after oral and dermal exposure was evaluated in rabbits, rats and mice. A summary of these studies is provided in Table 6.1.

A slight, but statistically significant, reduction in growth or body weight gain was reported in female rats fed ≥4 % DMP (approximately ≥2000 mg/kg bw/d) in their diet over two years (Lehman 1955), or exposed dermally to 2400 mg/kg bw/d during gestational days (GD) 6–15 or 1–20 (Hansen & Meyer 1989). Rats fed ~3600 mg/kg bw/d during GD 6–15 also showed reduced food consumption and body weight gain (Field et al. 1993). There were no significant body weight changes or clinical findings in mice after dermal application of DMP (0.1 mL/kg) for one year (NTP 1995).

While chronic nephritis (kidney inflammation) occurred in rats at very high doses of ≥4000 mg/kg bw/d (Lehman 1955) and in rabbits at ≥2400 mg/kg bw/d (Draize et al. 1944; 1948) after a two-year diet or 90-day dermal exposure respectively, animal livers were more sensitive to the effects of DMP. DMP exposure led to increased liver weight in rats at ≥1000 mg/kg bw/d after a seven-day diet (Oishi & Hiraga 1980) or 50-day dermal application (Gleiberman et al. 1975*). Decreased liver total lipid and cholesterol at 500 mg/kg bw/d was also observed in a 21-day feeding study in rats (Bell et al. 1978). In rabbits, increased bilirubin and liver damage were seen at 600 mg/kg bw/d after a 50-day dermal exposure (Gleiberman et al. 1975*). No information on histopathology or mode of action was available from these studies.

Kwack et al. (2009) reported no changes in kidney or liver weight, but a reduction in haemoglobin at 500 mg/kg bw/d after 28 days of gavage treatment in rats. Other NOAELs suggested for kidney effects in rats were ~3600, 2000 and 1000 mg/kg bw/d (Field et al. 1993; Lehman 1955; Oishi & Hiraga 1980 respectively) and for liver weight changes 500, 840 and 2000 mg/kg bw/d (Bell et al. 1978; Field et al. 1993; Lehman 1955 respectively).

However, these studies had diverse methodologies. Most were not conducted according to accepted regulatory or standardised protocols with insufficient doses, observations, or documentation of study designs and observed effects. Accordingly, no valid dose response information or a reasonable NOAEL for kidney and liver effects of DMP could be derived based on their collective results. For the purposes of this assessment, the 16-week dietary study in rats by Brown et al. (1978) that is considered critical in identifying a NOAEL for repeated dose effects

of DEP, a LMW phthalate analogue to DMP (NICNAS 2011), was used to fill data gaps for DMP on the basis of the category approach (refer to Section 3 and US EPA 2010 for the definition of a LMW phthalate).

In this DEP study, relative kidney and liver weights were increased significantly in both sexes at 3160 mg/kg bw/d. In female rats, increases in relative liver weights were dose-dependent and statistically significant at all doses. In male rats, small intestine weights were increased at 3160 mg/kg bw/d whereas stomach weights were increased at ≥750 mg/kg bw/d. There was neither abnormal histopathology of the kidney, liver or digestive organs, nor significant effects on haematology, serum enzymes or urinary parameters. Considering DEP and DMP treatment led to the onset of macroscopic kidney and liver effects at comparable doses in rats (3160 vs 4000 and 750 vs 1000 mg/kg bw/d, respectively), the read-across approach is considered valid. A conservative NOAEL of 150 mg/kg bw/d was established from the Brown et al. (1978) study for both DEP and DMP (read-across), based on the dose-dependent increased liver weight in females and increased stomach weight in males at 750 mg/kg bw/d. No histological or biochemical evidence of peroxisome proliferation was found and so the extent to which this may explain the observed liver hypertrophy is unclear. There was also no histological or biochemical evidence to explain the mechanism of hypertrophy in other organs. In conclusion, although some organ weight changes could be partially explained on the basis of inconsistencies in control data, from a mechanistic perspective these organ effects could not be discounted and therefore are regarded as relevant to a human risk assessment.

6.5 Genotoxicity and carcinogenicity

In bacterial reverse mutation (Ames) tests, positive results were observed in the absence of metabolic activation with *Salmonella typhimurium* TA100 in 2/5 studies (Agarwal et al. 1985; Kozumbo et al. 1982; Kubo et al. 2002; Seed 1982; Zeiger et al. 1985) and with TA1535 in 1/2 studies available (Agarwal et al. 1985; Zeiger et al. 1985). Other tested strains such as TA98, TA1537, TA1538 and TA2637 showed negative responses to DMP with or without activation. Addition of a metabolic activation (S9) abolished the mutagenic effects of DMP in TA100 and TA1535 cultures (Agarwal et al. 1985; Kozumbo et al. 1982; Seed 1982), which was consistent with the finding that the metabolite monoester MMP collected from the urine of rats treated intraperitoneally with 2000 mg/kg bw/d DMP was not mutagenic in the Ames test (Kozumbo & Rubin 1991).

In tests with mammalian cells, DMP with activation increased mutation frequency in a mouse lymphoma assay (Barber et al. 2000) and induced sister chromatid exchanges but not chromosomal aberrations in Chinese hamster ovary cells (Loveday et al. 1990). DMP did not cause chromatid-type aberrations in human leukocytes (Tsuchiya & Hattori 1976) or increase transformation frequency in mouse cells (Barber et al. 2000).

In vivo, the increased chromosomal aberrations in the liver of rats exposed dermally (five times a week for one month) to DMP at 1250 mg/kg bw/d was considered equivocal given that rat liver S9 microsomal preparations were shown to be capable of blocking the mutagenic action of DMP in bacteria (Kozumbo & Rubin 1991). DMP was negative in both bone marrow chromatid exchange test (intraperitoneal injection of 1400 mg/kg bw/d) and dominant lethal mutation tests in mice (dermal application of 1250 mg/kg bw/d at five times a week for two months) (Yurchenko 1977*).

In humans, the urinary metabolite MMP collected from 141 male partners of subfertile couples was found not to be associated with increased DNA damage in sperm using the neutral Comet assay (Duty et al. 2003; Hauser et al. 2007).

Carcinogenicity studies using DMP are limited. The only available one-year initiation/promotion study indicated that neither DMP nor DEP was able to initiate or promote skin carcinogenesis with or without the presence of known skin tumour initiators/promoters (NTP 1995).

The evaluation of DEP carcinogenicity in two-year dermal studies in both rats and mice is thus taken into consideration. DEP at the mid dose tested (520 mg/kg bw/d) was shown to increase non-neoplastic basophilic foci in the liver of male mice. This effect was not dose-related and not reported in female mice. Marginally increased incidences of combined hepatocellular adenomas and carcinomas were noted in both sexes, but they were statistically significantly dose-related only in male mice. Due to lack of a dose-response relationship in female mice and similar incidences of hepatocellular neoplasms between the high dose male mice and historical controls, the increases were considered equivocal evidence of carcinogenic activity for DEP. In a similar two-year carcinogenicity study in rats, no evidence of increased neoplasia was found other than acanthosis at the skin site of application, which was considered an adaptive response to irritation. No other lesions or neoplasms were noted in these two-year studies (NTP 1995).

Overall, on the basis of weight of evidence, the available data do not support a mutagenic, genotoxic or carcinogenic potential for DMP.

6.6 Reproductive toxicity

6.6.1 Effects related to fertility and sexual development

Similarly to DEP, DMP had no effects on testis weight or testis atrophy in rats after oral doses of ≤1400 mg/kg bw/d (Foster et al. 1980; Gray et al. 2000; Oishi & Hiraga 1980; Kwack et al. 2009). DMP did not alter male rat sexual differentiation such as decreased AGD (anogenital distance), increased nipple retention or testicular pathology at ≤750 mg/kg bw/d (Gray et al. 2000; Liu et al. 2005). Decreased implantations, litter sizes or viable litters were also not observed following DMP or DEP exposure (cf. DBP or DEHP exposure, NICNAS 2010; 2013) at gavage doses of 3500 mg/kg bw/d during GD 7–14 in mice or intraperitoneal injections of 2400 mg/kg bw/d on GD 3, 6 and 9 in rats (Hardin et al. 1987; Peters & Cook 1973 respectively). However, levels of testosterone and dihydrotestosterone (a more potent androgen than testosterone, essential for sexual differentiation, male genital and prostate development) in the testes and serum were significantly reduced in rats treated with 2 % (~1000 mg/kg bw/d) DMP or 2 % DEP (Oishi & Hiraga 1980). Considering all together, a reasonable NOAEL for DMP effects on fertility and sexual development cannot be determined based on these limited animal studies.

In vitro, both DMP (9, 94, 940 µmol/L) and DEP (33, 330, 3300 µmol/L) decreased sperm motility at the mid and high doses (which were statistically significant and dose dependent), although some sperm motion parameters were more resistant to DMP than to DEP, possibly due to the lower doses of DMP tested. For example, LIN (linearity or a measure of swimming pattern) and VSL (straight line velocity or a measure of progression) were similarly reduced by DMP and DEP at the high doses, whereas reduction of VCL (curvilinear velocity or a measure of vigour) was statistically significantly induced by DEP but not DMP (Fredricsson et al. 1993).

In human studies, statistically significant higher levels of phthalates (including DMP, DEP, DBP and DEHP) were identified in the semen samples of infertile men compared with fertile men (Pant et al. 2008; Rozati et al. 2002). MMP and MEP (urinary monoester metabolites of DMP and DEP respectively) did not show an overall pattern of reduction in LIN, VSL or VCL compared with MBP and MEHP (urinary monoester metabolites of DBP and DEHP respectively) (Duty et al. 2004). There was also no correlation found between DMP or DEP and MMP or MEP levels (depending whether semen or urine samples were analysed respectively) and sperm motility (Duty et al. 2003; Hauser et al. 2006; Pant et al. 2008). However, Duty et al. (2003) reported a weak (statistically non-significant) association of MMP with sperm morphology, although this was not seen in other studies by Hauser et al. (2006) or Pant et al. (2008). Reduced sperm concentration was unrelated to DMP or MMP levels, but was found to have a statistically significant association with DEP and MEP (Pant et al. 2008; Wirth et al. 2008). Reports of lack of correlations between urinary MEP and sperm concentration were also available (Duty et al. 2003; Hauser et al. 2006).

Breast milk levels of MMP and MEP were positively correlated with the ratio of luteinising hormone (LH) to free testosterone (a measure of Leydig cell function) in infants aged three months (62 cryptorchid/68 healthy boys) (Main et al. 2006). This finding is limited by questions concerning the reliability of breast milk samples as indicators of DMP and DEP exposure and by other confounding factors such as the measured presence of other phthalate metabolites. The anogenital index (AGI = AGD/weight) among male infants was statistically significant and inversely related to maternal urinary concentrations of MEP and MBP, but not with MMP, MEHP or other two metabolites of DEHP (Swan et al. 2005). The AGD was suggested to be an indication of androgen levels or action and a masculinisation process (Sharpe 2005). In a follow-up study, when the AGD was corrected for weight percentile (the expected weight for age) using the Centers for Disease Control and Prevention (CDC) growth charts, the relation of this corrected AGD with DEHP metabolites had become statistically significant while those with MMP were of borderline significance ($p = 0.053$) (Swan 2008). However, Suzuki et al. (2012) did not find any significant associations between MMP, MEP or other phthalate monoesters (except MEHP) and the AGI.

The relationship between adverse reproductive effects in women and phthalate exposures has been poorly studied and mostly limited to cases of endometriosis. The one study available for DMP stated that women with endometriosis showed significantly higher serum concentrations of phthalates, including DMP, DEP and DBP

compared with the control group (Rozati et al. 2008). However, there were inconsistencies in reporting statistical results and the detection of DEP in this study precluded drawing conclusions from this publication.

Overall, the studies reported above indicate that DMP is not likely to be a more potent developmental toxin than DEP to the male reproductive system.

6.6.2 Other foetal/developmental effects

Perinatal exposure to DMP at oral doses up to 3570 mg/kg bw/d (cf. DEP at 3200 mg/kg bw/d) and dermal doses of 2400 mg/kg bw/d showed no foetal or neonatal toxicity in a number of rodent studies (Clewell et al. 2010; Field et al. 1993; Gray et al. 2000; Hansen & Meyer 1989; Hardin et al. 1987; Liu et al. 2005; Plasterer et al. 1985).

Singh et al. (1972) reported decreased foetal weight and skeletal malformations such as elongated and fused ribs, and abnormal or incomplete skull bones in rats after intraperitoneal exposure (GD 5, 10, 15) to DMP and DEP at 400 and 500 mg/kg bw/d respectively (the lowest doses tested). DMP at 1340 mg/kg bw/d also induced foetal abnormalities and deaths. However, the effects were considered inconsistent with findings from the Peters and Cook (1973) study using a similar exposure regime and with other studies that used a larger sample size and oral and dermal routes of administration. In addition, the human relevance of the observed effects after intraperitoneal exposure is questionable.

Considering all these factors together, a reasonable NOAEL for DMP-induced developmental effects cannot be determined based on these limited animal studies.

In humans, maternal urinary LMW phthalate monoesters (sum of MMP, MEP, MBP and MIBP) from a cohort of 404 New York women had a positive association with gestational age and head circumference, but not with birth length or weight. The extent to which these birth outcomes were related to maternal anthropometry was not known (Wolff et al. 2008). It should be noted that the Phthalate Esters Panel classifies DBP as a transitional phthalate, rather than a LMW phthalate (see Section 2.1). The relationship between prenatal exposure to phthalates (whether measured as individual monoesters MMP, MEP, MBP or their sum) and birth outcomes, however, was not significant in a study of 149 Japanese pregnant women and their newborns by Suzuki et al. (2010).

6.6.3 Determination of NOAELs for fertility-related and developmental effects

Table 6.1 provides a summary of fertility-related and developmental effects of DMP.

Animal data for DMP are limited, with no available one- or two-generation reproductive toxicity studies. In addition, inconsistent correlations have been obtained from human studies that could be due to different study populations with potentially different genetic susceptibilities to the phthalate effects as well as different sampling designs (Wirth et al. 2008). Therefore, given DMP and DEP share similar toxicity profiles, particularly at comparable doses, based on the available studies on male sexual function, a well-conducted two-generation dietary study in rats by Fujii et al. (2005) was used for the purposes of this assessment. This study was considered critical in identifying a NOAEL for reproductive effects of DEP (NICNAS 2011) and was used to fill gaps in DMP data based on a category approach.

In this study, there was no effect on testis weight at doses up to 1016 mg/kg bw/d; however, reduced testosterone levels were observed in F0 males from doses of 197 mg/kg bw/d. In addition, there was a slight, but statistically significant and dose-dependent, increase in the frequency of abnormal and tailless sperm in the F0 and F1 generations, although it did not affect fertility outcomes. Based on this study, a NOAEL of 40 mg/kg bw/d was established for fertility-related effects given the reduced testosterone levels and the increased incidence of abnormal sperm at 197 mg/kg bw/d. DEP was also found to reduce pup weight at weaning and delay onset of pinna detachment and vaginal opening in the high dose rats (m-f 1016–1375 mg/kg bw/d), thus the NOAEL for developmental effects was determined to be 197 mg/kg bw/d (Fujii et al. 2005).

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

Historically, health impacts associated with phthalates have been linked most strongly to reproductive effects. The majority of data on the mode of action of phthalates in inducing reproductive effects involve studies of mid molecular weight (so-called 'transitional') phthalates such as DEHP (reviewed by Foster, 2005; Ge et al. 2007; Hu et al. 2009; NICNAS 2010). These studies support a mode of action for transitional phthalates in rodents

involving effects on steroidogenesis and expression of genes critical for reproductive system development. The extent to which this mode of action for transitional phthalates reflects the mode of action for LMW phthalates such as DMP is not certain. Compared with transitional phthalates such as DEHP, there is insufficient information to examine the mode of action of DMP on male reproductive tract development and sexual function.

In in vitro studies, DMP and DEP exhibited no detectable binding to human oestrogen receptors (hER) (Nakai et al. 1999; Toda et al. 2004) and showed extremely weak oestrogenic activity in both recombinant and two-hybrid yeast assays (Harris et al. 1997; Nishihara et al. 2000). Neither DMP nor DEP demonstrated hER-mediated oestrogenic activity or antiandrogenic activity in a reporter gene assay (Takeuchi et al. 2005). Phthalate monoesters, including MMP and MEP, were also found to be inactive on the proliferation of MCF-7 human breast cancer cell line (Okubo et al. 2003). Considering the in vitro findings with LMW phthalates (refer to NICNAS 2011 for DEP) and the previously assessed transitional phthalate DEHP (NICNAS 2010) and HMW phthalate DINP (NICNAS 2012) collectively, it appears that direct binding to oestrogen or androgen receptors is not the likely mode of action for phthalates to mediate their effects on testes and testicular hormones.

No in vivo mode of action studies are available for DMP.

Overall, the available human data are limited and do not provide sufficient evidence for a causal relationship between exposure to DMP or DEP and possible adverse health effects. There are also uncertainties with respect to the exact mechanism of DMP or DEP action on developmental and fertility-related parameters in rodents, although the mechanism appears to involve alterations of the endocrine function. In the absence of more detailed information, the mode of action for DMP (read-across) and DEP effects on testosterone production, pup weight and onset of development are considered to be parallel in rats and humans if the exposure to DMP or DEP is high and within a critical window of development. Therefore, the effects observed in animal studies are regarded as relevant to a human risk assessment.

Table 6.1: Summary of repeated dose toxicity effects of DMP

Species **Route and duration of exposure**	**Doses (mg/kg bw/d)** **NOAEL/LOAEL and effects**	**References**
Repeated dose studies (oral)		
Rats (f), 10/group	2, 4, 8 % (~1000, 2000, 4000)	Lehman 1955
Diet, 2 years	1000 NOAEL	BIBRA 1994
	2000: ↓ growth	
	4000: ↓ growth, chronic nephritis	
Rats (m), SD, 8/group	0.5 % (~500)	Bell et al. 1978
Diet, 21 days	500: ↓ liver total lipid & cholesterol	BIBRA 1994
Repeated dose studies (dermal)		
Rabbits	4 mL/kg (~4800)	Dow Chemical 1946*
Dermal, occlusive	4800: ↓ HCT	ECB 2000
25 applications/33 days		HSDB 2012
Rabbits	0.5, 1, 2, 4 mL/kg (~600, 1200, 2400, 4800)	Draize et al. 1944; 1948
Dermal, non-occlusive		Lehman 1955
90 days	1200 NOAEL	BIBRA 1994
	2400: nephritis	
	4800: lung oedema, chronic nephritis and liver damage	

Species Route and duration of exposure	Doses (mg/kg bw/d) NOAEL/LOAEL and effects	References
Rabbits Dermal 50 days	600 600:↑ bilirubin, ↑ globulins, kidney and liver damage	Gleiberman et al. 1975* ECB 2000 REACH Dossier
Rats Dermal 50 days	1250 1250: ↑ glucose, ↑ globulins, ↑ liver weight	Gleiberman et al. 1975* ECB 2000 REACH Dossier
Rats (m) Dermal 3 months	200, 1250, 2000 200 NOAEL 1250: altered kidney function and nervous system	Timofievskaya et al. 1976* ECB 2000 REACH Dossier
Mice, CD-1, 50/group Dermal, non-occlusive 1 year (5 times/week)	0.1 mL/kg 0.1 mL NOAEL No effects at the sole dose used	NTP 1995
Studies on testes and testicular function		
Rats, SD, 12/group Gavage, 4 days	1400 1400 NOAEL	Foster et al. 1980
Rats, Wistar, 10/group Diet, 7 days	2 % (~1000) 1000: ↓ testosterone, ↓ dihydrotestosterone, (↑ liver weight)	Oishi & Hiraga 1980
Rats, SD, 6/group Gavage, 28 days	500 (DMP) or 250 (MMP) 500 NOAEL (sperm count and motility) 500: (↓ Hb)	Kwack et al. 2009
Prenatal developmental toxicity studies		
Rats, SD, 5/group Intraperitoneal GD 5, 10, 15	0.34, 0.68, 1.13 mL/kg (400, 800, 1340) ***Developmental*** 400: ↓ foetal weight, ↑ skeletal abnormalities 1340: ↑ foetal abnormalities, resorptions and deaths	Singh et al. 1972 BIBRA 1994
Rats, SD, 5/group Intraperitoneal GD 3, 6, 9	0.5, 1, 2 mL/kg (600, 1200, 2400) ***Developmental*** 2400 NOAEL ***Fertility-related*** 2400 NOAEL ***Maternal*** 600 NOAEL	Peters & Cook 1973

Species Route and duration of exposure	Doses (mg/kg bw/d) NOAEL/LOAEL and effects	References
Mice, CD-1, 36/group Gavage, GD 7–14	3500 ***Developmental*** 3500 NOAEL ***Maternal*** 3500 NOAEL	Plasterer et al. 1985
Mice, CD-1, 43-50/group Gavage, GD 6–13	3500 or 5000 ***Developmental*** 5000 NOAEL ***Maternal*** 3500 NOAEL 5000: 12/43 deaths	Hardin et al. 1987
Rats, Wistar, 24–25/group Dermal, Occlusive GD 6–15 or 1–20 (2 hours/day)	0.5, 1, 2 mL/kg (600, 1200, 2400) ***Developmental*** 2400 NOAEL ***Maternal*** 1200 NOAEL 2400: ↓ body weight gain	Hansen & Meyer 1989
Rats, SD, 25–28/group Diet, GD 6–15	0.25, 1, 5 % (200, 840, 3570) ***Developmental*** 3570 NOAEL ***Maternal*** 840 NOAEL 3570: ↓ food consumption and body weight gain; ↑ relative liver weight	Field et al. 1993
Rats, SD, 5/group Gavage, GD 12–19	500 ***Developmental*** 500 NOAEL	Liu et al. 2005
Rats, SD, 2–3/group GD 12–19	500 ***Developmental*** 500 NOAEL	Clewell et al. 2010
Postnatal developmental toxicity studies		
Rats, SD, 5/group Gavage, GD 14–PND 3	750 ***Developmental*** 750 NOAEL ***Fertility-related*** 750 NOAEL ***Maternal*** 750 NOAEL	Gray et al. 2000

↓ = decreased; ↑ = increased; F0 = parental generation; F1= first filial/offspring generation; F2 = second filial/offspring generation; GD = gestational day; Hb = haemoglobin; HCT = haematocrit; m-f = male-female; NOAEL (shading) = no observed adverse effect level; LOAEL = low observed adverse effect level; PND = postnatal day; SD = Sprague Dawley.

6.7 Summary

DMP is rapidly and almost completely absorbed following oral administration. The bioavailability via the oral route is assessed as 100 % for both adults and children. Bioavailability via dermal absorption is not likely to exceed 10 % in humans. Data on DMP absorption via the inhalation route are limited; a default bioavailability of 100 % is considered appropriate for this route.

Tissue distribution of DMP is widespread including breast milk and the placenta but there is no evidence of accumulation. DMP is also rapidly metabolised and excreted, predominantly as a metabolite, monomethyl phthalate (MMP), via the urine.

DMP exhibits low acute toxicity in animals and is not expected to have significant acute toxicity in humans. Also, DMP is not expected to have eye or skin irritation, or skin sensitising potential in humans.

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

Toxic effects related to repeated DMP exposure that are regarded as relevant to a human health risk assessment include those in the liver and reproductive system, particularly in male rats. Similar effects are observed in rodents exposed to the structurally related phthalate, DEP, at comparable doses (NICNAS 2011).

Therefore, for the systemic organ effects, by applying the LMW phthalate category approach and read-across from DEP data, a NOAEL of 150 mg/kg bw/d is derived for DMP based on increased liver weight at 750 mg/kg bw/d (Brown et al. 1978).

Similarly, evaluations of the potential toxicity of DMP and DEP to the male rat reproductive system have consistently found no effect on testis weight or testis atrophy at oral doses of ≤1000 mg/kg bw/d. Both also did not alter sexual differentiation such as decreased AGD, increased nipple retention or testicular pathology at ≤750 mg/kg bw/d, as commonly noted with C4–6 transitional phthalates. However, reduced testosterone in the testes and/or in serum have been reported with DMP and DEP as well as with the transitional (DEHP) and HMW (DINP) phthalates of various potencies (NICNAS 2010; 2011; 2012). For DEP, the increased incidence of abnormal and tailless sperm in the F0 and F1 generations (which did not affect fertility outcomes) were statistically significant and dose-dependent. Reduced pup weight and developmental delay were also observed with DEP and certain other phthalates (e.g. DEP at ~1000 mg/kg bw/d cf. DINP at ~100 mg/kg bw/d). On the basis of read-cross and trend analysis of the assessed phthalate data, a two-generation dietary study in rats by Fujii et al. (2005) is considered appropriate for filling data gaps by identifying a NOAEL of 40 mg/kg bw/d and 197 mg/kg bw/d based on the fertility-related and developmental effects of DMP at higher doses, respectively.

Table 6.2 lists the critical studies for DMP (read-across from DEP), the health effects observed and the effect levels selected for risk characterisation.

Table 6.2: Endpoints selected for risk characterisation of DMP

Toxicity	NOAEL (mg/kg bw/d)	LOAEL (mg/kg bw/d) & effects	Species and age at treatment	Reference
Systemic organ effects (increased liver weights)	150	750: ↑ relative liver weight	Rat, CD Adults	Brown et al. 1978
Fertility-related effects (reduced testosterone)	40	197: ↓ serum testosterone (F0), ↑ abnormal and tailless sperm (F0, F1)	Rat, SD Adults	Fujii et al. 2005
Developmental effects (reduced pup weight)	197	1016: ↓ pup weight PND 21 (F1, F2) & PND 4–21 (f, F1), delayed pinna detachmen (m, F1) and vaginal opening (F1)	Rat, SD Adults	Fujii et al. 2005

↓ = decreased; ↑ = increased; F0 = parental generation; F1= first filial/offspring generation; F2 = second filial/offspring generation; m-f = male-female; NOAEL = no observed adverse effect level; LOAEL = low observed adverse effect level; PND = postnatal day; SD = Sprague Dawley.

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/NOAEC and deriving a MOE as follows:

1. Identification of critical health effect(s);
2. Identification of the most appropriate/reliable NOAEL (if available) for the critical health effect(s);
3. Where appropriate, comparison of the estimated or measured human dose or exposure (EHD) to provide a MOE:

MOE = NOAEL/EHD; and

4. Characterisation of 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 judgment 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 database, the nature and severity of effect(s) and intra/interspecies variability.

In this assessment, the MOE methodology was used for characterising the public health risks from DMP exposure through use of:

- toys and childcare articles for children; and
- cosmetic products for the general population.

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 liver and reproduction/development at future life stages related to long-term exposure through repeated handling and mouthing of toys. Table 7.1 provides the MOE calculated from the internal DMP dose in children (see Table 5.3) and the dose at which no adverse effect is observed on target organs and/or systems in laboratory animals, i.e. the NOAEL (see Table 6.2).

Table 7.1: Calculated MOE in children for the critical health effects of DMP 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 organ effects (increasec liver weight)	150	428000	72000
Fertility-related effects (reduced testosterone)	40	114000	19000
Developmental effects (reduced pup weight)	197	562000	95000

The risk estimates for the toxicity effects of DMP on the liver and reproductive/developmental system in both exposure scenarios of toys used by children derive MOEs above 10000 (Table 7.1) and hence indicate a low risk of these adverse health effects under these conditions of exposure.

A 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 DMP arise mainly from inadequate data and include:

- absence of Australian-specific data on DMP 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 DMP from plastic matrices through the skin;
- the 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 DMP in children following repeated exposure.

Areas of concern

The risk estimates above do not indicate particular areas of concern from exposure of children to DMP via handling/mouthing of toys and childcare articles. Exposure of children to DMP can also occur from application of personal care products such as baby lotions and creams (Tables 5.5 and 7.4). However, the contribution of exposure through handling/mouthing of toys and childcare articles to the combined exposure scenarios to DMP is unlikely to represent a concern, given the large magnitudes of MOE for use of toy and childcare articles.

It should be noted that DMP is not found in toys in isolation, but generally with primary and secondary plasticisers such as DINP, DBP or DEHP (at maximum 1 %; ACCC 2011). These combined exposures to DMP together with multiple phthalates acting on the same biological targets from use of toys, and from the combination of the two exposure scenarios considered in this assessment are discussed in the estimation of cumulative risks in Appendix A below.

7.2.2 Estimation of MOE for the general population from use of cosmetics

Given the low acute toxicity, low skin and eye irritation and skin sensitising potential for DMP, the risk of adverse acute effects for consumers from use of DMP-containing cosmetics is low.

The potential risks from cosmetic use are related to long-term exposure through repeated use, especially of leave-on products. Table 7.2 provides the MOE calculated from the internal DMP dose in adults arising from both dermal and inhalation contact with cosmetics (289.08 µg/kg bw/d, see Table 5.7) and the conservative NOAELs selected for the liver and reproductive effects (see Table 6.2).

Table 7.2: Calculated MOE in adults for the critical health effects of DMP from use of cosmetic and personal care products

Toxicity	NOAEL (mg/kg bw/d)	MOE for worst-case exposure scenario
Systemic organ effects (increased liver weight)	150	519
Fertility-related effects (reduced testosterone)	40	138

The risk estimates for the liver and reproductive toxicity of DMP derive MOEs above 100 (Table 7.2) and hence indicate a low risk of these adverse health effects in the general population from simultaneous use of multiple cosmetic products containing DMP.

As the DMP concentration in the body lotion increases the MOE in adults reduces (Table 7.3) without any other changes in the exposure modelling assumptions.

Table 7.3: Calculated MOE in adults for the reproductive effects of DMP at varying concentrations from the estimated aggregate exposure to multiple cosmetic products

	MOE			
	[a]0.25 %	0.5 %	0.75 %	1 %
$D_{int,\ dermal+inh}$ (μg/kg bw/d)	259.60+29.48	287.53+29.48	315.46+29.48	343.38+29.48
MOE	138	126	116	107

[a] the upper limit of the surrogate DEP in body lotion reported by the Australian industry.

From Table 5.4, the only cosmetic product that could be applied repeatedly on large areas of the body of infants or young children is body lotion. Thus, exposure to DMP from the use of body lotions was also estimated specifically for children from three different age groups based on the SA/BW ratios provided by SCCP (2006). Based on the estimates for use of body lotion containing 0.25 % DMP (the maximum level reported for the surrogate DEP in this type of product in Australia), the MOE for reproductive effects of DMP, using the NOAEL of 40 mg/kg bw/d, is also found to be well above 100. At higher DMP concentrations in body lotion, the MOE in children will be lower. In particular, at 0.75 % DMP, the MOE in newborns is marginally above 100 and is of concern (Table 7.4). The MOE at 0.75 % for 6–12 month infants also gives rise to concern, especially if there are combined exposures to DMP and other phthalates acting on the same biological targets from handling and mouthing of toys and childcare articles.

Table 7.4: Calculated MOE in children for the reproductive effects of DMP at varying concentrations from the estimated exposure to body lotion

Infant age	$D_{int,derm}$ at 0.25 % (μg/kg bw/d)	MOE			
		[a]0.25 %	0.5 %	0.75 %	1 %
Newborn	123.21	324	162	108	81
6 months	96.43	414	207	138	103
12 months	85.71	466	233	155	116

[a] the upper limit of the surrogate DEP in body lotion reported by the Australian industry.

Uncertainties in the risk estimate

Uncertainties involved in the risk characterisation for the general population from cosmetic use results from database limitations. Australian data on the use patterns of consumer products are not available, therefore there is no precise exposure assessment of DMP in cosmetics. Given the limited data available, conservative plausible assumptions, such as daily use of multiple cosmetics containing DMP, have been used to determine the risk to consumers.

In addition, Australian-specific data are not available on typical or maximum DMP content in identified types of cosmetic products. Therefore, for this risk characterisation, the DMP content in products is assumed to be similar to that currently reported for DEP across different types of cosmetic products in Australia (see Section 5.3 and Table 5.4). The extent to which this assumption of substitution overestimates DMP exposure via cosmetics currently, or in the future, is not known.

The exposure and MOE estimates assume a reasonable worst-case scenario where all possible DMP-containing cosmetic products are used daily. However, use patterns of cosmetics are likely to vary greatly among individuals. For most adult consumers, this assumption will lead to an overestimation of risk. In addition, the MOE estimates do not consider specific subpopulations such as children and teenagers, who may differ significantly in their use patterns of cosmetics. Use of several products of one preferred manufacturer with DMP as an ingredient in their formulations may also contribute to increased exposure and a decrease of MOE in subpopulations inclined to brand loyalty.

There is a high degree of uncertainty associated with the exposure and risk estimates in newborns and infants as there are very limited data on use of DMP in baby lotions or creams (Koniecki et al. 2011). In addition, information related to use pattern and/or levels of personal care products for babies and children are not available.

The inadequate human data on the health effects of DMP in adults and young children following repeated exposure also represents an additional uncertainty factor in these risk estimates.

Areas of concern

The risk estimates for the liver and reproductive toxicity of DMP above indicate low risk for both children and the general population from use of cosmetic products containing DMP at the current reported or likely levels. However, there is a concern for one type of cosmetic product, body lotion, which could be applied repeatedly on large areas of the body particularly for infants or young children, if the concentration of DMP used in this product increases (Table 7.4). These MOE findings are supportive of the current prohibition of the use of DMP at >0.5 % in body lotion (SUSMP).

As discussed above, use patterns of cosmetic products are likely to vary among individuals and even subpopulations in the general population (e.g. women, men, young adults/teenagers) and the assumptions used in the exposure scenario may lead to overestimation of risk for certain individuals. In addition, the sensitivity of individuals and subpopulations to the critical health effects associated with DMP might vary significantly. Determining the level of exposure to DMP for the different subpopulations that may be at highest risk in the cosmetic use scenario is difficult. However, the results of the biomonitoring studies (see Section 5.3), where substantial differences were detected between the average levels for the population (mean or median) compared with the outliers, clearly indicate that some members of the population have been exposed to much higher DMP doses than the average population. For example, the 95th percentile biomonitoring value reported for cosmetic use in infants aged 2–28 months is 228.3 µg/g creatinine, compared with 1.6 µg/g creatinine for the median (Sathyanarayana et al. 2008). This indicates that high exposure scenarios might be applicable to a subset of the population. Increases in DMP concentrations above those currently reported to be used in Australia, especially in infants or young children, is of concern as these subgroups of the population are considered most sensitive to the reproductive toxicity of phthalates including DMP.

In addition, cumulative risks due to combined exposures can arise from:

- use of cosmetics containing multiple phthalates acting on the same biological targets;
- the effects of other components in a mixed phthalate plasticiser used in children's toys and childcare articles; and
- the combination of the two exposure scenarios considered in this assessment or from multiple sources.

The estimation of cumulative risks is discussed in Appendix A below.

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 DMP.

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

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

In Australia, DMP 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 toy company specified that DMP content in imported toys for children aged four years and older is 0.28 %.

8.2 Public health risk standards—Cosmetics

In Australia, the listing of DMP in Appendix C of SUSMP (Poisons Standard) excludes it from use 'in sunscreens, personal insect repellents or body lotion preparations for human use except in preparations containing 0.5 per cent or less of DMP'.

Limited Australian information indicates that DMP is introduced as a raw material with potential downstream use in the cosmetic and perfumery industry. It is also imported as a component of finished cosmetic products and fragrances at a concentration range of 0.00004–34 %.

Labelling

There are currently no specific labelling requirements for consumer goods that contain DMP. 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—Cosmetics & 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).

Appendix A Cumulative risk estimates from combined exposures to multiple phthalates

Cumulative risks due to combined exposures can arise 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 DMP 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 and 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 % + DMP 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 % + DMP 0.5 % + DEHP 1 %) in toys and DEP 0.5 % (or DMP 0.5 %) in cosmetics.
- The combined exposure to a mixed phthalate plasticiser (DINP 41.5 % + DBP 0.5 % + DEHP 1 %) in toys and DMP 0.5 % in cosmetics.

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

- $D_{int,\ oral+dermal}$ = 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.
- $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/d (Table 5.5) for DMP or DEP at 0.5 % from dermal exposure to body lotion.

The relevant cumulative MOEs are calculated from the equations:

- For 'use of toys' scenario:

  1/[(42.5/MOE of DINP + 0.5/MOE of DMP)/43] or

  1/[(41.5/MOE of DINP + 0.5/MOE of DMP + 1/MOE of DEHP)/43] or

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

- For ‘use of cosmetics’ scenario:

  DMP or DEP is currently allowed to be used in body lotion at maximum 0.5 % in Australia (SUSMP) and they share the same NOAEL, hence MOE = NOAEL/EHD.

- For combined scenarios:

  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 in children (Table A.1) and support the current prohibition of the use of DMP at >0.5 % in body lotion (SUSMP). These MOEs are specifically calculated for six-month-old infants demonstrate 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 SA/BW ratio (Table 5.5).

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 DMP[c] or DEP[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%		*DMP 0.5%*					*DEP 0.5% (or DMP 0.5%)*		
Fertility-related	50	283	40	226			282	40	207	119
Developmental	50	283	197	1113			285	197	1021	223
	DINP 41.5%		*DMP 0.5%*		*DEHP 1%*			*DEP 0.5% (or DMP 0.5%)*		
Fertility-related	50	283	40	226	4.8	27	231	40	207	109
Developmental	50	283	197	1113	46	260	284	197	1021	222
	DINP 41.5%		*DBP 0.5%*		*DEHP 1%*			*DMP 0.5%*		
Fertility-related	50	283	10	57	4.8	27	223	40	207	108
Developmental	50	283	50	283	46	260	282	197	1021	221

NOAEL = no observed adverse effect level, derived from PEC assessments of DEHP, DEP, DINP and DBP (NICNAS 2010; 2011; 2012; 2013); MOE = margin of exposure (i.e. NOAEL/EHD) (Section 7.1).

[a] DINP = primary plasticiser; DMP, DEP, 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 (http://www.productsafety.gov.au; ACCC 2011).

[b] For 'use of toys' scenario, the estimated human dose (EHD) or Dint, 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 DMP)/43] or 1/[(41.5/MOE of DINP + 0.5/MOE of DMP + 1/MOE of DEHP)/43] or 1/[(41.5/MOE of DINP + 0.5/MOE of DBP + 1/MOE of DEHP)/43].

[c] From the SUSMP (Poisons Standard), DMP or DEP at >0.5 % is excluded from use in body lotion; DEHP is excluded from cosmetic use. DBP is recommended for exclusion from cosmetic use, similarly to DEHP, based on the NICNAS PEC assessment of DBP.

[d] For 'use of cosmetics' scenario, the EHD or Dint, dermal = 96.43 × 2 = 192.86 µg/kg bw/d (Table 5.5) for DMP or DEP at 0.5 % from dermal exposure to body lotion.

For combined scenarios, cumulative MOE = 1/[1/MOE of a mixed phthalate plasticiser (in toys) + 1/MOE of DEP or DMP (in cosmetics)].

References

ACCC. 2008. Cosmetics—ingredients labelling. Canberra: Australian Competition & Consumer Commission. Accessed September 2013, http://www.productsafety.gov.au/content/index.phtml/itemId/971654/fromitemId/971652

ACCC. 2011. DEHP in children's plastic items. Canberra: Australian Competition & Consumer Commission. Accessed September 2013, http://www.productsafety.gov.au/content/index.phtml/itemId/977212

Adibi JJ, Perera FP, Jedrychowski W, Camann DE, Barr D, Jacek R, Whyatt RM. 2003. Prenatal exposures to phthalates among women in New York City and Krakow, Poland. Environmental Health Perspectives 111:1719–1722.

Adibi JJ, Whyatt RM, Williams PL, Calafat AM, Camann D, Herrick R, Nelson H, Bhat HK, Perera FP, Silva MJ, Hauser R. 2008. Characterization of phthalate exposure among pregnant women assessed by repeat air and urine samples. Environmental Health Perspectives 116:467–473.

Agarwal DK, Lawrence WH, Nunez LJ, Autian J. 1985. Mutagenicity evaluation of phthalic acid esters and metabolites in Salmonella typhimurium cultures. Journal of Toxicology and Environmental Health 16:61–69.

AICS. Dimethyl phthalate, CAS No. 131-11-3. The Australian Inventory of Chemical Substances. Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/aics

Albertini R, Bird M, Doerrer N, Needham L, Robison S, Sheldon L, Zenick H. 2006. The use of biomonitoring data in exposure and human health risk assessments. Environmental Health Perspectives 114:1755–1762.

Albro PW, Moore B. 1974. Identification of the metabolites of simple phthalate diesters in rat urine. Journal of Chromatography 94:209–218.

Barber ED, Cifone M, Rundell J, Przygoda R, Astill BD, Moran E, Mulholland A, Robinson E, Schneider B. 2000. Results of the L5178Y mouse lymphoma assay and the Balb/3T3 cell in vitro transformation assay for eight phthalate esters. Journal of Applied Toxicology 20:69–80.

Bell FP, Patt CS, Brundage B, Gillies P J, Phillips WA. 1978. Studies on lipid biosynthesis and cholesterol content of liver and serum lipoproteins in rats fed various phthalate esters. Lipid 13:66–74.

BIBRA. 1994. Toxicity profile for dimethyl phthalate. Epsom, Surrey: BIBRA Information Services Ltd. Accessed September 2013, http://www.bibra-information.co.uk/profile-161.html

Bremmer HJ, Prud'homme de Lodder LCH, van Engelen JGM. 2006. Cosmetics Fact Sheet—To assess the risks for the consumers. Updated version for ConsExpo 4. The Netherlands: National Institute for Public Health and the Environment (RIVM). Report no. 320104001/2006. Accessed September 2013, http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf

Brown D, Butterworth KR, Gaunt IF, Grasso P, Gangolli SD. 1978. Short-term oral toxicity study of diethyl phthalate in the rat. Food and Cosmetics Toxicology 16:415–422.

Carpenter CP, Smyth HF. 1946. Chemical burns of the rabbit cornea. American Journal of Ophthalmology 29:1363–1372.

CDC. 2013. Revision to the fourth national report on human exposure to environmental chemicals (February 2009). Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. Accessed September 2013, http://www.cdc.gov/exposurereport/

Chanda M, Roy SK. 2006. Plastics Technology Handbook: Plastics Engineering Series. 4th ed. Boca Raton: CRC Press.

Chemical Gazette. 2006. Declaration of certain phthalate chemicals used in toys, childcare articles and cosmetics as priority existing chemicals. 7 March: 9–13. Commonwealth of Australia.

ChemIDplus. Dimethyl phthalate, CAS No. 131-11-3. ChemIDplus database. US National Library of Medicine. Accessed September 2013, http://chem.sis.nlm.nih.gov/chemidplus/

Chen SB. 1998. Appendix A Migration of DINP from polyvinyl chloride (PVC) children's products. US Consumer Product Safety Commission.

CIR. 2005. Annual review of cosmetic ingredient safety assessments—2002/2003. Cosmetic Ingredient Review Expert Panel. International Journal of Toxicology 24:1–102.

Clewell RA, Campbell JL, Ross SM, Gaido KW, Clewell III HJ, Andersen ME. 2010. Assessing the relevance of in vitro measures of phthalate inhibition of steroidogenesis for in vivo response. Toxicology in Vitro 24:327-334.

CosIng. Dimethyl phthalate, CAS No. 131-11-3. Cosmetic Ingredients & Substances Database. European Commission. Accessed September 2013, http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple

Deisinger P, Perry L, Guest D. 1998. In vivo percutaneous absorption of ^{14}C-DEHP from ^{14}C-DEHP plasticized polyvinyl chloride film in male Fischer 344 rats. Food and Chemical Toxicology 36:521–527.

Dirtu AC, Geens T, Dirinck E, Malarvannan G, Neels H, Gaal LV, Jorens PG, Covaci A. 2013. Phthalate metabolites in obese individuals undergoing weight loss: Urinary levels and estimation of the phthalates daily intake. Environment International 59:344–353.

Dow Chemical. 1946. TSCAT OTS0206677. Doc ID 878214827, N, 09.10.1946. Dow Chemical Co. Cited in IUCLID Dataset by ECB 2000.

Draize JH, Alvarez E, Whitesell MF, Woodard G, Hagan EC, Nelson AA. 1948. Toxicological investigations of compounds proposed for use as insect repellents. Journal of Pharmacology and Experimental Therapeutics 93: 26–39.

Draize JH, Woodard G, Calvery HO. 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. Journal of Pharmacology and Experimental Therapeutics 82:377–390.

Dupont. 1970. TSCAT 215032. Doc ID 878220373, S, 01.10.1970. E.I. Dupont Denemours & Co., Inc. Cited in IUCLID Dataset by ECB 2000.

Duty SM, Calafat AM, Silva MJ, Brock JW, Ryan L, Chen Z, Overstreet J, Hauser R. 2004. The relationship between environmental exposure to phthalates and computer-aided sperm analysis motion parameters. Journal of Andrology 25:293–302.

Duty SM, Calafat AM, Silva MJ, Ryan L, Hauser R. 2005. Phthalate exposure and reproductive hormones in adult men. Human Reproduction 20:604–610.

Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, Herrick RF, Christiani DC, Hauser R. 2003. Phthalate exposure and human semen parameters. Epidemiology 14:269–277.

Eastman. 2006. Eastman Plasticizers—Selector chart. Eastman Chemical Company.

ECB. 2000. IUCLID (International Uniform ChemicaL Information Database) dataset—Dimethyl phthalate, CAS No. 131-11-3. European Commission, European Chemicals Bureau.

ECB. 2003. Technical Guidance Document on Risk Assessment Part I in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Luxembourg: Office for Official Publications of the European Communities, European Chemicals Bureau.

ECETOC. 2003. Derivation of assessment factors for human health risk assessment. Technical Report No. 86. Brussels: European Centre for Ecotoxicology and Toxicology of Chemicals.

Elsisi AE, Carter DE, Sipes IG. 1989. Dermal absorption of phthalate diesters in rats. Fundamental and Applied Toxicology 12:70–77.

enHealth. 2012. Australian exposure factor guidance. Canberra: Environmental Health, Department of Health and Ageing. Accessed September 2013, http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-publicat-environ.htm

Field EA, Price CJ, Sleet RB, George JD, Marr MC, Myers CB, Schwetz BA, Morrissey RE. 1993. Developmental toxicity evaluation of diethyl and dimethyl phthalate in rats. Teratology 48: 33–44.

Foster PMD, Thomas LV, Cook MW, Gangoli SD. 1980. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. Toxicology and Applied Pharmacology 54:392–398.

Foster PMD. 2005. Mode of action: Impaired fetal Leydig cell function–Effects on male reproductive development produced by certain phthalate esters. Critical Reviews in Toxicology 35:713–719.

Fredricsson B, Moeller L, Pousette A, Westerholm R. 1993. Human sperm motility is affected by plasticizers and diesel particle extracts. Pharmacology and Toxicology 72:128–133.

Frosch PJ, Kligman AM. 1977. A method for appraising the stinging capacity of topically applied substances. Journal of the Society of Cosmetic Chemists 28:197–209.

Fujii S, Yabe K, Furukawa M, Hirata M, Kiguchi M, Ikka T. 2005. A two-generation reproductive toxicity study of diethyl phthalate (DEP) in rats. Journal of Toxicological Sciences 30:97–116.

Galleria Chemica. Dimethyl phthalate, CAS No. 131-11-3. Accessed September 2013, http://jr.chemwatch.net/galleria/

Ge RS, Chen GR, Tanrikut C, Hardy MP. 2007. Phthalate ester toxicity in Leydig cells: developmental timing and dosage considerations. Reproductive Toxicology 23:366–373.

General Motors. 1982a. Disposition of di(2-ethylhexyl) phthalate following inhalation and peroral exposure in rats. TSCATS OTS 0530339, Doc ID 86-910000683, 06.22.82.

General Motors. 1982b. Disposition of di(2-ethylhexyl) phthalate following inhalation and peroral exposure in rats. TSCATS OTS 84003A, Doc ID 878210878, 07.27.82.

Gleiberman SE et al. 1975. Collected scientific works 24:303–307. Cited in IUCLID Dataset by ECB 2000, REACH Dossier.

Gray Jr LE, Ostby J, Furr J, Price M, Veeramachaneni DNR, Parks L. 2000. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicological Sciences 58: 350–365.

Greenpeace International. 2003. PVC-free future: A review of restrictions and PVC free policies worldwide. 9th ed. Amsterdam, the Netherlands: Greenpeace International. Accessed September 2013, http://www.greenpeace.org/international/Global/international/planet-2/report/2003/6/pvc-free-future-a-review-of-r.pdf

Greenpeace International. 2005. An investigation of chemicals in 36 eaux de toilette and eaux de parfum. Amsterdam, the Netherlands: Greenpeace International. Accessed September 2013, http://www.greenpeace.org/international/Global/international/planet-2/report/2005/2/perfume-an-investigation-of.pdf

Hall B, Tozer S, Safford B, Coroama M, Steiling W, Lenevau-Duchemin MC, McNamara C, Gibney M. 2007. European consumer exposure to cosmetic products, a framework for conducting population exposure assessments. Food and Chemical Toxicology 45:2097–2108.

Hansen E, Meyer O. 1989. No embryotoxic or teratogenic effect of dimethyl phthalate in rats after epicutaneous application. Pharmacology and Toxicology 64:237–238

Hardin BD, Schuler RL, Burg JR, Booth GM, Hazelden KP, MacKenzie KM, Piccirillo VJ, Smith KN. 1987. Evaluation of 60 chemicals in a preliminary developmental toxicity test. Teratogenesis, Carcinogenesis and Mutagenesis 7:29–48.

Harris CA, Henttu P, Parker MG, Sumpter JP. 1997. The estrogenic activity of phthalate esters in vitro. Environmental Health Perspectives 105:802–811.

Hauser R, Meeker JD, Duty S, Silva MJ, Calafat AM. 2006. Altered semen quality in relation to urinary concentrations of phthalate monoester and oxidative metabolites. Epidemiology 17:682–691.

Hauser R, Meeker JD, Singh NP, Silva MJ, Ryan L, Duty S, Calafat AM. 2007. DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites. Human Reproduction 22:688–695.

Health Canada. 2008. Draft maximal list of substances prioritized by Health Canada for consideration in screening assessment under CEPA 1999. Accessed January 2013, http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/categor/max-list/index-eng.php

Hilton J, Woollen BH, Scott RC, Auton TR, Trebilcock KL, Wilks MF. 1994. Vehicle effects on in vitro percutaneous absorption through rat and human skin. Pharmaceutical Research 11:1396–1400.

Hines EP, Calafat AM, Silva MJ, Mendola P, Fenton SE. 2009. Concentrations of phthalate metabolites in milk, urine, saliva, and serum of lactating North Carolina women. Environmental Health Perspectives 117:86–92.

Johansson N, Appelgren M, Hakansson H. 2008. Phthalate diesters and their metabolites in human breast milk, blood or serum, and urine as biomarkers of exposure in vulnerable populations. Environmental Health Perspectives 116:334–339.

HSDB. 2012. Dimethyl phthalate, CAS No. 131-11-3. Hazardous Substances Data Bank. US National Library of Medicine. Accessed September 2013, http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

HSIS. Dimethyl phthalate, CAS No. 131-11-3. Hazardous Substances Information System. Canberra: Safe Work Australia. Accessed September 2013, http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Hu GX, Lian QQ, Ge RS, Hardy DO, Li XK. 2009. Phthalate-induced testicular dysgenesis syndrome: Leydig cell influence. Trends in Endocrinology and Metabolism 20:139–145.

IGHRC. 2004. Guidelines for good exposure assessment practice for human health effects of chemicals. Leicester, UK: Interdepartmental Group on Health Risks from Chemicals.

INCI. Dimethyl phthalate, CAS No. 131-11-3. International Nomenclature Cosmetic Ingredients Dictionary. Washington D.C.: Personal Care Products Council. Accessed September 2013, http://webdictionary.personalcarecouncil.org/jsp/Home.jsp

IPCS. 1994. Environmental Health Criteria 170. Assessing human health risks of chemicals: Derivation of guidance values for health-based exposure limits. Geneva: Word Health Organisation, International Programme on Chemical Safety. Accessed 2013, http://www.inchem.org/documents/ehc/ehc/ehc170.htm

IPCS. 2004. IPCS Risk assessment terminology. Geneva: International Programme on Chemical safety. Accessed September 2013, http://www.who.int/ipcs/methods/harmonization/areas/terminology/en/

Itoh H, Yoshida K, Masunaga S. 2007. Quantitative identification of unknown exposure pathways of phthalates based on measuring their metabolites in human urine. Environmental Science and Technology 41:4542–4547.

Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Berhulst FC, Witteman JC, Hofman A. 2006. The Generation R Study: design and cohort profile. European Journal of Epidemiology 21:475–484.

Kanerva L, Jolanki R, Alanko K, Estlander T. Patch-test reactions to plastic and glue allergens. Acta Dermato Venereologica 79:296–300.

Kaneshima H, Yamaguchi T, Okui T, Naitoh M. 1978. Studies on the effects of phthalate esters on the biological system (Part 2)—In vitro metabolism and biliary excretion of phthalate esters in rats. Bulletin of Environmental Contamination and Toxicology 19:502–509.

Kasper-Sonnenberg M, Koch HM, Wittsiepe J, Wilhelm M. 2012. Levels of phthalate metabolites in urine among mother–child pairs—Results from the Duisburg birth cohort study, Germany. International Journal of Hygiene and environmental Health 215:373–382.

Kluwe WM. 1982. Overview of phthalate ester pharmacokinetics in mammalian species. Environmental Health Perspectives 45:3–10.

Koniecki D, Wang R, Moody RP, Zhu J. 2011. Phthalates in cosmetic and personal care products: Concentrations and possible dermal exposure. Environmental Research 111:329–336.

Kozumbo WJ, Kroll R, Rubin RJ. 1982. Assessment of the mutagenicity of phthalate esters. Environmental Health Perspectives 45:103–109.

KozumboWJ, Rubin RJ. 1991. Mutagenicity and metabolism of dimethyl phthalate and its binding to epidermal and hepatic macromolecules. Journal of Toxicology and Environmental Health 33:29–46.

Krauskopf LG. 1973. Studies on the toxicity of phthalates via ingestion. Environmental Health Perspectives 3:61–72.

Kubo T, Urano K, Utsumic H. 2002. Mutagenicity characteristics of 255 environmental chemicals. Journal of Health Science. 48:545–554.

Kwack SJ, Kim KB, Kim HS, Lee BM. 2009. Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health Part A 72:1446–1454.

Lake BG, Phillips JC, Linnell JC, Gangolli SD. 1977. The in vitro hydrolysis of some phthalate diesters by hepatic and intestinal preparations from various species. Toxicology and Applied Pharmacology 39:239–248.

Lawrence WH, Malik M, Turner JE, Singh AR, Autian J. 1975. A toxicological investigation of some acute, short-term, and chronic effects of administering di-2-ethylhexyl phthalate (DEHP) and other phthalate esters. Environmental Research 9:1–11.

Lehman AJ. 1955. Insect repellents. Association of Food and Drug Officials 19:87–99.

Levinskas GJ. 1973. Inhalation toxicity tests. Tech Pap Reg Tec Conf, 95–100. Soc Plastics Engineers Inc.

Liggett MP. 1988. Irritant effects on the rabbit eye of dimethyl phthalate. Report 88387D/BPC 112/SE dated 27 April 1988. Huntingdon Research Centre Ltd.

Liu K, Lehmann KP, Sar M, Young SS, Gaido KW. 2005. Gene expression profiling following in utero exposure to phthalate esters reveals new gene targets in the etiology of testicular dysgenesis. Biology of Reproduction 73:180–92.

Loveday KS, Anderson BE, Resnick MA, Zeiger E. 1990. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. Environmental and Molecular Mutagenesis 16:272–303.

Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, Schmidt IM, Suomi AM, Virtanen HE, Petersen DV, Andersson AM, Toppari J, Skakkebaek NE. 2006. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. Environmental Health Perspectives 114:270–6.

McLaughlin RS. 1946. Chemical burns of the human cornea. American Journal of Ophthalmology 29:1355–1362.

Meek ME, Boobis AR, Crofton KM, Heinemeyer G, van Raaij M, Vickers C. 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS Framework. Regulatory Toxicology and Pharmacology 60:S1–S14.

Mortensen GK, Main KM, Andersson AM, Leffers H, Skakkebaek NE. 2005. Determination of phthalate monoesters in human milk, consumer milk, and infant formula by tandem mass spectrometry (LC-MS-MS). Analytical and Bioanalytical Chemistry 382:1084–1092.

Mose T, Mortensen GK, Hedegaard M, Knudsen LE. 2007. Phthalate monoesters in perfusate from a dual placenta perfusion system, the placenta tissue and umbilical cord blood. Reproductive Toxicology 23:83–91.

Nakai M, Tabira Y, Asai D, Yakabe Y, Shimyozu T, Noguchi M, Takatsuki M, Shimohigashi Y. 1999. Binding characteristics of dialkyl phthalates for the estrogen receptor. Biochemical and Biophysical Research Communications 254:311–314.

NICNAS. 2008a. Existing Chemical hazard assessment report—Dimethyl Phthalate (DMP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/other-assessment-reports/phthalates-hazard-assessment-reports

NICNAS. 2008b. Phthalates Hazard Compendium—A summary of physicochemical and human health hazard data for 24 ortho-phthalate chemicals. Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/other-assessment-reports/phthalates-hazard-assessment-reports

NICNAS. 2010. Priority Existing Chemical (PEC) assessment report—Diethylhexyl phthalate (DEHP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/pec-assessments

NICNAS. 2011. Priority Existing Chemical (PEC) assessment report—Diethyl phthalate (DEP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/pec-assessments

NICNAS. 2012. Priority Existing Chemical (PEC) assessment report—Diisononyl phthalate (DINP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/pec-assessments

NICNAS. 2013. Priority Existing Chemical (PEC) assessment report—Dibutyl phthalate (DBP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed September 2013, http://www.nicnas.gov.au/chemical-information/pec-assessments

Nishihara T, Nishikawa J, Kanayama T, Dakeyama F, Saito K, Imagawa M, Takatori S, Kitagawa Y, Hori S, Utsumi H. 2000. Estrogenic activities of 517 chemicals by yeast two-hybrid assay. Journal of Health Science 464:282–298.

NTP. 1995. Toxicology and carcinogenesis studies of diethyl phthalate (CAS No. 84-66-2) in F344/N rats and B6C3F1 mice (dermal studies) with dermal initiation/promotion study of diethyl phthalate and dimethyl phthalate (CAS No. 131-11-3) in male Swiss (CD-1) mice. National Toxicology Program technical report series 429:1–286.

OECD. 2004. SIDS Initial Assessment Profile—High molecular weight phthalate esters. SIAM 19, 19–22 October. The Organisation for Economic Co-operation and Development. Accessed September 2013,

Oishi S, Hiraga K. 1980. Testicular atrophy induced by phthalic acid esters: Effect on testosterone and zinc concentrations. Toxicology and Applied Pharmacology 53:35–41.

Okubo T, Suzuki T, Yokoyama Y, Kano K, Kano I. 2003. Estimation of estrogenic and anti-estrogenic activities of some phthalate diesters and monoesters by MCF-7 cell proliferation assay in vitro. Biological and Pharmaceutical Bulletin 26:1219–1224.

Oliwiecki S, Beck MH, Chalmers RJG. 1991. Contact dermatitis from spectacle frames and hearing aid containing diethyl phthalate. Contact Dermatitis 25:265.

Pant N, Shukla M, Kumar Patel D, Shukla Y, Mathur N, Kumar Gupta Y, Saxena DK. 2008. Correlation of phthalate exposures with semen quality. Toxicology and Applied Pharmacology 231:112–116.

Perez-Fernandez V, Gonzalez MJ, Garcia MA, Marina ML. 2013. Separation of phthalates by cyclodextrin modified micellar electrokinetic chromatography: Quantitation in perfumes. Analytic Chimica Acta 782:7–74.

Peters JW, Cook RM. 1973. Effect of phthalate esters on reproduction in rats. Environmental Health Perspectives 3:91–94.

Phthalate Esters Panel HPV Testing Group of the American Chemistry Council. 2006. High Production Volume (HPV) Chemical Challenge Program Test Plan for the Phthalate Esters Category. Revision to Test Plan dated December 10, 2001. Prepared by ExxonMobil Biomedical Sciences, Inc. Accessed September. 2013, http://www.epa.gov/hpv/pubs/summaries/benzene/c13467rt3.pdf

Plasterer MR, Bradshaw WS, Booth GM, Carter MW, Schuler RL, Hardin BD. 1985. Developmental toxicity of nine selected compounds following prenatal exposure in the mouse: Naphthalene, p-nitrophenol, sodium selenite, dimethyl phthalate, ethylenethiourea, and four glycol ether derivatives. Journal of Toxicology and Environmental Health Part A 15:25–38.

REACH Dossier. Dimethyl phthalate, CAS No. 131-11-3. Registered substances. Helsinki: European Chemicals Agency. Accessed September 2013, http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Rozati R, Reddy PP, Reddanna P, Mujtaba R. 2002. Role of environmental estrogens in the deterioration of male factor fertility. Fertility and Sterility 78:1187–1194.

Rozati R, Simha B, Bendi N, Sekhar C. 2008. Evaluation of the phthalate esters in south Indian women with endometriosis. International Journal of Fertility and Sterility 1:165–170.

Sanchez-Prado L, Llompart M, Lamas JP, Garcia-Jares C, Lores M. 2011. Multicomponent analytical methodology to control phthalates, synthetic musks, fragrance allergens and preservatives in perfumes. Talanta 85:370–379.

Saravanabhavan G, Guay M, Langlois E, Giroux S, Murray J, Haines D. 2013. Biomonitoring of phthalate metabolites in the Canadian population through the Canadian Health Measures Survey (2007–2009). International Journal of Hygiene and Environmental Health [in press].

Sarigiannis DA, Hansen U, Karakitsios SP. 2010. Appendix 4 Mixture risk assessment methodology—evaluating the health risk due to exposure to mixtures of chemicals. In: Methodologies for quantifying health effects of exposure by multiple routes and the effects of mixtures in the light of the case studies, including a report on suitable indices of exposure (Sarigiannis DA, ed). Sixth Framework Programme—Thematic Priority 6.3, Health and Environment Integrated Methodology and Toolbox for Scenario Development (HEIMTSA).

Sathyanarayana S, Karr CJ, Lozano P, Brown E, Calafat AM, Liu F, Swan SH. 2008. Baby care products: Possible sources of infant phthalate exposure. Pediatrics 121:e260–e268.

SCCP. 2006. The Notes of Guidance for the testing of cosmetic ingredients and their safety evaluation. 6th ed. Scientific Committee on Consumer Products. European Commission. Accessed September 2013, http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_03j.pdf

SCCP. 2007. Opinion on phthalates in cosmetic products. Scientific Committee on Consumer Products. SCCP/1016/06. European Commission. Accessed September 2013, http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_106.pdf

SCCS. 2012. The Notes of Guidance for the testing of cosmetic substances and their safety evaluation. 8th ed. Scientific Committee on Consumer Safety. SCCS/1501/12. European Commission. Accessed September 2013, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

Schulsinger C, Mollgaard K. 1980. Polyvinyl chloride dermatitis not caused by phthalates. Contact Dermatitis 6:477–480.

Scott RC, Dugard PH, Ramsey JD, Rhodes C. 1987. In vitro absorption of some o-phthalate diesters through human and rat skins. Environmental Health Perspectives 74:223–227.

Scott RC, Dugard PH, Ramsey JD, Rhodes C. 1989. Errata: In vitro absorption of some o-phthalate diesters through human and rat skins. Environmental Health Perspectives 79:323.

Seed JL. 1982. Mutagenic activity of phthalate esters in bacterial liquid suspension assays. Environmental Health Perspectives 45:111–114.

Sharpe RM. 2005. Guest Editorial: Phthalate exposure during pregnancy and lower anogenital index in boys: Wider implications for the general populations? Environmental Health Perspectives 113:A504–A505.

Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, Brock JW, Needham LL, Calafat AM. 2004. Urinary levels of seven phthalate metabolites in the US population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environmental Health Perspectives 112:331–338.

Singh AR, Lawrence WH, Autian J. 1972. Teratogenicity of phthalate esters in rats. Journal of Pharmaceutical Sciences 61:51–55.

Sjoberg P, Lindqvist NG, Ploen L. 1986. Age-dependent response of the rat testes to di(2-ethylhexyl) phthalate. Environmental Health Perspectives 65:237–242.

SPIN. Dimethyl phthalate, CAS No. 131-11-3. Substances in Preparations in Nordic Countries. Accessed September 2013, http://90.184.2.100/DotNetNuke/Home/tabid/58/Default.aspx

SUSMP. Dimethyl phthalate. The Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard). Commonwealth of Australia. Accessed September 2013, http://www.comlaw.gov.au/Details/F2012L01685/Html/Text#_TOC330287172

Suzuki Y, Niwa M, Yoshinaga J, Mizumoto Y, Serizawa S, Shiraishi H. 2010. Prenatal exposure to phthalate esters and PAHs and birth outcomes. Environment International 36:699–704.

Suzuki Y, Yoshinaga J, Mizumoto Y, Serizawa S, Shiraishi H. 2012. Foetal exposure to phthalate esters and anogenital distance in male newborns. International Journal of Andrology 35:236–244.

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL. 2005. Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environmental Health Perspectives 113:1056–1061.

Swan SH. 2008. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. Environmental Research 108:177–184.

Takenaka T et al. 1970. L'irritation primaire cutanee provoquee par les parfums. Parfum Cosmet Savons 13:699–706. Cited in BIBRA; REACH Dossier.

Takeuchi S, Iida M, Kobayashi S, Jin K, Matsuda T, Kojima H. 2005. Differential effects of phthalate esters on transcriptional activities via human estrogen receptors α and β, and androgen receptor. Toxicology 210:223–233.

Timofievskaya LA et al. 1976. In: Major Problems of Remote After-Effects of Exposure to Occupational Poisons. Collected scientific works (Plyasunov AK, Pashkova M, eds):40–43. Cited in BIBRA; REACH Dossier.

Toda C, Okamoto Y, Ueda K, Hashizume K, Itoh K, Kojima N. 2004. Unequivocal estrogen receptor-binding affinity of phthalate esters featured with ring hydroxylation and proper alkyl chain size. Archives of Biochemistry and Biophysics 431:16–21.

Tsuchiya K, Hattori K. 1976. Chromosomal study on leucocytes cultures treated with phthalate acid ester [in Japanese]. Hokkaidoritus Eisei Kenkyusho Ho 26:114.

US CPSC. 2011. Toxicity review for dimethyl phthalate (DMP CASRN 131-11-3). Bethesda, MD: United States Consumer Product Safety Commission. Accessed September 2013, http://www.cpsc.gov//PageFiles/125767/dmp.pdf

US EPA. 1989. Inert ingredients of pesticide products—List 2: Potentially toxic other inerts/high priority for testing. United States Environmental Protection Agency. Accessed September 2013, http://www.epa.gov/opprd001/inerts/fr54.htm

US EPA. 2010. Screening-level hazard characterization—Phthalate esters category. United States Environmental Protection Agency. Accessed September 2013, http://www.epa.gov/chemrtk/hpvis/hazchar/Category_%20Phthalate%20Esters_March%202010.pdf

US EPA. 2012. Phthalates Action Plan. Revised 03/14/2012. United States Environmental Protection Agency. Accessed September 2013, http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/phthalates_actionplan_revised_2012-03-14.pdf

US Household Products Database. Dimethyl phthalate, CAS No. 131-11-3. US National Library of Medicine. Accessed September 2013, http://householdproducts.nlm.nih.gov/

Varga F, Csáky TZ. 1976. Changes in the blood supply of the gastrointestinal tract in rats with age. Pflügers Archiv: European Journal of Physiology 364:129–133.

VKM. 2005. Risk assessment of diethyl phthalate (DEP) in cosmetics—Opinions of the panel on food additives, flavourings, processing aids, materials in contact with food and cosmetics of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet). Accessed September 2013, http://www.vkm.no/dav/2c29e54788.pdf

White PD, Carter DE, Earnest D, Mueller J. 1980. Absorption and metabolism of three phthalate diesters by the rat small intestine. Food and Cosmetics Toxicology 18:383–386.

WHO. 2005. Principles of characterizing and applying human exposure models. Geneva: World Health Organization. Accessed September 2013, http://www.inchem.org/documents/harmproj/harmproj/harmproj3.pdf

Wirth JJ, Rossano MG, Potter R, Puscheck E, Daly DC, Paneth N, Krawetz SA, Protas BM, Diamond MP. 2008. A pilot study associating urinary concentrations of phthalate metabolites and semen quality. Systems Biology in Reproductive Medicine 54:143–154.

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, Wetmur J, Calafat AM. 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environmental Health Perspectives 116:1092–1097.

Wormuth M, Scheringer M, Vollenweider M, Hungerbühler K. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Analysis 26:803–824.

Ye X, Pierik FH, Angerer J, Meltzer HM, Jaddoe VWV, Tiemeier H et al. 2009. Levels of metabolites of organophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa). International Journal of Hygiene and Environmental Health 212:481–491.

Ying G, H A, Cho HS, Tu BM, Mustafa AM, Haruhiko N, Kurunthachalam K. 2011. Occurrence of phthalate metabolites in human urine from several Asian countries. Environmental Science and Technology 45:3138–3144.

Younoszai MK, Ranshaw J. 1973. Gastrointestinal growth in the fetus and suckling rat pups: Effects of maternal dietary protein. The Journal of Nutrition 103:454–461.

Yurchenko VV. 1977. Cytogenetic investigation of mutagenic properties of the repellents dimethyl phthalate and phenoxyacetic acid N,N-dimethylamide. Farmakol Toksikol 40:454–457.

Zeiger E, Haworth S, Mortelmans K, Speck W. 1985. Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in Salmonella. Environmental Mutagenesis 7:213–232.