Priority Existing Chemical Assessment Report 39

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

Diisodecyl phthalate
Di-n-octyl phthalate

MAY 2015

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), to aid in the protection of the Australian people and the environment by assessing the risks of industrial chemicals, providing information and making recommendations to promote their safe use.

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

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

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

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

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

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

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

Contents

Acronyms and glossary

ACCC	Australian Competition and Consumer Commission
AICS	Australian Inventory of Chemical Substances
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BBP	butylbenzyl phthalate
bw	body weight
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CHAP	Chronic Hazard Advisory Panel
CIUCUS	Complication of Ingredients Used in Cosmetics in the United States
CosIng	Cosmetic Ingredients and Substances Database
CPSC	Consumer Products Safety Commission
d	day
DBP	dibutyl phthalate, di-n-butyl phthalate
DEHP	diethylhexyl phthalate
DEP	diethyl phthalate
DIBP	diisobutyl phthalate
DIDP	diisodecyl phthalate
DINP	diisononyl phthalate
DMEP	di(methoxyethyl) phthalate
DMP	dimethyl phthalate
DnOP	di-n-octyl phthalate
DPHP	bis (2-propylheptyl) phthalate
e.g.	*exempli gratia*, for example
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EGME	ethylene glycol monomethyl ether
EHD	estimated human dose
EPA	Environmental Protection Agency
ESIS	European Chemical Substances Information System
et al.	*et alii*, and others
EU	European Union
g	gram
GD	gestational day
GI	gastrointestinal tract
GLP	Good Laboratory Practice
HI	hazard index
HMW	high molecular weight
HPV	high production volume
hr	hour
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
i.e.	that is
INCI	International Nomenclature Cosmetic Ingredient Directory
INSL3	insulin-like factor 3 (Leydig cell)
IPCS	International Programme on Chemical Safety
kg	kilogram
kPa	kilopascal
L	litre
LD50	median lethal dose
LH	luteinizing hormone
LMW	low molecular weight
LOAEL	lowest observed adverse effect level

m^3	cubic metre
MCHpP	mono-(7-carboxy-n-heptyl) phthalate
MCINP	monocarboxyisononyl phthalate
MCIOP	monocarboxyisooctyl phthalate
MCL	mononuclear cell leukaemia
MCMP	monocarboxy methyl phthalate
MCPP	monocarboxy propyl phthalate
MCPeP	mono-(5-carboxy-n-pentyl) phthalate
MHIDP	mono-hydroxyisodecyl phthalate
MHOP	mono-hyrdoxy-n-octyl phthalate
m/f	male/female
µg	microgram
mg	milligram
µL	microlitre
mL	millilitre
MIDP	mono-isodecyl phthalate
MNOP	mono-n-octyl phthalate
MOE	margin of exposure
MOIDP	monooxoisodecyl phthalate
MOOP	mono-(7-oxo-octyl) phthalate
mPa•s	millipascal second
MW	molecular weight
NHANES	National Health and Nutrition Examination Survey
NJDHSS	New Jersey Department of Health and Senior Services
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
PA	phthalic acid
PEC	Priority Existing Chemical
PND	postnatal day
ppm	parts per million
PVA	polyvinyl acetate
PVC	polyvinyl chloride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SA/BW	surface area to body weight ratio
SCCP	Scientific Committee on Consumer Products
SD	Sprague Dawley (rats)
SPIN	Substances in Preparations in Nordic Countries Database
StAR	Steroidogenic Acute Regulatory protein
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
USA	United States of America
vs	*versus*, against
w/w	weight/weight
WHO	World Health Organization

Glossary

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

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

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

Overview

Background and scope of the assessment

The chemicals, 1,2-benzenedicarboxylic acid, di-C9–11-branched alkyl esters C10-rich (CAS No. 68515-49-1) (DIDP), 1,2-benzenedicarboxylic acid, diisodecyl ester (CAS No. 26761-40-0) (DIDP) and 1,2-benzenedicarboxylic acid, dioctyl ester (CAS No. 117-84-0) (DnOP), were declared Priority Existing Chemicals (PECs) for public health risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 7 March 2006. The decision for declaration was based on:

- the ubiquitous use of phthalates as solvents and plasticisers in industrial and consumer products;
- consumer products being potentially significant sources of repeated and long-term exposure of DIDP or DnOP, both directly and through migration and leaching from products, to the public;
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from DIDP or DnOP exposure; and
- overseas regulatory activities including restrictions and reviews of phthalate use, including DIDP or DnOP, 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 DIDP or DnOP in consumer products such as cosmetics, children's toys and childcare articles, particularly from repeated or prolonged exposure.

Manufacture and importation

DIDP

Data collected through calls for information specific to the assessment of DIDP indicate that it is not manufactured in Australia. It is introduced into Australia in finished products or articles, and imported as a raw chemical for local product manufacture. The total volume of DIDP imported was 1000–9999 tonnes in 2002, and over 10000 tonnes in 2004 and 2006. There is no available information on the current importation volume of DIDP.

DnOP

Data collected through calls for information specific to the assessment of DnOP indicate that the chemical is not manufactured in Australia. It is introduced into Australia in finished products or articles, and imported as a raw chemical for local product manufacture. There is no available information on the current importation volume of DnOP.

Uses

DIDP

In Australia, DIDP is used industrially as a plasticiser (a substance added to make another material softer and more flexible) for polyvinyl chloride (PVC) products, including toys. DIDP is used in manufacturing PVC for automotive parts, hoses, gaskets, cable and wire coatings. Imported products containing DIDP include packaging materials, industrial flooring, paints, surfactants, adhesives, flame resistant plastics, PVC films and children's toys. Children's toys and PVC products made with DIDP include inflatable water products, hoppers, and play and exercise balls, with a maximum concentration of 40% (possibly in combination with other phthalates).

Internationally, DIDP-plasticised PVC is used in film, sheet and coated products, flooring, roofing and wall coverings, and car undercoating and sealants. Extrusion and injection moulding processes are used to incorporate it in PVC for hoses, wires and cables, footwear and miscellaneous articles. Non-PVC uses included in polymers such as pressure-sensitive adhesives, printing inks, anti-corrosion and anti-fouling paints (ECB, 2003).

DnOP

DnOP is manufactured in the United States of America (USA), predominantly as a minor component of C6–10 phthalate (approximately 20%). DnOP is used in this form in PVC for manufacturing a variety of products including flooring and carpet tiles, canvas tarpaulins, swimming pool liners, notebook covers, traffic cones, toys and dolls, vinyl furniture upholstery, shower curtains and gloves, garden hoses, leather stripping, flea collars and shoes. DnOP-containing PVC is also used in food applications. Other non-PVC applications of DnOP include its use as a dye carrier in plastics production, and for manufacturing adhesives, plastisols and nitrocellulose lacquer coatings.

In Australia, DnOP is imported for use as plasticiser in automotive and industrial hose, and for manufacturing PVC conveyer belts, insulation materials, polyurethane surface coatings, floor finishes and adhesives. Imported PVC products include inflatable water products, hoppers, and play and exercise balls at a maximum concentration of 40% (possibly in combination with other phthalates). DnOP is also distributed to various institutions for research purposes.

Current European Union (EU) and Canadian legislation restricts the use of DINP, DIDP and DnOP in certain toys and childcare articles that can be placed in the mouth. A similar restriction is also imposed by the USA on an interim basis, although based on the recent Chronic Hazard Advisory Panel (CHAP) report (CHAP 2014), this is likely to be reviewed.

The information provided by Australian industry on DIDP and DnOP use did not indicate that these phthalates are used in cosmetic or personal care products. Furthermore, the available information from overseas indicates that neither chemical is used in cosmetics. There is also no information that supports the substitutability of high molecular weight (HMW) phthalates, such as DIDP and DnOP, for the low molecular weight (LMW) phthalates commonly used in cosmetics.

Therefore, risk characterisation for adults using cosmetics containing DIDP and DnOP is not addressed in this report.

Health effects

DIDP

DIDP absorption through the gastro intestinal tract is incomplete. As the saturation point is reached, the absorption decreases as the dose increases following oral administration. The bioavailability of DIDP from oral exposure is assessed as 100% for both adults and children. Bioavailability from dermal absorption is low (2–4%). The available data suggest that dermal absorption through human skin may be significantly less than through rat skin. Data on absorption of inhaled DIDP are limited; therefore, a default bioavailability of 100% is considered appropriate for the purposes of this assessment.

DIDP has low acute oral, dermal and inhalation toxicity. It is a mild skin and eye irritant. It is not considered a skin sensitiser.

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

Toxic effects related to repeated DIDP exposure are liver toxicity (increased liver weight in rats) and developmental toxicity (increased incidence of skeletal variations in rats).

For the systemic and developmental effects, no observed adverse effect levels (NOAELs) of 60 and 100 mg/kg bw/day were determined, respectively.

DnOP

DnOP is rapidly absorbed from the gastrointestinal tract following oral administration. It is metabolised predominantly to mono-*n*-octylphthalate (MnOP) and eliminated in urine. The bioavailability of DnOP from oral exposure is assessed as 100% for both adults and children. Information on dermal absorption of DnOP is not available. Similarly to other HMW phthalates, the bioavailability of DnOP from dermal absorption is expected to be low (2–4%). The available data suggest that dermal absorption of DIDP through human skin may be significantly less than through rat skin. Data on absorption of inhaled DnOP are also not available; therefore, a default bioavailability of 100% is considered appropriate for the purposes of this assessment.

DnOP has low acute oral, dermal and inhalation toxicity.

DnOP is a mild skin and eye irritant. Data are insufficient to determine the sensitisation potential of DnOP. However, it should be noted that phthalates, in general, have low skin sensitisation potential.

DnOP is non-genotoxic and non-mutagenic. Limited data on its carcinogenic potential suggest that DnOP could act as a promoter of pre-neoplastic hepatic (liver) lesions in rats through a non-peroxisome proliferative mechanism. Based on the weight of evidence, the available data do not a support carcinogenic potential for DnOP in humans.

The liver appears to be the primary target organ from repeated exposure to DnOP. Liver toxicity (weight, histological or clinical chemistry changes) was observed in several repeated dose studies. Developmental effects (skeletal variations) in the absence of maternal toxicity were reported at a concentration of 250 mg/kg bw/day, following repeated exposure to DnOP.

For systemic toxicity, a NOAEL of 37 mg/kg bw/day has been established based on histological changes in the liver and thyroid observed at 350 mg/kg bw/day (lowest observed adverse effect level—LOAEL). A NOAEL of 83 mg/kg bw/day for developmental toxicity is derived for DnOP by applying a factor of three for the LOAEL to NOAEL extrapolation (see Section 6.6.2).

Public exposure and health risk

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

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

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 reasonable typical and worst-case mouthing times of 0.8 hours/day and 2.2 hours/day, respectively. These are also considered applicable to the time a child spends handling toys.

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

The long-term adverse health risks for children include liver toxicity and developmental effects associated with repeated combined handling and mouthing toys containing DIDP or DnOP. The risk assessment compares the DIDP and DnOP doses at which there is no observed adverse effect on target organs and/or systems in laboratory animals (i.e. NOAEL) with the estimated human dose (EHD) of DIDP and DnOP for children. Based on this assessment approach, margins of exposure (MOEs) above 300 and 200, respectively (see Table 7.1 and 7.2), were derived for worst-case scenarios of toy use, indicating an adequate safety margin or a negligible risk of these adverse health effects in children.

Cumulative risks may arise through exposure to multiple phthalates acting on the same biological targets from a range of sources, such as the simultaneous use of cosmetics and children's toys and childcare articles. The determination of risk from combined exposures to multiple phthalates takes into account any risk mitigation measures recommended in the PEC assessment for each phthalate. The estimated cumulative MOEs for the critical liver effects of phthalates, including DIDP and DnOP, indicate an adequate safety margin for children's exposure to toys and childcare articles.

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 any change occurs in circumstances that may warrant a reassessment of its hazards, exposures or risks.

For DIDP and DnOP, specific circumstances include:

- additional information becoming available on the adverse health effects of DIDP and DnOP;
- DIDP and DnOP being used in cosmetics;
- additional sources of potentially high public exposure to DIDP and DnOP other than in toys and childcare articles; or
- additional information or events that change the assumptions in estimating the cumulative risks in this assessment.

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

1 Introduction

1.1 Declaration

The chemicals, 1,2-benzenedicarboxylic acid, di-C9–11-branched alkyl esters C10-rich (CAS No. 68515-49-1) (DIDP), 1,2-benzenedicarboxylic acid, diisodecyl ester (CAS No. 26761-40-0) (DIDP) and 1,2-benzenedicarboxylic acid, dioctyl ester (CAS No. 117-84-0) (DnOP), were declared as Priority Existing Chemicals (PECs) under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 7 March 2006 (*Chemical Gazette* 2006) for assessing the public health risk from their use in children's toys, childcare articles and cosmetics. The basis for the declaration was the actual and potential use of DIDP and DnOP in children's toys, childcare articles and cosmetics.

1.2 Objectives

The objectives of this assessment are to:

- characterise the properties of DIDP and DnOP;
- determine the use and function of DIDP and DnOP 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 DIDP or DnOP from these applications;
- determine any adverse health effects associated with exposure to DIDP or DnOP;
- characterise the risks to humans posed by exposure to DIDP or DnOP from use in these applications;
- determine the extent to which any risk is capable of being reduced; and
- recommend appropriate risk mitigation measures.

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

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

1.3 Sources of information

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

1.3.1 Industry

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

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

This call for information was followed in July 2006 with a voluntary call for information to importers of toys and childcare articles containing phthalates (including DIDP and DnOP). 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 diisodecyl phthalate (DIDP) (NICNAS 2008a);
- Existing Chemical hazard assessment report on di-n-octyl phthalate (DnOP) (NICNAS 2008b);
- *Phthalates Hazard Compendium*—A summary of physicochemical and human health hazard data for 24 ortho-phthalate chemicals (NICNAS 2008c);
- 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);
- Priority Existing Chemical (PEC) assessment report on dimethyl phthalate (DMP) (NICNAS 2014a); and
- Priority Existing Chemical (PEC) assessment report on di(methoxyethyl) phthalate (DMEP) (NICNAS 2014b).

Assessments by international bodies:

- Chronic Hazard Advisory Panel (CHAP)—Report to the US Consumer Product Safety Commission (CPSC) by the *Chronic Hazard Advisory Panel on phthalates and phthalate alternatives* (CHAP 2014).

DIDP

- European Chemicals Bureau (ECB)—*European Union risk assessment report—1,2-benzenedicarboxylic acid, di-C9–11-branched alkyl esters C10-rich and di-"isodecyl" phthalate* (DIDP) (ECB 2003a);
- National Toxicology Program (NTP)—NTP Centre for the Evaluation of Risks to Human Reproduction (CERHR)—*Monograph on the potential human reproductive and developmental effects of di-isodecyl phthalate* (DIDP) (NTP 2003a);
- US Consumer Product Safety Commission's (CPSC) Health Sciences—*Toxicity review of di(isodecyl) phthalate* (DIDP) (CPSC 2010a); and
- European Chemicals Agency (ECHA)—Evaluation of new scientific evidence concerning DINP and DIDP (ECHA 2013).

DnOP

- US Department of Health and Human Services—Agency for Toxic Substances and Disease Registry (ATSDR)—*Toxicological profile for di*-n-*octylphthalate* (ATSDR 1997);
- National Toxicology Program (NTP)—*NTP -CERHR Monograph on the potential human reproductive and developmental effects of di*-n-*octyl phthalate* (DnOP) (NTP 2003b);
- European Chemicals Agency (ECHA)—*Review of new available information for di*-n-*octyl phthalate* (DnOP) (ECHA 2010); and
- US Consumer Product Safety Commission's (CPSC) Health Sciences—*Toxicity review of di*-n-*octyl phthalate* (DnOP) (CPSC 2010b).

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 July 2014. For more details, refer to the References section of this report.

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

1.4 Peer review

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

1.5 Applicants

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

DIDP

Following the declaration of DIDP as a PEC, two organisations and two companies applied for assessment of this chemical:

Marchem Australasia Pty Ltd
558–562 Geelong Road
BROOKLYN VIC 3012

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

Sigma Aldrich Pty Ltd
12 Anella Avenue
CASTLE HILL NSW 2154

Vinyl Council Australia
65 Leakes Road
LAVERTON NORTH VIC 3026

DnOP

Following the declaration of DnOP as a PEC, two organisations and two companies applied for assessment of this chemical:

Amtrade International Pty Ltd
Level 6, 574 St Kilda Road
MELBOURNE VIC 3004

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

Sigma Aldrich Pty Ltd
12 Anella Avenue
CASTLE HILL NSW 2154

Vinyl Council Australia
65 Leakes Road
LAVERTON NORTH VIC 3026

2 Background

2.1 International perspective

DIDP and DnOP are members 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 and Co-operative 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, DIDP and DnOP belong to the HMW phthalates group.

The physicochemical properties of phthalates that impart their usefulness as plasticisers also permit their migration and leaching from polymer matrices. The potential for leaching from plastics and their 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. Particular concerns exist when there is the potential for young children to be exposed to phthalates in toys and childcare articles, or for prolonged exposure of the general population through cosmetic use.

Historically, studies of the health effects of certain phthalates have identified that developmental toxicity, especially affecting the testes and testicular hormones, is of particular concern. Accordingly, overseas jurisdictions have taken regulatory action on a number of phthalates, particularly transitional phthalates (diethylhexyl phthalate, DEHP; dibutyl phthalate, DBP; and butylbenzyl phthalate, BBP), and HMW phthalates (diisononyl phthalate, DINP; DIDP; and DnOP), for particular uses.

In the European Union (EU), restrictions on the use of DINP, DIDP and DnOP as plasticisers in toys and childcare articles took effect in January 2007. The restriction sets a content limit of 0.1% weight/weight (w/w) of the plasticised material for DINP, DIDP and DnOP, on toys and childcare articles for children under three years of age that can be placed in the mouth. This restriction is also referred to as Entry 52 of Annex XVII to REACH.

DIDP has been registered with ECHA and registration dossiers were submitted. DnOP has been pre-registered under REACH. DnOP (CAS No. 117-84-0) was pre-registered by about 350 legal entities. The CAS No. 8031-29-6, which has been used to describe DnOP (see Section 3), was pre-registered by about 500 legal entities. However, at the date of this report, there have been no REACH registration dossiers submitted for either CAS No. 117-84-0 or CAS No. 8031-29-6, supporting ECHA's conclusion in their review report in July 2010 that DnOP may no longer be in use in the EU.

Based on the conclusion of the recent ECHA report (ECHA 2013), as well as the opinion of the ECHA Risk Assessment Committee (RAC), the European Commission made the following comments concerning DINP, DIDP and DnOP: (a) 'the existing restriction should be maintained as its withdrawal could lead to a situation where children would be at risk which is currently avoided due to the existing ban of the presence of these substances in these articles', and (b) 'on the basis of the available information, no unacceptable risk has been characterised for the uses of these phthalates in articles other than toys and childcare articles which can be placed in the mouth (European Commission 2014).' The existing restrictions in Entry 52 of Annex XVII to REACH will remain in place for DINP, DIDP and DnOP.

In the USA, interim prohibitions of the sale of 'toys that can be placed in a child's mouth' or 'childcare articles' containing more than 0.1% DIDP and DnOP are in place, pursuant to Section 108 of the Consumer Product Safety Improvement Act (CPSIA) of 2008. Eight phthalate esters, including DIDP and DnOP, are included in the US EPA's *Phthalates action plan* (US EPA 2012a revised). However, the Chronic Hazard Advisory Panel (CHAP) recommended in a recent report that the current bans on DIDP and DnOP be lifted (CHAP 2014). DIDP and DnOP are not listed in the *Compilation of ingredients used in cosmetics in the United States* (CIUCUS) (Personal Care Products Council 2011), which indicates that there were no reports provided to the Food and Drug Administration (FDA) that these chemicals were used in cosmetics.

In Canada, the Phthalates Regulations were made under the authority of the Hazardous Product Act to restrict the sale, importation and advertising of toys and childcare articles composed of vinyl containing phthalates. For DIDP and DnOP, the requirements of these regulations were that 'the vinyl in any part of a toy or child care article that can, in a reasonably foreseeable manner, be placed in the mouth of a child under four years of age must contain not more than 1000 mg/kg of DIDP or DnOP when tested in accordance with a method that conforms to good laboratory practice (Government of Canada 2010).

2.2 Australian perspective

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

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

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

DIDP and DnOP are not listed in the Hazardous Substances Information System (HSIS) (Safe Work Australia) or the Poisons Standard (the *Standard for Uniform Scheduling of Medicines and Poisons* (SUSMP)).

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

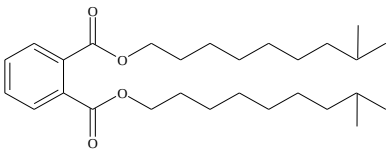
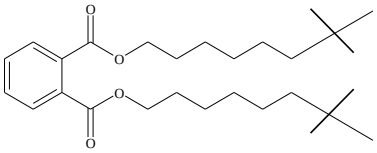
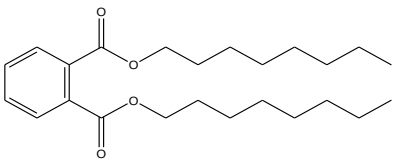
3 Identity and properties

The chemicals, DIDP (CAS Nos. 68515-49-1 and 26761-40-0) and DnOP (CAS No. 117-84-0) are listed on the Australian Inventory of Chemical Substances (AICS). However, it is noted that CAS No. 8031-29-6 (1,2-benzenedicarboxylic acid 1,2-dioctyl ester), which is not listed on AICS, has also been used to describe DnOP. Furthermore, there appears to be potential confusion between DnOP and di-octyl phthalate (DOP), which has been used as a synonym for both DEHP and DnOP.

DIDP is a complex mixture containing mainly C10 methyl-branched isomers. The composition of DIDP is reported as a substance comprising 0–10% trimethyl heptyl chains (C7), 70–78% dimethyl octyl chains (C8) and 0–10% methyl nonyl chains (C9) (ECB 2003a, CPSC 2010a). In comparison, DnOP is described as a mono constituent substance consisting of a pair of eight carbon linear alcohols esterified with a benzenedicarboxylic acid ring. DnOP is a significant component (20%) of C6–10 phthalate mixture (CPSC 2010b).

3.1 Chemical identity

Table 3.1: Chemical identity of DIDP and DnOP

	DIDP	DnOP
Chemical name:	1,2-benzenedicarboxylic acid, di-C9–11-branched alkyl esters C10-rich (CAS No. 68515-49-1); 1,2-benzenedicarboxylic acid, diisodecyl ester (CAS No. 26761-40-0)	1,2-benzenedicarboxylic acid, dioctyl ester
CAS No.:	68515-49-1 and 26761-40-0	117-84-0
Synonyms:	DIDP diisodecyl phthalate	DnOP or DOP di-*n*-octyl phthalate bis(*n*-octyl) phthalate di-*n*-octyl phthalate dioctyl-o-benzenedicarboxylate *n*-dioctyl phthalate *n*-octyl phthalate octyl phthalate phthalic acid, dioctyl ester
Molecular formula:	$C_{28}H_{46}O_4$ (average)	$C_{24}H_{38}O_4$
Molecular weight:	447 (average)	390.6
Purity/impurities:	Purity : ≥99.5% w/w	Impurities: none identified
Structural formula:	CAS No: 68515-49-1  CAS No: 26761-40-0  The structures above represent only a few of the many possible isomers that comprise DIDP.	

3.2 Physical and chemical properties

Table 3.2: Summary of physicochemical properties

Properties	DIDP	DnOP
Physical state	Oily viscous liquid	Colourless, odourless liquid
Boiling point	>400 ºC	390 ºC
Freezing / melting point	−45 ºC (average)	−25 ºC
Density, kg/m^3	970 kg/m^3 (20 ºC)	978 kg/m^3 (25 ºC)
Vapour pressure, kPa	5.1×10^{-8} (25 ºC)	1.92×10^{-5} (25 ºC)
Water solubility, g/L	2×10^{-7} (20 ºC)	3.0×10^{-3} (25 ºC)
Partition co-efficient octanol/water (log K_{ow})	8.8	5.22
Henry's Law constant, atm m^3/mol (25 ºC)	1.12×10^{-6}	6.68×10^{-5}
Flash point	>200 ºC	219 ºC

Source: DIDP (NTP 2003a), ECB (2003a); DnOP (ATSDR 1997)

DIDP

DIDP is soluble in most organic solvents but insoluble in glycerol, glycols and some amines (HSDB).

Conversion factors based on 25 ºC and 1 atmosphere:

1 ppm = 18.32 mg/m^3
1 mg/m^3 = 0.05 ppm

DnOP

DnOP is soluble in many organic solvents and oils (HSDB).

Conversion factors based on 25 ºC and 1 atmosphere:

1 ppm = 16.00 mg/m^3
1 mg/m^3 = 0.06 ppm

4 Manufacture, importation and use

4.1 Manufacture and importation

DIDP and DnOP are introduced into Australia through importation in finished (ready-to-use) products and as raw chemicals or in mixtures for local manufacture and processing. There are no data from NICNAS calls for information indicating that these chemicals are manufactured in Australia.

The total volume of DIDP imported into Australia for industrial uses was 1000–9999 tonnes each year between 1999 and 2002, and in 2006, according to responses received to calls for information on phthalates. There is no information available on the volume of DnOP imported for industrial use.

In 2004, DIDP and DnOP were imported for use in children's toys and childcare articles; however, specific volumes for these uses were not available.

4.2 Uses of DIDP and DnOP

4.2.1 Uses in Australia

Following calls for information on phthalates in 2004 and after this PEC declaration in 2006, the information obtained from Australian industry indicated that DIDP and DnOP were not used in cosmetics. However, DIDP and DnOP were reported to be present in imported toys at concentrations of 0.4–40% and 0.02–40%, respectively.

DIDP

DIDP is used industrially as a plasticiser for PVC in automotive parts, hoses, gaskets, and cable and wire coatings. It is also used in non-vinyl applications such as adhesives and surfactants. Imported products containing DIDP include packaging materials, industrial flooring, paints, flame resistant plastics, PVC films, children's toys and exercise balls.

DnOP

DnOP is imported for use as a plasticiser in automotive parts, industrial hoses and for manufacturing PVC conveyer belts, insulation materials, polyurethane surface coatings, floor finishes and adhesives, children's toys, and play and exercise balls. DnOP is also distributed to various institutions for research purposes.

4.2.2 Uses overseas

In 2010, the total global market for phthalates was estimated at six million tonnes, with 1.4 million tonnes in the EU, the Middle East and Africa; 1.1 million tonnes in the Americas and 3.5 million tonnes in Asia (ECHA 2013). Current EU and Canadian legislation restricts DINP, DIDP and DnOP from being used in certain toys and childcare articles that can be placed in the mouth. A similar restriction is also imposed by the USA on an interim basis, although given the recent CHAP report (CHAP 2014), this restriction may be reviewed.

There is no current information available overseas on the use of DIDP and DnOP in cosmetics.

DIDP

DIDP and DINP (and other C9/C10 phthalates) represent approximately 30% of the global consumption of plasticisers (ECHA 2013).

In Europe, approximately one million tonnes of phthalates are manufactured each year, of which approximately 93% are used to manufacture soft and flexible PVC. In the ECHA report (ECHA 2013), the European Council for Plasticisers and Intermediates (ECPI) indicated that the consumption of DINP, DIDP and bis (2-propylheptyl) phthalate (DPHP; CAS No. 53306-54-0) has increased from approximately 50% of total phthalate sales in the EU in 2001 to approximately 83% in 2010, which corresponds to approximately 830,000 tonnes per year. Annual production and/or importation volumes of DIDP were reported to be around 4826 tonnes in Nordic countries in 2011 (SPIN).

DIDP is listed in the *Chemical book* and offered for sale by 16 suppliers world-wide, including seven European- and seven US-based companies. No further information on the specific volumes of DIDP for either industrial or consumer applications is publicly available.

Internationally, DIDP is mainly used as a plasticiser for PVC. DIDP-plasticised PVC is used in film, sheet and coated products, flooring, roofing and wall coverings and car undercoating and sealants. Extrusion and injection moulding processes are used to incorporate it in PVC for hoses, wires and cables, footwear and miscellaneous articles. Non-PVC uses included in polymer applications such as pressure sensitive adhesives, textile inks, sealing compounds, and anti-corrosion and anti-fouling paints (ECB 2003a). DIDP is also used as a lubricant/additive, and has been found in children's toys (CPSC 2010a). The chemical is typically used as a plasticiser for heat resistant electrical cords, leather for car interiors and PVC flooring because of its properties of volatilisation resistance, heat stability and electric insulation. DIDP is preferred to DINP or low molecular weight phthalates in car interiors because it can meet the low fogging thresholds set by car manufacturers. In the EU, the typical concentration of DIDP in flexible PVC products was reported as 25–50% (w/w) (ECHA 2013).

The following uses or functions (see also Section 4.3) of DIDP have been identified in the:

- Substances in Preparations in Nordic Countries (SPIN) database: adhesives, paints, lacquers, varnishes, binding agents, colouring agents, construction materials, lubricants and additives;
- Galleria Chemica: adhesives, binding agents, fillers, construction materials, paints, lacquers, varnishes, abrasives, lubricants and additives; and
- US National Library of Medicine Household Products Database: home maintenance products such as polyurethane masonry and concrete sealants, interior and exterior caulk, and plumbing caulk.

DIDP is **not** listed in the following databases the:

- European Commission Cosmetic Ingredients and Substances (CosIng) database;
- Personal Care Products Council International Nomenclature Cosmetic Ingredient (INCI) dictionary; and
- Personal Care Products Council Compilation of Ingredients Used in Cosmetics in the USA (CIUCUS 2011).

DnOP

The available information on current uses and introduction volumes (manufacture and/or import) of DnOP is very limited and contradictory. According to industry, there is no commercial use of DnOP within the EU (ECHA 2013). However, a survey conducted on exposure of two-year-old children by the Danish EPA found DnOP in soap packaging products. Levels of DnOP in the environment and house dust mite samples were detected in Bulgaria. DnOP was found in toys marketed in California, USA (ECHA 2010), although US NTP (2003b) indicated that there are no uses identified in toys for plasticiser mixtures containing DnOP.

To date, there were no REACH registration dossiers for DnOP submitted to ECHA, which supports the assumption that there is no significant commercial market in the EU for DnOP. The annual production and/or importation volumes of DnOP were reported to be approximately 75 tonnes in Nordic countries between 2008 and 2012 (SPIN). In Canada, approximately 1 tonne is used annually, but there are no identified Canadian producers of DnOP (Health Canada 2003). In the USA, approximately 4.5 tonnes of DnOP was reported to be produced each year (NTP 2003b).

DnOP is listed in the *Chemical book* and offered for sale by 46 suppliers world-wide, including 15 Europe- and 24 US-based companies. No further information on the specific volumes of DnOP for either industrial or consumer applications is publicly available.

Internationally, it has commonly been reported that DnOP is used as a plasticiser for PVC. The NTP report (2003b) indicated that there are no known commercial uses of pure DnOP. However, DnOP makes up 20% of the component of the commercial phthalate mixture of C6–C10 phthalate, which is used to manufacture flooring and carpet tiles, tarpaulins, pool liners and garden hoses. The SPIN database indicated that DnOP was used in filling agents, paints, lacquers, varnishes and adhesives. There was no reported use of DnOP after 2011

DnOP is **not** listed in the following databases:

- US National Library of Medicine's Household Products Database;
- European Commission's Cosmetic Ingredients and Substances (CosIng) database;
- Personal Care Products Council's International Nomenclature Cosmetic Ingredient (INCI) dictionary; and

- Personal Care Products Council's Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS 2011).

4.3 Phthalate uses and possible substitutes

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 phthalate use patterns generally indicates that lower molecular weight phthalates are used as solvents, whilst higher molecular weight phthalates are used as plasticisers (NICNAS 2008c).

The physicochemical factors expected to affect the choice of a specific phthalate for a particular use include viscosity, water solubility and the 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 2008c). Viscosity varies from 9 mPa•s for DEP, 15 mPa•s for DBP to 52 mPa•s for DINP and up to 190 mPa•s for ditridecyl phthalate (Eastman 2006).

Thus, an HMW phthalate ester (e.g. DINP) will be quite different from an 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 that these are the key considerations, substituting a particular phthalate for another phthalate of similar molecular weight for any given application—for example, substituting DIDP or DnOP for DINP as a plasticiser in PVC products—is more probable than substituting a phthalate of a very different molecular weight, such as DEP.

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

Among the phthalate plasticisers, DINP, DIDP and DnOP are 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 can be used as a secondary plasticiser) and is normally used for cellulose nitrate (Chanda & Roy 2006).

Therefore, while it is clear that phthalates can be considered as substitutable by other phthalates of similar properties, there are likely to be limits on the extent to which dissimilar phthalates can be used for a specific purpose. DIDP and DnOP are high molecular weight phthalates and thus not likely to substitute for DEP—a low molecular weight phthalate commonly used in cosmetics. However, DIDP and DnOP are more likely to substitute for DINP in any of its applications. In the absence of data on the use of DIDP and DnOP in children's toys, assumptions need to be made in modelling exposures. In this report, for example, migration or leaching rates reported for DINP are used to undertake an exposure assessment for DIDP and DnOP as the predominant plasticiser in a mixed phthalate plasticiser (DIDP+DEHP or DnOP+DEHP) in relation to uses in children's toys and childcare articles.

5 Public exposure

Although DIDP and DnOP were declared PECs for assessment of their use in children's toys, childcare articles and cosmetics, there is no evidence to suggest that either chemical is currently used in cosmetic products in Australia. While there may be potential for use of DIDP and DnOP in cosmetic products based on potential for substitution of phthalates, there are uncertainties over the substitutability of HMW phthalates such as DIDP and DnOP for low and mid molecular weight phthalates such as DEP and DBP, the predominant phthalate cosmetic ingredients. DIDP and DnOP are not listed as cosmetic ingredients in the ICIDH/CIUCUS databases, or CosIng and INCI (see Section 4.2).

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

Thus, cosmetic use of DIDP and DnOP is likely to be rare to non-existent. Consequently, assessing public exposure to DIDP and DnOP from their use in cosmetics is not considered further in this assessment.

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

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. Further, the use of Australian data is also preferred. However, if Australian data are not available, overseas data can 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).

The reasonable worst-case scenario is used to assess specific exposure pathways; estimates are based on worst-case, but plausible, exposure scenarios. It is believed that this approach will consider practically 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.

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

DIDP and DnOP are reported to be used in children's toys and childcare articles in Australia.

Oral exposure was modelled by:

- estimating the highest plausible concentration of DIDP or DnOP as a primary component of a mixed plasticiser in children's toys and childcare articles in Australia;
- estimating children's mouthing time of toys and childcare articles based on overseas data that are not expected to be markedly different from Australian children's mouthing activities and behaviours;
- estimating the migration rate of the mixed plasticiser from a PVC matrix into saliva, based on experimental studies on the extractability of phthalate plasticisers under various mouthing conditions;
- estimating the oral bioavailability of DIDP or DnOP (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 DIDP or DnOP as a component of a mixed plasticiser in children's toys and childcare articles in Australia;

- estimating children's dermal contact time with toys and childcare articles;
- estimating the migration rate of the mixed plasticiser from a PVC matrix through the skin, based on experimental studies; and
- using default values for children's body weight and exposed surface area.

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

According to data provided by local suppliers, several phthalates including DIDP and DnOP are used in children's plastic toys sold in Australia. However, data on the phthalate content of the toys were limited and import volumes relating specifically to toys were not available. Therefore, it is necessary to use overseas data to quantify the presence of phthalates in soft PVC toys and establish possible levels of children's exposure to the chemicals.

The limited Australian information, obtained through a voluntary call for information in 2004, showed one company importing articles for children aged four and above with a DIDP and DnOP content of 0.4% and 0.02%, respectively. Another company reported importing playballs, hoppers and exercise balls containing 40% of total phthalates consisting of DBP, DIDP, DINP, DnOP and DMEP. The concentration of DIDP or DnOP alone in the playballs was not provided. Since the information provided for the assessment only covered a small proportion of the toys available on the Australian market, available overseas data were also examined to establish a reasonable worst-case scenario for children exposed to DIDP and DnOP through toys.

The overall findings from available overseas studies indicated that phthalates were typically present in toys at weight concentrations of approximately 5–50%, with the predominant phthalates being DINP and DEHP. Available overseas data indicate that 20% and 15.7% DIDP were found in two samples of teethers tested (Greenpeace 1997*; ECB 2003a). As the detection of DIDP and DnOP was not common, these values cannot be taken as representing the maximum possible concentrations.

Available exposure estimates arising from toys are much lower for DIDP (17 µg/kg bw/day) compared with DINP (145 µg/kg bw/day). The calculation of exposure to DIDP and DnOP in this assessment is based on the assumption that either chemical is completely substituted for DINP (a primary plasticiser) at a maximum concentration of 43% w/w. This concentration of DIDP or DnOP was based on a literature review of analytical studies of toys, as well as the measured concentration of DINP associated with studies on the extractability of phthalates from plastic articles (Chen 1998). The DINP PEC assessment has detailed calculations under this scenario, explaining the derivation of all relevant parameters (NICNAS 2012).

5.2.1 Oral exposure

The daily internal oral doses for the reasonable typical and worst-case scenarios for DIDP and DnOP as primary plasticisers are calculated using Equation 1 and shown in Table 5.1 based on the following assumptions:

- The exposure estimates are made for a six-month-old infant who has the lowest body weight among the group and who demonstrates the maximum mouthing behaviour with a typical and reasonable worst-case mouthing time of 0.8 hours/day and 2.2 hours/day, respectively (for a review of children's mouthing time studies, refer to the PEC assessment for DINP— NICNAS 2012).
- Based on the weight of evidence, Chen's (1998) mean and highest *in vivo* migration rates of DINP from chewing/mouthing toys and articles are regarded as applicable for the typical and worse-case exposure estimates, i.e. 26.03 µg/cm^2/hour and 57.93 µg/cm^2/hour, respectively.
- The extractability data for DINP (measured at 43% w/w of the articles studied by Chen (1998)) are also applicable for 43% DIDP or DnOP. In addition, the phthalate migration rate from articles appears largely determined by the magnitude of the mechanical force applied to an article and the properties of the PVC grade comprising the article, and less affected by the physicochemical characteristics or concentration of a particular phthalate (NICNAS 2012).
- The child's mean body weight is 7.5 kg based on the 50th percentile value for males and females combined.
- The surface area of a child's open mouth or the surface of an article available for mouthing at any one time is approximately 10 cm^2.
- Phthalate bioavailability from oral exposure is 100% (see Section 6.1).

Equation 1

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

Where:

$D_{int,oral}$ = Internal dose by oral exposure, μg/kg bw/day
M = Migration rate of the phthalate from toys, μg/cm²/hour
S_{mouth} = Surface area of a child's open mouth, cm²
t = Mouthing time, hours
n = Frequency per day
B_{oral} = Bioavailability by the oral route, %
BW = Body weight, kg

Table 5.1: Estimated daily internal doses for DIDP/DnOP from oral exposure to toys and childcare articles in children

	DIDP/DnOP $D_{int,oral}$ **(μg/kg bw/day)**
Typical exposure scenario	27.77
Reasonable worst-case exposure scenario	169.93

The daily exposure estimate using the worst-case scenario is comparable with the estimate in the ECHA report (2013) of 145 μg/kg bw/day for oral exposure to DIDP from using children's toys and childcare articles. This estimate was based on slightly different assumptions of 6.21 kg infant mouthing a toy with an area of 10 cm² for two hours every day. The value was estimated using a migration rate of 45 μg/cm²/hour from an *in vitro* study conducted on a PVC disk containing 40.7% w/w DINP (ECHA 2013). In the current assessment, the worst-case migration rate (57.93 μg/cm²/hour) used is the highest *in vivo* migration rate observed for DINP in a well-conducted study (Chen 1998) from evaluating several extractability studies of phthalate plasticisers (NICNAS 2010).

5.2.2 Dermal exposure

The daily internal dermal doses for the typical and worst-case scenarios for DIDP and DnOP 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 area of exposure/body weight ratio, and therefore the combined dermal and oral exposure is expected to be highest for this age group.
- A typical time the child spends handling toys is 0.8 hours/day and a reasonable worst-case contact time is 2.2 hours/day.
- Based on the weight of evidence, Deisinger et al. (1998) determined that the mean dermal absorption rate of 0.24 μg/cm²/hour for DEHP migrating from sheets of PVC film through rat skin can be regarded as applicable for DIDP and DnOP, given the lack of available migration rate data or quantitative dermal absorption data for these phthalates (for a review of dermal absorption studies, see the DINP PEC assessment, NICNAS 2012).
- The *in vivo* dermal absorption rate data for DEHP (measured by Deisinger et al. (1998) at 40.4% w/w of the articles) are also applicable for DIDP and DnOP.
- The child's mean body weight is 7.5 kg based on the 50th percentile value for male and female combined.
- The child's hands and lips (surface area approximately 100 cm²) are the most likely body parts to be exposed while handling toys and childcare articles.

Equation 2

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

Where:

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

Table 5.2: Estimated daily internal doses for DIDP/DnOP from dermal exposure to toys and childcare articles in children

	DIDP/DnOP $D_{int,dermal}$ (μg/kg bw/day)
Typical exposure scenario	2.56
Reasonable worst-case exposure scenario	7.04

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/day)	Reasonable worst-case $D_{int, oral+dermal}$ (μg/kg bw/day)
Oral	27.77	169.93
Dermal	2.56	7.04
Combined	30.33	176.97

5.4 Biomonitoring data

There are a number of overseas biomonitoring studies that investigate DIDP and DnOP metabolite levels in urine and, to a lesser extent, in blood and breast milk (ECHA 2013).

Biomonitoring data for a particular chemical or its metabolites represent exposure to the chemical from all sources and pathways. The toxicokinetic data for DIDP and DnOP demonstrate that these chemicals are rapidly excreted and do not appear to accumulate in tissues (**Section 6.1**). Therefore, single day measurements approximate the daily dosing. However, population estimates of specific phthalate levels may differ by age, gender, and race/ethnicity (Silva et al. 2004; CDC 2009).

The analytical approaches and uncertainties 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 purposes of this assessment, modelling is the most suitable approach. The assumptions made in the scenarios used to calculate the exposure to DINP (NICNAS 2012) are also considered reasonable and applicable to DIDP and DnOP on the basis that they are assumed to be used as a primary plasticiser completely substituting DINP at a concentration of 43% in children's toys.

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 DIDP and DnOP exposures in the Australian general population or specific subpopulations are not available. Several international biomonitoring investigations provide measured urinary metabolite concentrations of the:

- urinary metabolites of DIDP—mono-isodecyl phthalate (MIDP), mono-hydroxyisodecyl phthalate (MHIDP, OH-MIDP), monocarboxy isononyl phthalate (MCINP), monocarboxyisooctyl phthalate (MCIOP) and monooxoisodecyl phthalate (MOIDP, oxo-MIDP); and
- urinary metabolites of DnOP—(mono-(3-carboxypropyl) phthalate (MCPP, 3cx-MPP) and mono-n-octyl phthalate (MnOP))
  (Silva et al. 2004; Ye et al. 2008; Berman et al. 2009; CDC 2009; Koch and Calafat 2009; Koch et al. 2011; Wittassek et al. 2011).

In Canada, urine samples for 3236 people aged 6–49 were tested for MCPP and MnOP. More than 90% had MCPP while less than 20% had MnOP in their urine. Children had a higher concentration of MCPP than adolescents and adults and the fasting status significantly affected the concentrations of MCPP metabolites (Saravanabhavan et al. 2013).

In an earlier study by Saravanabhavan et al. (2012), DIDP and DINP showed overlapping chromatographic peaks suggesting that common constituents for these chemicals were present. The commercial DINP/DIDP formulation contains several structural isomers; hence, exposure to such a mixture is expected to result in structurally similar metabolites.

Estimates of internal doses of DIDP or DnOP associated with the biomonitoring results have not been reported. The 95th percentile urinary metabolite concentrations have been reported as approximately 190 µg/L for DIDP and/or DPHP (Silva et al. 2007; Koch and Calafat 2009) and 24.7 µg/L for DnOP (CDC 2009). Urine concentrations of the metabolites of DIDP and DnOP were generally comparable with DINP; the reported 95th percentile concentration was 106.6 µg/L (Calafat et al. 2011). This comparison indicates that the calculated 95th percentile internal dose of 11.43 µg/kg bw/day for DINP, based on urinary metabolite concentrations (Kransler et al. 2012), translates to internal dose estimates of approximately 20.25 and 2.63 µg/kg bw/day for DIDP and DnOP, respectively.

Overall, there is a wide range between the measure of central (mean or median) and the 95th percentile values, indicating that some members of the population have been exposed to much higher DIDP and DnOP levels than the population average. There are also significant variations in the urinary metabolite concentrations, possibly due to the differences in the study design and the metabolites chosen as biomarkers. Given that the commercial forms of DINP and DIDP contain C8–10 isomers, there is an overlap between the two substances. It is, therefore, expected that there will also be an overlap in the urinary metabolites arising from exposure to these chemicals, which leads to uncertainty in the quantification of exposure to DIDP alone, or exposure of DIDP together with DINP.

The calculated reasonable worst-case DIDP and DnOP exposure from toys and child-care articles in this assessment is greater than the internal dose estimates from the biomonitoring data for the DIDP and DnOP metabolites. There are no biomonitoring data for the population expected to have the maximum exposure through mouthing toys and child-care articles (i.e. infants aged six months). However, for DIDP, the calculated exposure from the typical mouthing scenario is close to the 95th percentile estimated for a population where the worst-case exposure pathway is not expected to be relevant. The biomonitoring data indicate that the calculated exposures for DnOP are an overestimate of actual exposure, but are due to the lower usage of DnOP compared with DIDP, which may result in a lower frequency of high exposures to DnOP.

The lack of biomonitoring data for infants means that it is not possible to compare and validate the worst-case estimate for infant-specific behaviour.

6 Human health hazard characterisation

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

Given that there is limited information available from human studies on the potential health effects associated with exposure to DIDP and DnOP, 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. The assessment information was obtained from NICNAS assessment reports, international reviews and journal articles on DIDP, DnOP and relevant analogue phthalates published up to July 2014. References marked with an asterisk (*) were not reviewed, but were quoted as secondary citations from the key documents listed in Section 1.3 of this report.

The NICNAS *Phthalates Hazard Compendium* (NICNAS 2008c) contains a comparative analysis of toxicity endpoints across 24 ortho-phthalates, including DIDP and DnOP. DIDP is a complex mixture of branched C9–11 isomers containing mainly C10 phthalate isomers (NTP 2003a, CPSC 2010a). DnOP consists of a pair of C8 linear chains linked to a benzenedicarboxylic acid ring and is the straight chain analogue of DEHP (CPSC 2010b). DIDP and DnOP are considered as HMW phthalates (refer to Section 2 for definition).

6.1 Toxicokinetics

6.1.1 Absorption

Absorption from oral exposure

DIDP

Sprague Dawley (SD) rats were treated with a single oral gavage dose of 0.1, 11.2 or 1000 mg/kg bw of ^{14}C-DIDP in corn oil. The amounts absorbed were estimated from the total radioactivity excreted in urine and bile, or retained in the carcass 72 hours after exposure (General Motors Research Laboratories 1983*; NTP 2003a). The total absorbed dose decreased as the dose increased (56%, 46% and 17% for the low, medium and high doses, respectively). DIDP absorption from the gastrointestinal tract (GIT) was reported to be incomplete or partially saturated within the dose range tested. There was also evidence of some enterohepatic recirculation.

DnOP

There are limited data to indicate that DnOP is readily absorbed, and quantitative estimates are not available on the rate and extent of absorption following oral exposure (Albro & Moore 1974*; Oishi 1980*; Poon et al., 1997*). In Albro and Moore's 1974 study conducted in rats, 31% of the administered dose (0.2 mL) by gavage was recovered in the urine by 48 hours after exposure. The monoester, MnOP and phthalic acid (PA) were detected, but no parent DnOP was present in the urine.

No data are available on the differences in absorption and bioavailability of orally administered DIDP and DnOP between adult and juvenile animals or between animals and humans. The oral bioavailability of the most studied phthalate, DEHP, appears to be higher in young rats (Sjoberg et al. 1986). Based on the urinary excretion data, the oral absorption of DIDP and DnOP is rapid and may become saturated or incomplete following high single doses and on repeated dosing. Information on the total excretion via all routes and/or extent of faecal excretion, whether as a result of biliary elimination or saturated urinary excretion, is lacking. Therefore, the bioavailability of DIDP and DnOP from oral exposure is assumed to be 100% for both adults and children.

Absorption by the dermal route

When phthalates, including DIDP, were applied to male Fischer 344 (F344) rat skin at 5–8 mg/cm^2 (^{14}C-DIDP) under semi-occlusive conditions, the total cumulative percentage dose recovered over seven days was 82%. Approximately 80% of the applied dose was recovered at the site of application and only 2% was recovered in tissues and excreta. Using urinary and faecal excretion as an index of dermal absorption, up to 50% of the applied DEP (side chain length = 2), approximately 5% of DEHP (side chain length = 8) and 0.5% of DIDP (side chain length = 10) were absorbed after seven days, suggesting that DIDP was the most slowly absorbed

among the phthalates tested. Further, the phthalate absorption rate decreased as the side chain length increased or became branched, with a shift noted in the excretion route from urine to faeces (Elsisi et al. 1989). In this study, dermal absorption of DIDP is approximately ten times less than DEHP.

A similar rate of dermal absorption was observed when DIDP (^{14}C-DIDP) was applied to rat skin at 16.3 mg/cm^2. Approximately 93 % of the applied dose was recovered at the application site, with only trace amounts found in other tissues and excreta. The total absorbed dose was approximately 4% of the applied dose (Midwest Research Institute 1983*).

Information on dermal absorption of DnOP is not available.

Dermal absorption of DIDP and DnOP has not been tested in humans. However, in a comparative *in vitro* study, the percutaneous absorption of four phthalates (DEHP, DBP, DEP and DMP) between human and rat skin (epidermal membranes) showed that human skin was consistently less permeable than the rat skin, and as the phthalates became more lipophilic and less hydrophilic, the absorption was reduced. For DEHP, the highest molecular weight phthalate tested, the rate of absorption through human skin was approximately four times less than through rat skin (5.6 vs 22.4 µg/cm^2/hour) (Scott et al. 1987; 1989 Errata). A similar reduction *in vitro* dermal absorption of 4.2 (human skin compared with rat skin) was also obtained for DEHP using human stratum corneum versus full thickness rat skin (0.10 vs 0.42 µg/cm^2/hour) (Barber et al. 1992*).

In two separate experiments, Deisinger et al. (1998) investigated the *in vivo* percutaneous absorption of DEHP leaching from sheets of PVC (15 cm^2) plasticised with ^{14}C-DEHP (40.4% w/w) onto the shaved skin of rats. In the first study, the PVC film was removed after 24 hours and excreta collected daily for seven days, while the second study was terminated after 24 hours, and the excreta collected. A similar percutaneous absorption rate of 0.24 µg/cm^2/h was calculated from both studies based on the sum of radioactivity at the exposure site that was systemically absorbed and then eliminated. This study examined the combined rate of DEHP migration from PVC and absorption through the skin, although the relative rates between the two processes cannot be determined.

In summary, the dermal absorption of DIDP is low (0.5–4% over seven days) in rats. It is assumed that the dermal absorption of DnOP will also be low, based on its long chain length and high molecular weight. Absorption of DIDP and DnOP through human skin is expected to be lower than rat skin, based on *in vitro* comparative studies. Quantitative dermal absorption rates for DIDP and DnOP are either limited or lacking. Therefore, the mean dermal absorption rate of 0.24 µg/cm^2/hour for the DEHP migrating from the PVC film in a rat study is considered appropriate to apply to DIDP and DnOP, without the need to use a correction factor for extrapolating from rats to humans.

Absorption by the inhalation route

When rats were exposed to 100 mg/m^3 of an aerosol of ^{14}C-DIDP for six hours by inhalation (head only), absorption from the lung was about 73% (General Motors Research Laboratory 1981*). Three days following administration, 27%, 8%, 9% and 10% of the dose was found in the lung, gut, liver and kidney, respectively. Excretion was via urinary and faecal routes (45% and 41% of the total dose, respectively).

Quantitative information on inhalation absorption of DnOP is not available.

On this basis, a default bioavailability of 100 % for DIDP and DnOP is considered appropriate for this route.

6.1.2 Distribution

DIDP

Following a single oral gavage in rats (0.1, 11.2 or 1000 mg/kg bw of 14C-DIDP in corn oil), tissue residue levels of radioactivity were less than 1% after 72 hours, with 99% of the administered dose eliminated via urine and faeces, regardless of dose. The highest concentration of radioactivity was observed in the GIT, liver and kidney (General Motors Research Laboratories 1983*).

Seven days after dermal administration of 5–8 mg/cm^2 (^{14}C-DIDP) under semi-occlusive conditions, only trace amounts of ^{14}C-DIDP were detected in the body and showed no specific tissue distribution. Most of the DIDP was found in the muscle, adipose tissue and skin (Elsisi et al. 1989).

In rats, the majority of DIDP was found in the lungs—a lesser amount was found in the GIT, liver and kidney, 72 hours following a six-hour inhalation exposure.

DnOP

DnOP is distributed in the blood and tissue compartment as the metabolite, MnOP. In rats gavaged with 2000 mg/kg of DnOP, blood levels of the chemical peaked at three hours and levels in the testes peaked at six hours, indicating that systemic absorption and distribution is rapid (CPSC 2010b). Low levels of DnOP were reported in the liver and adipose tissues of rats following administration in the diet over 13 weeks (Poon et al. 1997*).

Based on the above studies, other literature reviews and comparative studies on phthalate kinetics (Albro & Moore 1974; Kluwe 1982; McKee et al. 2002; NICNAS 2008b), and findings from the previous NICNAS PEC assessments for DMP and DEP (LMW phthalate) (NICNAS 2014a; NICNAS 2014b), DBP and DEHP (transitional) (NICNAS 2010; NICNAS 2013) and DINP (HMW phthalate) (NICNAS 2012), phthalate distribution is generally, or for DIDP and DnOP in particular, assumed to be widespread in the body after exposure, with no evidence of accumulation.

6.1.3 Metabolism

DIDP

In a single gavage study in rats, phthalic acid (PA) and oxidised monoester derivatives of DIDP were detected in urine, while the parent DIDP, monoester derivative (monoisodecyl phthalate, MIDP) and oxidised monoester derivative were detected in faeces. The metabolite distribution for MIDP in the faeces is consistent with a proposed metabolic pathway through which DIDP is de-esterified to the monoester MIDP, which is further metabolised by oxidation to form oxidative metabolites, or by hydrolysis to phthalic acid.

Urinary metabolites of DIDP in female rats were identified after a single oral administration of 300 mg/kg. Consistent with the above study, the hydrolytic monoester of DIDP, MIDP, was detected as a minor metabolite with the oxidative metabolites, mono(carboxyisononyl) phthalate (MCINP) detected as the most abundant urinary metabolite. Other secondary metabolites of DIDP included mono(hydroxy-isodecyl) phthalate, mono(oxo-isodecyl) phthalate, mono(carboxy-isoheptyl) phthalate, mono(carboxy-isohexyl) phthalate, mono(carboxy-isopentyl) phthalate, mono(carboxy-isobutyl) phthalate and mono(carboxy-ethyl) phthalate. Oxidative metabolites related to diisoundecyl phthalate (DIUDP) and diisononyl phthalate (DINP) were also detected, indicating that DIUDP and DINP were present as constituents of the DIDP formulation (Kato et al. 2007). The high content of secondary DIDP metabolites in urine is consistent with a proposed metabolic pathway of DIDP, which suggests that DIDP is de-esterified to the monoester MIDP that is further metabolised by oxidation to form oxidative metabolites, including metabolites where the side chain length is decreased (ECHA 2013).

DnOP

In vivo and *in vitro* animal studies have been conducted on the metabolism of DnOP following acute oral exposure (ATSDR, 1997; NTP 2003b; Silva et al. 2005). As with other phthalates, DnOP undergoes hydrolysis to form the primary metabolite, MnOP, which subsequently metabolises further into oxidative metabolites and phthalic acid. The secondary metabolites may undergo Phase II detoxification to produce glucuronide conjugates with increased water solubility, before being excreted in the urine and/or faeces. MnOP in blood was measured in rats dosed with 2000 mg/kg of DnOP by gavage. The biological half-life in the blood was 3.3 hours, with peak blood levels observed three hours after administration. MnOP was also detected in the testes within 1–2 hours of administration, with peak levels observed six hours after administration (Oishi 1990*). In male rats treated for two days with 559 mg/kg/day of DnOP, 31% of the administered dose recovered in the urine was as straight chain monoesters with varying alkyl side chain lengths. The remaining amount in the urine was represented by PA and MnOP. The parent compound was not found in the urine (Albro & Moore 1974).

Similar results were obtained from the oral studies conducted by Silva et al. (2005) where PA, MnOP and monocarboxy propyl phthalate (MCPP) were detected in the urine of adult female rats after a single oral dose of 300 mg/kg. There were also five other oxidative metabolites identified in the urine: mono-carboxymethyl phthalate (MCMP), mono-(5-carboxy-n-pentyl) phthalate (MCPeP), mono-(7-carboxy-n-heptyl) phthalate (MCHpP), one isomer of mono-hydroxy-n-octyl phthalate ((MHOP) i.e. mono-(7-hydroxy-n-octyl) phthalate), and one isomer of mono-oxo-n-octyl phthalate ((MOOP) mono-(7-oxo-n-octyl) phthalate). The metabolite levels decreased significantly 24 hours after administration. The higher concentrations of oxidative metabolites derived from DnOP compared with MnOP suggest that oxidative metabolites are better biomarkers of DnOP than MnOP. The same authors studied the role of the liver in the metabolism of D_4-DnOP and MnOP by incubating D_4-DnOP and MnOP in the presence of live rat microsome homogenates. As expected, D_4-DnOP resulted in the formation of D_4-MnOP, D_4-MHOP and D_4-PA, whereas MnOP resulted in the formation of

MHOP and PA, suggesting that the liver is capable of hydrolysing DnOP to MnOP, and further oxidising MnOP. The hydrolysis of D_4-DnOP was rapid (2.78 nmol/mL/h) and D_4-MnOP was the main metabolite detected.

Overall, the higher concentrations of DIDP and DnOP oxidative metabolites than of their monoester derivatives (MIDP and MnOP, respectively) suggest that oxidative metabolites are better biomarkers of DIDP and DnOP.

6.1.4 Elimination and excretion

DIDP

The majority of the ^{14}C-DIDP dose administered as a single gavage dose was excreted in faeces (57%, 65% and 81% for the low, medium and high doses, respectively). Excretion in urine was biphasic and the excretion rate of the administered dose decreased as the dose increased (41%, 32% and 12% for, the low, medium and high dose, respectively) over 72 hours following exposure.

Following dermal exposure of rats, radioactivity in faeces and the GIT suggests the absorbed radioactivity is excreted through the biliary route.

Radioactivity excreted in the urine over 72 hours following inhalation exposure was described using first order kinetics. The half-life (T1/2) of elimination was 16 hours with an elimination rate constant (Ke) of 0.042/hour, based on 12-hour interval excretion data. ^{14}C-DIDP was excreted in urine and faeces during the 72 hours post-exposure at 45% and 41%, respectively.

DnOP

In the oral study conducted by Silva et al. (2005), the metabolism of DnOP in rats (administered at 300 mg/kg bw/day via gavage) resulted in PA, MnOP and MCPP being excreted in the urine. At least five other oxidative metabolites at concentrations much higher than MnOP were also detected: MCMP, MCPeP, MCHpP, MHOP and MOOP. MCPP was the major metabolite excreted (mean urinary level of 163.3 µg/mL) followed by MCHpP (mean urinary level of 71.6 µg/mL) after 24 hours. Furthermore, the toxicokinetics of DnOP metabolites supports the postulated biphasic elimination pattern of DnOP with initial rapid clearance of all *in vivo* DnOP metabolites followed by a slow elimination phase. It was also suggested that, in rats, the major pathway for DnOP metabolism involves ω-oxidation followed by β oxidation *in vivo*. The metabolite levels decreased significantly over the following 24 hours, although MCPP, MCHpP, MHOP and MOOP were still detectable four days after dosing. The average levels of oxidative urine metabolites when collected 48-hours (day2) after dosing were approximately 95% lower than in the first 24-hour urine collection.

Overall, elimination of DIDP, DnOP and their respective metabolites is rapid, as for other assessed phthalates (DEHP, DINP, DEP, DBP, DMP and DMEP) (NICNAS 2010, 2011, 2012, 2013, 2014a and 2014b).

6.2 Acute toxicity

6.2.1 Acute oral, dermal and inhalation toxicity

Most of the animal studies considered were either not available as detailed reports or were performed before good laboratory practice (GLP), OECD or EU Test Guidelines were established. Thus, details on the treatment methods were often not available. The acute toxicity of DIDP and DnOP are summarised in tables 6.1 and 6.2, respectively.

DIDP

Table 6.1: Acute animal toxicity studies of DIDP

Study	Species	Result (LD50/LC50)	References
Oral	Rat	>62080 mg/kg bw	Smyth et al., 1962*
	Rat	>29100 mg/kg bw	BASF, 1961*
Dermal	Rat	>2910 mg/kg bw	Inveresk Research International, 1981*
	Rabbit	>3160 mg/kg bw	Industrial Bio-test Laboratory, 1975*
	Rabbit	>3160 mg/kg bw	Hazleton Laboratories America, 1978*
Inhalation (4-hour)	Rat	>12540 mg/m^3	Inveresk Research International, 1981*

The available animal data indicate that DIDP has low acute oral, dermal and inhalation toxicity (refer to ECB 2003a; NICNAS 2008a; NICNAS 2008c; CPSC 2010a; ECHA 2013 for review).

DnOP

Table 6.2: Acute animal toxicity studies of DnOP

Study	Species	Result (LD50/LC50)	References
Oral	Rat	53700 mg/kg bw	Dogra et al. 1987*
	Mouse	13000 mg/kg bw	Dogra et al. 1989*
	Mouse	>12800 mg/kg bw	Eastman Kodak Company 1978*
Dermal	Guinea pig	75 mL/kg bw	Bisesi 1994*; CMA 1999*

The available animal data indicate that DnOP has low acute oral toxicity. A dermal LD50 was reported in guinea pigs, although the concentration of the applied substance was not available. No data were available for inhalation toxicity (refer to NICNAS 2008b, CPSC 2010b; ECHA 2010 for review).

6.3 Irritation and sensitisation

6.3.1 Skin irritation

DIDP

Minimal skin irritation, including mild erythema and mild oedema, was observed in rabbits treated with undiluted DIDP under occlusive conditions (BASF 1979c*; BASF 1979d*).

In human patch tests, undiluted DIDP did not produce any signs of irritation in 15 subjects after 24 hours (Hill Top Research 1995a* and b*). However, when 5% (w/w) DIDP was applied to two groups of patients (114 or 310 patients), irritation was observed in 2/114 and 2/310 patients, respectively (Kanerva et al. 1996*, 1999*).

The available data suggest that DIDP causes minimal skin irritation in rabbits and in humans (refer to ECB 2003a; NICNAS 2008a; CPSC 2010a; ECHA 2013 for review).

DnOP

In guinea pigs and rabbits, DnOP was reported to be a slight skin irritant (Eastman Kodak Company 1978* and Marhold 1986*, respectively). Human patch tests indicated an irritation incidence of 1.2%— essentially a negative result (Kanerva et al. 1997*). Overall, DnOP caused minimal irritation when tested in laboratory animals and in humans (refer to NICNAS 2008b; CPSC 2010b; ECHA 2010 for review).

6.3.2 Eye irritation

DIDP

In rabbits, undiluted DIDP causes reversible slight redness of the conjunctivae (Industrial Bio-test Laboratories 1975*; BASF 1979a*; Inveresk Research International 1981*; BASF 1986*)

The available data suggest that DIDP causes minimal eye irritation in rabbits (refer to ECB 2003a; NICNAS 2008a; CPSC 2010a; ECHA 2013 for review).

DnOP

Slight conjunctival irritation was observed in guinea pigs treated with DnOP (Eastman Kodak Company 1978*). Equivocal results were obtained from two studies conducted in rabbits (Marhold 1986*; Anonymous 1946*).

An eye irritation case report of workers exposed to phthalates including dioctyl phthalate (isomer unspecified) was identified (Government of Canada 1993).

Overall, DnOP causes minimal eye irritation in guinea pigs. Limited data suggest similar effects in humans (refer to NICNAS 2008b; CPSC 2010b; ECHA 2010 for review).

6.3.3 Respiratory irritation

DIDP

No indication of upper airway irritation was reported following acute inhalation exposure in animals (ECB 2003a; ECHA 2013).

DnOP

A case report of irritation of the upper respiratory tract of workers exposed to phthalates, including dioctyl phthalate (isomer unspecified), was identified (Government of Canada 1993).

Overall, the data are insufficient to determine the respiratory irritation potential of DIDP and DnOP.

6.3.4 Sensitisation

DIDP

There are several skin sensitisation studies available for DIDP. A positive response was reported from a Buehler test (Exxon Biomedical Sciences 1992*), while other guinea pig studies gave negative results with no irritatant effects (Inveresk Research International 1981*; Huntingdon Research Centre 1994*).

No positive reactions were reported in human patch tests (Hill Top Research 1995b*; Kanerva et al. 1996*; Medeiros et al. 1999*). A case of allergic contact dermatitis was reported in a 64-year-old woman from an identity wrist band made from PVC that contained 5% DIDP (Hills & Ive 1993*).

Overall, there is insufficient information to indicate that DIDP causes skin sensitisation (refer to ECB 2003a; NICNAS 2008a; CPSC 2010a; ECHA 2013 for review).

DnOP

The skin sensitisation potential for DnOP was evaluated in animal studies, human patch tests and from occupational exposure.

In animals, no sensitisation reactions were reported in guinea pigs (Eastman Kodak Company 1978*; ECB 2000*).

In humans, 2% DnOP did not produce a sensitisation reaction in 173 subjects in an occlusive human patch test (Kanerva et al. 1997*). In contrast, when plastic shoe factory workers were patch tested for sensitivity to a "standard battery of substances" including four widely used plasticisers, sensitisation reactions were reported in a number of workers. The test was conducted on a group of 30 plastic shoe factory workers with skin lesions and an additional group of 30 plastic shoe workers without skin lesions. Six workers in the group with skin lesions had positive reactions to phthalates and five were positive to coal tar.

There are several studies available that investigated the correlation between exposure to phthalates and the incidence of allergic diseases. In a case report of occupational asthma, DnOP was reported to induce asthmatic symptoms in a patient following exposure to DnOP vapours. Administering sodium cromoglycate, a mast cell stabiliser, inhibited the asthmatic symptoms (NICNAS 2008b; CPSC 2010b; ECHA 2010). Furthermore, Jaakkola and Knight (2008) conducted a review and meta-analysis on a number of animal and human sensitisation studies on phthalates including DnOP. Based on the review, the authors concluded that asthma reported from case reports was likely to have been caused by fumes emitted from PVC film that contained phthalates. There was also a positive association found between heated PVC fumes and respiratory symptoms obtained in epidemiological studies in occupational settings. Children exposed to PVC surface materials in the home were reported to have higher risks of asthma and allergies, although it is difficult to ascertain the correlation between individual phthalates and the specific effects observed.

A study in a murine model suggested that phthalates and phthalate monoesters, including DnOP and MnOP, were capable of stimulating IgE and IgG1 production (Larsen et al. 2002). In another study, the potential of phthalates (including DIDP and DnOP) and their monoesters to induce histamine release *in vitro* was investigated. Basophils from human peripheral blood were pre-incubated with diester phthalates and phthalate monoesters. None of the phthalates were found to induce histamine release. However, when pre-treated basophils were stimulated with an anti-IgE antibody, phthalates and phthalate monoesters with alkyl side chain lengths containing eight carbon atoms (DnOP, MnOP, DEHP and MEHP) had the strongest histamine release potential, compared with four, nine or 10 carbon atoms side chains for which there was little or no potential for histamine release (Glue et al. 2005).

There are some indications of DnOP having a sensitising potential. However, overall the data available are not sufficiently conclusive to determine the sensitising activity of DnOP, and phthalates in general are not considered to be skin sensitisers (NICNAS 2010, 2011, 2012, 2013, 2014a, 2014b).

6.4 Repeated dose toxicity

6.4.1. Animal studies

DIDP

Several repeated dose oral toxicity studies were described in risk assessment reports from international organisations and regulatory bodies (ECB 2003a; SCCP 2007; NICNAS 2008a; SCHER 2008; CPSC 2010a; ECHA 2013). In short-term studies on DIDP in rats and dogs, the main effects were increased liver weights and lipid metabolism in the liver, with or without associated pathology. Substantial changes in liver peroxisome proliferator enzyme activity were also reported in rodent studies. These are considered as species-specific, and have debatable relevance to human health (CPSC 2010a; ECHA 2013). Key studies used to determine the appropriate NOAEL for risk assessments are summarised in Table 6 and described below.

In a 21-day feeding study designed to assess peroxisomal proliferation, F344 rats (five/sex/dose) were administered dietary doses of 0, 0.3, 1.2 and 2.5% DIDP (approx 264/304; 1042/1134; and 1972/2100, males/females mg/kg bw/day) (BIBRA 1986*). No treatment-related clinical signs were noted. Males dosed at 1.2% and 2.5%, and females at 2.5% showed decreases in weight gain during treatment (statistically significant in both sexes at the 2.5% dose only). Males dosed at 2.5% consumed significantly less food throughout the treatment period. Significant increases in absolute and relative liver weights were seen in males at all dose levels and in females dosed at 1.2% and 2.5%. Serum triglycerides and cholesterol levels were reduced in males dosed

at 1.2% and 2.5% in a non-dose related manner. Cyanide-insensitive palmitoyl-CoA oxidation was significantly increased in treated animals at 1.2% and 2.5%, but not at 0.3%. Significant increases in lauric acid 11- and 12-hydroxylase levels were observed in all treated males, but in females levels of lauric acid 12-hydroxylase were increased only at the 2.5% dose. Electron microscopy examinations revealed marked but variable increases in the number and size of hepatocyte peroxisomes in both sexes at the 2.5% dose. Relative kidney weights were significantly higher in all treated groups apart from females dosed at 0.3%, while absolute kidney weights were lower in both sexes at the 2.5% dose, and higher in males dosed at 1.2%. Absolute testis weights were slightly, but significantly, decreased at the 2.5% dose; however, relative testis weights were significantly increased at the same dose. No histological evidence of testicular atrophy was found. A NOAEL of 304 mg/kg bw/day (0.3%) was identified for females, but no NOAEL was identified for males due to the increased liver weight and increases in 11-and 12 hydroxylase levels in males at all dose levels.

A 28-day dietary study in male F344 rats (five/dose) using 0, 0.02, 0.05, 0.1, 0.3 and 1% DIDP (approx 0, 25, 57, 116, 353, 1287 mg/kg bw/day) noted no changes in body weight, but recorded dose-related increases in absolute (statistically significant at ≥0.3%) and relative (statistically significant at ≥0.1%) liver weights. Liver palmitoyl-CoA oxidation activity was increased in a statistically significant and dose related manner at ≥0.1% dose. No testicular atrophy was reported. The NOAEL was determined to be 57 mg/kg bw/day (0.05%) (Lake et al. 1991*).

A 90-day dietary study was conducted in SD rats (20/sex/dose) using 0, 800, 1600, 3200 and 6400 ppm DIDP doses (approx. 0, 55–60, 100–120, 200–250 and 400–500 mg/kg bw/day males and females, respectively) (BASF 1969*). No clinical signs of toxicity were noted in either sex. No differences in food intake or body weight gains were observed in female rats; in males, food intakes were normal but body weight gains were decreased slightly from day 77 onwards at ≥1600 ppm. Absolute liver weights were increased in all males but statistically significantly only at the highest dose (6400 ppm). Relative liver weights were significantly increased in all male animals, but without a clear dose relationship. In females, dose related increases in absolute liver weights were reported at all doses, but the increases were only significant at ≥3200 and 6400 ppm. Relative liver weights were also increased significantly from ≥1600ppm. Absolute kidney weights were unchanged. In males, relative kidney weights were significantly increased in all treated groups, but had no dose relationship. In females, relative kidney weights were increased at 1600 ppm and 3200 ppm, but not at 6400 ppm. No histopathological changes were observed in any organ. A NOAEL of 800 ppm (60 mg/kg bw/day) and a LOAEL of 1600 ppm (120 mg/kg bw/day) were determined based on dose-related and statistically significant increases in relative/absolute liver weights in females.

In another 90-day dietary study, Charles River CD rats (10/sex) were administered 0, 0.05, 0.3 or 1% DIDP (approximately 28/35, 170/211 and 586/686 mg/kg/day, males/females respectively) (Hazelton Laboratories 1968a*). Absolute and relative liver weights were significantly increased at the highest dose (1%) for both sexes. Relative kidney weights were increased in males at 0.3% and 1%. There were no effects on food consumption, body weight or chemistry parameters. There were no histopathological abnormalities observed in the liver, kidneys or testes. A NOAEL of 170–211 mg/kg/day for both sexes was determined from the study. The LOAEL was 586–686 mg/kg/day for males, based on the increased liver weights observed at this dose.

A 13-week dietary study was conducted in beagle dogs (three/sex/dose) at 0, 0.05, 0.3 and 1% DIDP (reported to be approximately 0, 15, 75 and 300 mg/kg bw/day, respectively) (Hazelton Laboratories 1968b*). No clinical signs of toxicity were noted. Three of six dogs at the highest dose showed body weight loss. Only in one animal was this related to decreased food consumption. Clinical chemistry analyses were normal. Gross organ examinations following euthanasia did not reveal DIDP-related effects. Increased liver weights in all animals were dose related. The low number of animals at each dose precluded statistical analysis. Microscopic examinations revealed slight to moderate swelling and vacuolation of hepatocytes at the 0.3% and 1% doses. The severity of these changes and the number of animals affected were not dose-related (2/3 males at 0.3% vs 1/3 males at 1%; 2/3 females at 0.3% vs 3/3 females at 1%). Measurements of serum alanine and aspartate aminotransferases and sulfobromophthalein clearance were unchanged, suggesting a lack of overt hepatic damage. A NOAEL of 15 mg/kg bw/day (0.05%) was derived from this study based on hepatic effects observed at the 0.3% dose (75 mg/kg bw/day).

In a two-year carcinogenicity study (non-guideline and non-GLP), F344 rats (52/sex/dose) were fed diets containing 400, 2000 and 8000 ppm DIDP (approximately 22/23, 100/128 and 479/620 mg/kg bw/day for males/females respectively) (Cho et al. 2008 and erratum 2010). There was a significant decrease in the overall survival and significant increases in relative kidney and liver weights of the rats in both sexes in the highest

dose group (8000 ppm). Histopathological examination of the liver showed a low, but statistically significant, incidence of spongiosis hepatis (changes in the perisinusoidal liver cells) in all treated males. Oval cell hyperplasia, hypertrophy and peliosis (multiple cyst-like, blood-filled cavities) were significantly increased in males at the 8000 ppm dose. Altered cell foci in the liver were decreased significantly at the 2000 and 8000 ppm doses in males and at the 8000 ppm dose in females. Microgranuloma incidence was statistically increased in all treated males, but with no clear dose response, compared with decreases in microgranuloma incidence at the 8000 ppm dose in females. Liver necrosis was significantly increased in both sexes at 8000 ppm. Inflammation and hyperplasia of the prostate were increased at all doses, while the incidence of prostate degeneration was increased at the 400 and 2000 ppm doses, but not at the 8000 ppm dose. In the kidneys, mineralisation and interstitial nephritis were significantly increased in males at the 8000 ppm dose. In females, hyaline cast and interstitial nephritis were significantly decreased at the 8000 ppm dose. The NOAEL was determined to be 100–128 mg/kg bw/day (400 ppm), based on significant increases in the liver weight and histopathological changes observed at the higher doses.

The carcinogenic potential of DIDP was investigated in transgenic mice (15 rasH2 mice/sex/dose) fed with a diet containing 0.1%, 0.33% and 1% DIDP, and in wild type mice (15/sex) fed with a diet containing 1% DIDP for 26 weeks (Cho et al. 2011). At the 1% dose, liver and kidney weights were significantly increased in both sexes of the rasH2 and wild type mice, also at the 0.33% dose in rasH2 males. Testes, spleen and brain weights were statistically increased in rasH2 and wild type mice at the 1% dose. In the liver, increases in parenchymal inflammation and diffuse hepatocyte hypertrophy with eosinophilic granules (in both sexes), focal necrosis, pigmented hepatocytes, and pigmented and prominent Kupffer cells were statistically significant in rasH2 and wild type mice. In the kidneys of males, a higher incidence of tubular basophilia and tubular hyperplasia was seen at the 1% dose in both the rasH2 and wild type mice.

Two 2-generation reproductive toxicity studies also contained information on repeated dose toxicity. In the first study (Exxon Biomedical Sciences 1997*; Hushka et al. 2001), rats (30/sex/dose) received 0, 0.2, 0.4 or 0.8% of DIDP (approximately 0, 103–379, 211–761, 427–1424 mg/kg bw/day, males/females, respectively) in the diet for 10 weeks before mating and then during the mating period. Females continued to be treated throughout gestation and lactation until the offspring were weaned on post natal day (PND) 21. Statistically significant increases in mean absolute liver weights were observed in all females in both generations (F_0 and F_1); in F_0 males at the 0.4% dose and F_1 males at the 0.8% dose (Hushka et al. 2001). These were accompanied by dose-dependent microscopic evidence of centrilobular or diffuse hepatocellular hypertrophy. There was a statistically significant increase in the absolute kidney weight observed in all treated male groups at the 0.4% dose in F_0 females and at the 0.4% and 0.8% doses in F_1 females. In females, the effect on kidney weight was not dose related and no kidney damage was observed microscopically. Microscopic findings in males were reported to be consistent with male-rat-specific alpha-2μ globulin nephropathy. Right caudal epididymis weights were increased in the 0.4% and 0.8% dose groups in both male generations and left ovarian weights were decreased in the 0.8% dose in both female generations. For parental systemic toxicity (both generations), a LOAEL of 103–379 mg/kg bw/day (0.2%), based on the liver effects, was established. No NOAEL could be derived.

In the second two-generation study, (Exxon Biomedical Sciences 2000*; Hushka et al. 2001) rats (30/sex/dose) received 0, 0.02, 0.06, 0.2 or 0.4% of DIDP (approximately 0, 12/40, 33/114, 114/352 or 233/747 mg/kg bw/day, males/females, respectively) in the diet for 10 weeks before mating and then during the mating period. Females continued treatment throughout gestation and lactation. Statistically significant increases in the mean absolute liver weights were observed at the 0.4% dose in both sexes of both parental generations, and at the 0.2% dose in F_1 females. This was consistent with findings from the previous two-generation study. Statistically significant increases in mean absolute kidney weights were seen in male rats of both generations at the 0.4% dose and in F_1 males at the 0.2% dose. This effect was also reported in the 0.2% group of F_1 females. For parental systemic toxicity, a NOAEL of 33–114 mg/kg bw/day (0.06%) was derived, with a LOAEL of 114–352 mg/kg bw/day (0.2%), based on the kidney changes in F_1 males and females.

There are no studies on effects from repeated dermal exposure to DIDP in animals or humans.

There is one study in rats on repeated inhalation exposure to DIDP. Male rats (eight/group) were exposed by inhalation to an aerosol containing 505 mg/m^3 DIDP for six hours/day, five days/week for two weeks (General Motors Research Laboratories 1981*). No signs of systemic toxicity were observed. Body weight gains were unchanged. On examination following euthanasia, lung tissue showed moderate increases in alveolar septal widths with signs of mixed inflammatory reactions. The histology of the liver, spleen and kidneys was unremarkable. Haematological and biochemical parameters were not investigated. The NOAEL was 505 mg/m^3 based on only local irritant effects being observed at this dose.

Table 6.3: Summary of repeated dose toxicity effects of DIDP

Species, study duration, and administration mode	Doses	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	References
Rat 21 days (5/sex/dose), diet	0, 0.3, 1.2 and 2.5%; approximately 0, 264/304 1042/1134 and 1972/2100 (female/male) mg/kg bw/day	Male: none Female: 264	Male: 304; Female: 1042 increased liver weight (absolute and relative);lauric acid 11- and 12-hydroxylase level (males)	BIBRA, 1986*
Rat 28 days (5/sex/dose), diet	0, 0.02, 0.05, 0.1, 0.3 and 1%; approximately 0, 25, 57, 116, 353, 1287 mg/kg bw/day	57	116; increased liver weights, increased cyanide-insensitive palmitoyl-CoA oxidation	Lake et al., 1991*
Rat 90 days (20/sex/dose), diet	0, 800, 1600, 3200 and 6400 ppm; approximately 0, 55/60, 100/120, 200/250, 400/500 male/female mg/kg bw/day	Male: 200 Female: 60	Male: 400; increased liver weights (absolute) Female: 120; increased liver weights (relative)	BASF, 1969*
Rat 90 days (10/sex/dose), diet	0, 0.05, 0.3 or 1%; approximately 0, 28/35, 170/211 or 586/686 male/female mg/kg bw/day	170–211 male/ female	586–686 male-female; increased liver weight	Hazelton Laboratories, 1968a*
Dog 13 weeks (3/sex/dose), diet	0, 0.05, 0.03 and 1%; approximately 0, 15, 75, 300 mg/kg bw/day	15	75; increased liver weight, slight to moderate swelling and vacuolation of hepatocytes	Hazelton Laboratories, 1968b*
Rat 2 years (52/sex/dose), diet	0, 400, 2000 and 8000 ppm Approximately 0, 22/33, 100/128, 479/620 male/female mg/kg bw/day	100–128	479–620; significantly increased liver weight	Cho et al. 2008
Rat 2-generation reproductive study (30/sex/dose), diet	0, 0.2, 0.4 or 8% Approximately 0, 103/379, 211/761, 427/1424 male/female mg/kg/bw/day	None	103–379: statistically significant increased liver weight	Exxon Biomedical Sciences 1997*, Hushka et al. 2001
Rat 2-generation reproductive study (30/sex/dose), diet	0, 0.02, 0.06, 0.2 or 0.4% Approximately 0, 12/40, 33/114, 114/352, 233/747 male/female mg/kg/ bw/day	33–114	114–352; kidney changes	Exxon Biomedical Sciences 1997*, Hushka et al. 2001
Rat 2 weeks, 6 h/d, 5 days/week (8 males), inhalation	0, 505 mg/m^3	505 mg/m^3	None; no systemic effects	General Motors Research Laboratories, 1981*

DnOP

Administration of DnOP (2% in the diet) to male JCL:Wistar rats for one week resulted in statistically significant increases in absolute and relative liver weights, but not kidney weights (Oishi & Hiraga 1980).

In a short-term study, Wistar rats received DnOP orally at doses of 2266 mg/kg bw/day for three days, 2078 mg/kg bw/day for 10 days, and 1906 mg/kg bw/day for 21 days. The livers of treated rats had a pale greasy appearance. There were statistically significant increases in relative liver weights after 10 and 21 days of treatment, but not after three days of treatment. After three days, loss of centrilobular glycogen, proliferation and dilation of the smooth endoplasmic reticulum, loss of the rough endoplasmic reticulum, and shortened microvilli in some biliary canaliculi were observed. No significant changes were noted in the enzyme parameters associated with peroxisome proliferation. After the 10- or 21-day treatment, centrilobular glycogen reduction became more severe and was associated with fat accumulation and some necrosis. Small, but statistically significant increases were also noted for hepatic cyanide-insensitive palmitoyl CoA oxidase and peroxisomal catalase activities for these longer treatments (Mann et al. 1985*).

Thyroid effects were examined in samples taken from the above study. Serum from four Wistar rats that were administered DnOP for 21 days was assayed (Hinton et al. 1986*). Statistically significant decreases in serum thyroxine (T4) levels, but not triiodothyronine (T3) levels, were observed. In addition, ultrastructural changes consisting of increases in the numbers and sizes of lysosomes, enlargement of the Golgi apparatus and damage to mitochondria were also detected in the thyroid.

To examine whether liver metabolism and biochemical changes are associated with peroxisome proliferation, six SD rats/dose were treated by gavage with DnOP at 1000 or 2000 mg/kg bw/day for 14 days. Relative liver weights were increased in both groups. There were no increases in peroxisomal enzyme activities (Lake et al. 1984*; Lake et al. 1986*).

In an incomplete report of a study in which male rats were exposed to 0, 300 or 600 mg/kg bw/day of DnOP in the diet for 11 weeks, liver damage (characterised by cellular enlargement and proliferation, vacuolisation, chronic inflammation, and necrosis) was observed at 300 mg/kg bw/day and above. Alterations in serum enzyme levels were consistent with the observed liver damage (DeAngelo et al. 1988*).

Systemic effects of DnOP were studied in SD rats (10/sex) fed with dietary concentrations of 0, 5, 50, 500, or 5000 ppm DnOP (0, 0.4/0.4, 3.5/4.1, 36.8/40.8, or 350/403 mg/kg bw/day males/females, respectively) for 13 weeks. At 5000 ppm, liver and thyroid effects were observed. Statistically significant increases in hepatic ethoxyresorufin-o-demethylase activity (a marker of activation of the aromatic hydrocarbon receptor, AhR) were also seen at this dose. Thyroid effects included decreases in follicle size and colloid density. The NOAEL was 500 ppm (37 mg/kg bw/day), based on liver and thyroid effects at 5000 ppm (Poon et al. 1997*).

In a further study, rats were treated with DnOP intraperitoneally at doses of 100, 300, or 600 mg/kg bw/day for 90 days. Microscopic examination of the kidneys revealed dose-dependent changes to glomeruli, proximal and distal tubules, the loop of Henle and collecting tubules in the medulla; many of the effects persisted after a 45-day recovery period (Khanna et al. 1990*).

The effects of DnOP treatment have also been studied in mice. Following a continuous breeding protocol, offspring CD-1 mice taken from the last litter of treated parental mice exposed to approximately 7500 mg/kg bw/day DnOP for 105 days including mating and gestation periods, were exposed to DnOP for 85–105 days, first via lactation, then through their diet. The average DnOP dose in these offspring over this period was calculated by the study authors as 8640 mg/kg bw/day. Statistically significant increases in absolute liver weights were observed in both sexes. Absolute kidney weights were also statistically significantly increased in females but not in males. However, no gross morphological or histopathological lesions were seen in these two organs (NTP 1985*; Heindel et al. 1989*; Morrissey et al. 1989*).

CD-1 mice dosed with DnOP in the diet at 1800, 3600, 7500, and 15000 mg/kg bw/day for 14 days showed no clinical symptoms of toxicity except for rough hair coats at the highest dose (Heindel et al. 1989*).

A single dose (175 mg/kg bw/day) of an unspecified isomer of dioctyl phthalate was administered in the diet to an unspecified species and strain of animals for 12 months. The reported effects were restricted to a decrease in body weights and increases in liver and kidney weights (Pieckacz 1971*). In another chronic toxicity study, ‘numerous’ liver nodules were reported in male rats given 1% DnOP (600 mg/kg bw/day) in the diet for 15 months. The activity of a number of lysosomal enzymes was also increased in these rats (Carter et al. 1989*).

There are no data on dermal and inhalation studies in animals following repeated exposure to DnOP.

6.4.2. Human studies

There are no human data available for repeated dose exposure to DIDP and few studies on repeated dose exposure were identified for DnOP.

Gilioli et al. (1978*) reported that 12/23 workers at a plasticiser manufacturing facility who had been exposed to phthalate esters (<1–60 mg/m^3, specific isomers not identified) for an average of 4.5 years had mild to moderate sensorimotor and motor polyneuropathy. Another study investigated Russian workers (87 females and 60 males) in the artificial leather industry in which several phthalate plasticisers, including DnOP, were used (Milkov et al. 1973*). Employment ranged from 0.5 to 19 years. Phthalates were found to be the principal air contaminants in the work areas, with ambient air concentrations of the phthalate plasticisers ranging from 1.7 to 66 mg/m^3. Neurological testing revealed that 32% of the employees had polyneuritis (inflammation of several nerves), the incidence of which correlated positively with length of service.

In a US New Jersey Department of Health and Senior Services hazardous substances fact sheet, repeated exposure of humans to DnOP is claimed to cause liver damage, while repeated skin contact is stated to cause dryness, cracking and rashes (NJDHSS 2002).

Conclusion

DIDP

In rats and dogs, the liver was the primary target organ in oral studies. Several studies reported liver weight and enzyme changes, and histological changes (swelling and vacuolation of hepatocytes) consistent with peroxisome proliferation. In dogs, peroxisome proliferation was not observed and the liver effects were less pronounced. Testicular effects were generally not found.

Dogs are considered a more relevant species to humans with respect to peroxisome proliferation (13-week diet study); however, there are limitations to the available study for human risk assessment. The study was not conducted according to the test guideline; it was conducted before the test guidelines were developed and Good Laboratory Practice established. The small numbers of test animals (three/dose) precluded the conduct of any reliable statistical evaluation. Although the increase in liver weight was dose related, there was no dose response in the severity of effects and the number of animals with histopathological changes in the liver. Furthermore, liver enzyme (ALT and AST) activities were not affected, suggesting the absence of liver injury. Therefore, a LOAEL of 120 mg/kg bw/day (1600 ppm) and a NOAEL of 60 mg/kg bw/day (800 ppm) are determined, based on the statistically significant increase in relative liver weights from a 90-day dietary study in rats.

DnOP

The liver appears to be the primary target organ for DnOP toxicity. Liver toxicity (weight, histological or clinical chemistry changes) was observed in several repeated dose studies. In a 21-day oral study, DnOP caused dose-related statistically significant increases in relative liver weights, loss of centrilobular glycogen and changes in liver histopathology including fat accumulation and necrosis. In other studies, DnOP also induced ultrastructural changes in the thyroid and kidneys.

Overall, liver effects from DnOP did not appear to be associated with peroxisome proliferation. Increases in peroxisomal enzyme activities generally were not observed. Therefore, a LOAEL of 350 mg/kg bw/day and a NOAEL of 37 mg/kg bw/day, based on histological changes in the liver and thyroid from a 13-week rat dietary study, are considered appropriate for the human risk assessment.

6.5 Genotoxicity and carcinogenicity

6.5.1 Genotoxicity

DIDP

Available studies conducted *in vitro* and *in vivo* to determine the genotoxic potential of DIDP are summarised in Table 6.4. Negative results were obtained from *in vitro* bacterial mutation assays and *in vitro* mouse lymphoma assays. An *in vivo* mouse micronucleus assay was also negative. DIDP is considered to be non-genotoxic.

Table 6.4: Summary of genotoxicity studies with DIDP

Test	Test system (species/strain)	Dose	Metabolic activation	Result	Reference
In vitro					
Reverse mutation	*Salmonella. typhimurium* TA98, TA100, TA1535, TA1537	100–1000 µg/plate	With and without	Negative	Zeiger et al. 1985*
Reverse mutation	*S. typhimurium* TA100	Not reported	Not reported	Negative	Seed 1982*
Mouse lymphoma mutation assay	L5178Y TK +/− mouse lymphoma cells	-S9:2000–10000nl/mL +S9: 250–10000 nl/mL	With and without	Negative	Hazelton Biotechnologies Company 1986*
Mouse lymphoma mutation assay	L5178Y TK+/−mouse lymphoma cells	-S9: 2–10 µl/mL +S9: 0.25–2 µl/mL	With and without	Negative	Barber et al. 2000
In vivo					
Micronucleus test	CD-1 mice (bone marrow)	Single oral (gavage) dose of 0, 1250, 2500 or 5000 mg/kg bw	N/A	Negative	Hazelton Washington 1994*

Two *in vitro* mammalian cell transformation assays were also available. In the first assay, DIDP was tested on Balb/c-3T3 mouse cells (Barber et al. 2000), with an exposure period of 72 hours and incubation over four weeks. DIDP did not induce statistically significant increases in transforming activity with concentrations up to 20 µL/mL. In the second assay, Balb/3T3 Clone A31 mouse embryo cells were treated for 20–24 hours and incubated for 4–6 weeks. Statistically significant increases in transforming frequencies were observed at 1 µL/mL, but not at the lower doses (0.01 or 0.1 µL/mL).

DnOP

Available studies conducted *in vitro* to determine the genotoxic potential of DnOP are summarised below and presented in Table 6.5

The ATSDR (1997) notes a substantial database of *in vitro* microbial assays for DnOP. DnOP (100–10000 µg/plate) in either the presence or absence of exogenous metabolic activation was not mutagenic in Ames tests using *S. typhimurium* (TA 1535, TA 1537, TA 98, TA 100) (Zeiger et al. 1982*; Zeiger et al.1985*).

DnOP at 2000 µg/mL with metabolic activation, and 100–2000 µg/mL without metabolic activation, did not induce DNA damage in *Escherichia coli* (Goodyear Tire & Rubber Company 1981*). Similar results are reported by Seed (1982) and Shibamoto and Wei (1986*). DnOP also showed a negative response in a prokaryotic SOS chromotest assay to detect DNA damage in *E. coli* (Sato et al. 1994*).

Data on mixtures containing DnOP were noted in NTP (2003b). Results from testing a C6-10 phthalate mixture (containing 20% DnOP) in a mouse lymphoma mutation assay were considered equivocal due to a non-dose related increase in mutations in the presence and absence of metabolic activation (Barber et al, 2000). According to CMA (1999*), di(*n*-octyl, *n*-decyl) phthalate containing DnOP as a component was reported to be negative in an Ames test and a Chinese hamster ovary (CHO)/HPRT locus assay.

No information is available regarding the genotoxic potential of DnOP in vivo. Based on negative results from in vitro bacterial mutation and DNA damage assays, DnOP is considered to be non-genotoxic.

Table 6.5: Summary of genotoxicity studies with DnOP

Test	Test system (species/strain)	Dose	Metabolic activation	Result	Reference
In vitro					
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100–10000 µg/plate	With and without	Negative	Zeiger et al. 1982*, 1985*
Reverse mutation	*S. typhimurium* TA100	100–10000 µg/plate	With and without	Negative	Seed 1982*
Reverse mutation	*S. typhimurium* TA98, TA100	100–10000 µg/plate	With and without	Negative	Shibamoto and Wei 1986*
Reverse mutation	*S. typhimurium* TA98	100–10000 µg/plate	With and without	Negative	Florin et al. 1980*
Reverse mutation	*S. typhimurium* TA98, TA100, TA1535, TA1537	100–10000 µg/plate	With and without	Negative	Goodyear Tire & rubber company 1981*
Reverse mutation	*S. typhimurium* TA98	100–10000 µg/plate	With and without	Negative	Sato et al. 1994*
DNA damage	*E. coli*	-S9:100–2000 µg/ml +S9: 2000 µg/mL	With and without	Negative	Goodyear Tire & rubber company 1981*
SOS induction	*E. coli*	100–10000 µg/plate	With and without	Negative	Sato et al. 1994*
Mouse lymphoma			With and without	Equivocal	Barber et al. 2000

6.5.2. Carcinogenicity

DIDP

A two-year carcinogenicity study (non-guideline and non-GLP) was conducted in F344 rats (52/sex/dose) fed with diets containing 0, 400, 2000 and 8000 ppm DIDP (approximately 0, 22/23, 100/128 and 479/620 mg/kg bw/day, males/females). For the assessment of peroxisome proliferating activity, rats (50 males) were fed diets containing a vehicle control, 400, 2000, 8000 ppm DIDP and 12000 ppm DEHP as a positive control. Animals were euthanised at 12 or 32 weeks after treatment to analyse the activity and levels of the catalase enzyme, a marker for cell peroxisome proliferating activity (Cho et al. 2008 and erratum 2010). While changes were seen in the liver and kidneys, there were no treatment-related effects observed in other organs such as the spleen, testes, ovary, brain, adrenal glands and heart. There was an increased incidence of mononuclear cell leukaemia (MCL). MCL is a common neoplasm in F344 rats with no comparable tumour type in humans and its increased incidence after chronic exposure to some substances is considered to be a strain-specific effect (Caldwell 1999). Therefore, MCL observed in F344 rats is not regarded as relevant to humans.

At the highest dose, catalase enzyme activity was increased after 12 weeks of treatment, but no differences in levels or activity were observed after 32 weeks. In the positive control, catalase enzyme level and activity were increased at both 12 and 32 weeks.

The carcinogenic potential of DIDP was investigated in transgenic mice (15 rasH2 mice/sex/dose) fed with a diet containing 0, 0.1, 0.33 and 1% DIDP, and in wild type mice (15/sex) fed with a diet containing 1% DIDP for 26 weeks (Cho et al. 2011). The rasH2 mouse is a hemizygous (one single copy of a gene) transgenic mouse known to be sensitive to both genotoxic and non-genotoxic carcinogens (Alden et al. 2002; Morton et al. 2002). At 1%, liver and kidney weights were significantly increased in both sexes in both rasH2 and wild mice, and at 0.33% in rasH2 males. Testes, spleen and brain weights were also statistically significantly increased in rasH2 and wild type mice at 1%. In the liver, increases in parenchymal inflammation and diffuse hepatocyte

hypertrophy with eosinophilic granules (in both sexes), focal necrosis, pigmented hepatocytes, and pigmented and prominent Kupffer cells were also significantly increased in rasH2 and wild type mice. In the kidneys of males, higher incidences of tubular basophilia and tubular hyperplasia were seen at 1% in both rasH2 and wild type mice.

Overall, data are insufficient to establish the carcinogenic potential of DIDP.

DnOP

Male SD rats were used to investigate the chemical's ability to promote the development of preneoplastic lesions. The rats were partially hepatectomised, injected intraperitoneally with the initiator diethylnitrosamine (DENA), and then exposed to 0.5% or 1% DnOP in the diet (approximately 250 mg/kg bw/day or 500 mg/kg bw/day) for 10 weeks. Significant increases in gamma-glutamyl transferase (GGT)-positive foci and in the overall foci area, and levels of glutathione-S-transferase staining in the liver were observed. A slight increase in carnitine acetyltransferase activity and mild fatty changes in the liver (without changes in the liver weight) were also reported, suggesting pre-tumour activity. Gamma-glutamyl transferase-positive foci are closely associated with neoplastic nodule development and hepatomas, and carnitine acetyltransferase activity is a known biomarker for peroxisome proliferation (DeAngelo et al. 1986*).

In a similar study by Carter et al. (1989*; 1992), the ability of DnOP to promote the expression of GGT and placental glutathione-s-transferase (GST-P) was investigated using male F344 rats. The animals were treated as above except with doses of 0, 0.5 and 1% DnOP in the diet, 10 days after an intraperitoneal injection of DENA. DnOP did not affect the absolute liver weight, but an increase in the relative liver weight was reported. Similar results to those above were reported including significant increases in the volume percent of liver expressing GGT, and the mass of liver expressing GGT and GST-P. These results indicate that DnOP was effective in promoting expression of both markers (GGT and GST-P) associated with neoplasia.

In a poorly-documented chronic toxicity study, 'numerous' liver nodules were reported in male F344 rats given 1% DnOP (600 mg/kg bw/day) in the diet for 15 months. The activity of a number of lysosomal enzymes was also increased in these rats (Carter et al. 1989*).

Data from an *in vitro* test, where a C6–10 phthalate mixture (containing 20% DnOP) was examined in a Balb/3T3 mammalian cell transformation assay, showed negative results (Barber et al. 2000).

These results suggest that DnOP may act as a tumour promoter. However, the liver foci assay was regarded as inappropriate for estimating carcinogenic activity in peroxisome-inducing compounds (Milman & Weisburger 1994), and there may be biases inherent in cutting and interpreting specimens for pathological assessment (CPSC 2010b). Available animal data were limited and genotoxicity data on animals were mostly negative. No human carcinogenicity studies were found. Overall, data are insufficient to determine the carcinogenic potential of DnOP.

6.6 Reproductive toxicity

6.6.1 Effects related to fertility and sexual development

DIDP

Repeat dose toxicity studies

In repeated dose toxicity studies conducted in rats, no changes in the histopathology of testes were reported (BIBRA 1986; Lake et al. 1991). However, relative testis weights were significantly increased at 2100 mg/kg bw/day DIDP in a 21-day feeding study in rats (BIBRA 1986).

The toxicity of nine phthalate diesters, including DIDP and DnOP, was investigated using SD rats (Kwack et al. 2009; Kwack et al. 2010). Animals were exposed orally by gavage to 500 mg/kg bw/day of DIDP or DnOP for two weeks. Short-term exposure to DIDP or DnOP resulted in significantly higher relative liver weights, which was considered to be associated with peroxisome proliferation leading to increased lysosomal activity and increased liver enzymes (lactate dehydrogenase and alanine aminotransferase). Testes weights were also significantly decreased following treatment with DEHP, DIDP or DnOP. Mean percent sperm motility was significantly lower following treatment with DEHP, DBP, DnOP and DIDP (Kwack et al. 2010).

One-generation reproductive toxicity studies

In a one-generation range-finding study, five groups of rats (10/sex/group) were fed with a diet containing 0, 0.25, 0.5, 0.75 and 1% DIDP (approximately 0, 132–264, 262–521, 414–776 and 542–1014 mg/kg/day) (Exxon

Biomedical Sciences 1997*) for 10 weeks before and during mating. Females continued to be treated throughout gestation and lactation. Statistically significant decreases in body weight gain and food consumption were observed at the 0.75% and 1% doses in the parental animals. Pups had statistically significant lower mean body weights than controls from the 0.5% dose and up. Decreased pup weight was also dose-dependent from the 0.5% dose and up. There were no differences in the observed reproductive indices between the treated animals and controls. A NOAEL of 0.5% (approximately 262 mg/kg/day) for systemic toxicity was determined for parental animals and 0.25% (approximately 165 mg/kg/day) for pups.

Two-generation reproductive toxicity studies

Reproductive toxicity was examined in two well-conducted two-generation studies. In the first study (Exxon Biomedical Sciences 1997*; Hushka et al. 2001), rats (30/sex/dose) were fed with 0.2, 0.4 or 0.8% DIDP (approximately 0, 103/379, 211/761, 427/1424 mg/kg bw/day, males/females, respectively) in the diet for 10 weeks before and during mating. Females continued to be treated throughout gestation and lactation.

Statistically significant reductions in bodyweight gains and food intake were observed at the 0.8% dose during the lactation period in females of both generations. Statistically significant increases in mean absolute and relative liver weights, accompanied by microscopic evidence of hepatocellular hypertrophy, were observed at the 0.4% and 0.8% dose in both sexes of both parental generations (F_0 and F_1). Statistically significant increased absolute and relative kidney weights were observed in all treated male groups and at the 0.4% and 0.8% doses in both parental generations. Significant decreases in uterine and left ovarian weights without histological changes were reported in the highest dose F_0 females. The length of oestrus cycles was also reduced in F_0 females of the highest dose group. These effects were not reported in the F_1 generation. There was a non-dose-related decrease in the number of normal sperm cells in F_0 treated males. Significant increases in relative testis, epididymis and seminal vesicle weights, without histological changes, were reported in the highest dose F_1 males. The effects in the reproductive system were not of sufficient severity or reproducibility between generations to be considered adverse. Mating performance, fertility and pregnancy indices were not affected by DIDP treatment in any generation. The NOAEL for fertility was 0.8% (427–1424 mg/kg bw/day).

In the second two-generation study (Exxon Biomedical Sciences 2000*; Hushka et al. 2001), rats (30/sex/dose) were fed 0, 0.02, 0.06, 0.2 or 0.4% of DIDP (approximately 0, 12/40, 33/114, 114/352, 233/747 mg/kg bw/day, males/females, respectively) in the diet for 10 weeks before and during mating. Females continued to be treated throughout gestation and lactation.

Bodyweight gains, mating performance, fertility and pregnancy indices were not affected by treatment. Statistically significant increases in mean absolute and relative liver weights were observed at the 0.4% dose in both sexes of both parental generations. Statistically significant increases in mean absolute and relative kidney weights in males of both generations at the 0.4% dose and in F_1 males at the 0.2% dose were observed. Relative kidney weights of F_0 females at the 0.4% dose and absolute kidney weights in F_1 females at the 0.2% dose also showed a statistically significant increase. There were no histological lesions or weight changes in the reproductive organs of either sex. The NOAEL established for fertility was 0.4% (233–747 mg/kg bw/day).

Embryotoxicity study

A Hershberger assay was used to investigate the antiandrogenic effects of phthalate diesters, including DIDP, in castrated male SD rats (Lee & Koo 2007). DIDP was administered to castrated rats by oral gavage at 0, 20, 100 or 500 mg/kg bw/day with testosterone propionate (0.4 mg/kg bw/day) for 10 consecutive days. There was no mortality or significant changes in body weights reported for all tested phthalates during treatment. At the highest dose (500 mg/kg bw/day), a significant increase in liver weights was observed in DIDP-treated rats. At the same dose, ventral prostate and seminal vesicle weights were significantly decreased compared with the testosterone positive control, suggesting that DIDP could possess antiandrogenic activity (Lee & Koo 2007; CPSC 2010a). The NOAEL for this study was determined to be 100 mg/kg bw/day.

Human studies

Urinary metabolites from phthalates, including DIDP and DINP, were examined in a cross-sectional analysis involving 10-year-old Norwegian children. Statistically significant associations between asthma and urinary metabolites of DIDP and DINP (mono(carboxynonyl) phthalate (MCNP) and mono(carboxyoctyl) phthalate (MCOP), respectively) were reported in the highest quartile for these chemicals. Most of the body burden of HMW phthalate metabolites was reported to have been likely sourced from foods contaminated with phthalates (Bertelsen et al. 2013).

Summary of effects on fertility
The embryotoxicity study suggests that antiandrogenic activity can occur following exposure to high concentrations of DIDP; however, no testicular lesions were reported in repeated dose studies (≤3 months long) in rats at doses up to 2100 mg/kg bw/day. In one and two-generation reproduction/developmental studies, mating performance, fertility and pregnancy indices were not affected by treatment. There were no histological lesions in the reproductive organs of either sex. The NOAEL for fertility was established as 0.8% (427–1424 mg/kg bw/day)—the highest dose used in the two-generation reproductive toxicity studies.

DnOP

Repeated dose toxicity studies
Male SD rats receiving DnOP by gavage at 2800 mg/kg bw/day for four or 10 days showed no testicular atrophy or histological lesions; testicular zinc loss; or prostate or seminal vehicle weight loss (Foster et al. 1980; Gray & Butterworth 1980*).

No effects on the testes weights or testicular concentrations of testosterone or zinc were observed in male Wistar rats fed a diet containing 0% or 2% MnOP (0, 1000 mg/kg bw/day) for one week (Oishi & Hiraga 1980). In addition, no effect on testes weights, gross morphology, or histopathology was found in male rats with dietary exposure to approximately 2000 mg/kg bw/day for 10 or 21 days (Mann et al. 1985).

In a subchronic study, SD rats received DnOP in their diet at doses as high as 5000 ppm (350/403 mg/kg bw/day males/females respectively) for 13 weeks. Testes weights were unaffected. There was no incidence of seminiferous tubule atrophy or reduction in sperm density at any dose tested. No reproductive effects were seen (Poon et al. 1997*).

Prenatal developmental toxicity studies
SD rats were administered DnOP daily at 0, 250, 500 or 1000 mg/kg/day by gavage on gestation days (GD) 6–20 (Saillenfait et al. 2011). There were no changes in maternal food consumption or body weight, or in the number of implantations, live foetuses, resorptions or the number of malformations reported. However, hepatic effects (slight elevation of serum AST and ALT, and an increase in absolute and relative liver weights) were observed at 1000 mg/kg/day.

Continuous breeding reproductive toxicity studies
In a continuous breeding protocol oral reproductive/developmental study, CD-1 Swiss mice (20 pairs/dose) were fed DnOP in the diet at 0, 1.25, 2.5, or 5% (0, 1800, 3600, and 7500 mg/kg bw/day) for 14 weeks (Gulati et al. 1985*; Heindel et al. 1989). Litters born during the 14-week period were evaluated and removed so that the adults could continue breeding.

In sexually mature F_1 adults mated within dose groups, DnOP similarly had no effects on fertility indices, litter size, pup weight or viability. In control and high-dose (7500 mg/kg bw/day) F_1 adults, increased absolute and relative liver weights and decreased relative seminal vesicles weights were observed in males. However, there was no evidence of morphological or histopathological changes in these organs. No changes were observed in the testes, cauda epididymis or prostate weights; sperm concentrations; or the percentage of mobile or abnormal sperm. Females at this high dose showed increased relative liver and kidney weights. However, no changes were observed in oestrous cycle length, in reproductive organ weights or histopathology. Over five successive litters, there was no effect on the number of litters, litter size, sex ratios, pup weight or viability. Overall, DnOP did not show significant reproductive effects in this study even at hepatotoxic doses. The NOAEL for reproductive and developmental effects was established as 7500 mg/kg bw/day, the highest dose tested.

Human studies
Human sperm suspensions incubated with DnOP (0, 64, 640 μM) for up to 18 hours showed dose-dependent decreases in motility (80% motility at 64 μM) (Fredricsson et al. 1993).

A group of 45 women with endometriosis showed significantly higher plasma concentrations of DnOP as well as DBP, BBP, DEHP and polychlorinated biphenyls compared with a control group of 135 women (Reddy et al. 2006a; Reddy et al. 2006b).

An association between 11 maternal urinary phthalate monoester concentrations and genital parameters such as the anogenital index (AGI), i.e. anogenital distance (AGD) normalised for body weight, and testicular descent in children, was investigated in 85 mother–son pairs (Swan et al. 2005). There was no significant association between maternal urinary mono-(3-carboxypropyl) phthalate (MCPP, a DnOP metabolite) concentration and infant AGI.

In the US (1151 girls aged 6–8), HMW phthalate metabolites including MCPP were weakly associated with early pubic hair development, while a positive trend was observed for LMW phthalate metabolites with early breast and pubic hair development. No significant differences in the urine concentrations of phthalate metabolites, including MCPP, between children with central precocious puberty (n = 28) and prepubertal girls (n = 28) were reported.

Summary of effects on fertility
Data were insufficient to determine the fertility effects of DnOP in humans.

In animals, no effects on the number of litters, litter size, sex ratios, pup weight or viability were observed for DnOP in an oral continuous breeding reproductive/developmental study in mice dosed with up to 7500 mg/kg bw/day. The NOAEL for fertility effects was established as 7500 mg/kg bw/day, the highest dose tested.

In a 13-week subchronic study in rats, no effects on testes weights or morphology were observed at the highest dose level (350 mg/kg bw/day). No testicular atrophy or histological lesions were observed in male rats gavaged with DnOP at 2800 mg/kg bw/day for four or 10 days. No effects on testes weights or testicular concentration of testosterone or zinc were observed.

6.6.2 Other foetal/developmental effects

DIDP

Two-generation reproductive toxicity studies
Two multi-generation animal studies were conducted by Exxon Biomedical Sciences in 1997* and 2000*, and by Hushka et al. (2001). In the first study, rats (30/sex/dose) were fed with 0, 0.2, 0.4 or 0.8% DIDP (approximately 0, 103/379, 211/761, 427/1424 mg/kg bw/day, males/females, respectively) in the diet for 10 weeks before and during mating. Females continued to be treated throughout gestation and lactation. The second multigenerational study was identical to the first study, except that rats were fed a diet containing 0, 0.02, 0.06, 0.2 or 0.4% of DIDP (approximately 0, 12/40, 33/114, 114/352, 233/747 mg/kg bw/day, males/females, respectively).

In the first multigenerational study (Exxon Biomedical Sciences 1997*; Hushka et al. 2001), the percentage of F1 pups that died by post natal day (PND) four was statistically significantly higher at the 0.8% dose compared with controls and was outside the historical control range for the laboratory. In the F_2 pups, there was a statistically significant, dose-dependent reduction in the survival rate of all treated groups during the first four days of lactation that was outside the historical control range. Reduced survival at the 0.8% dose was also observed on lactation day seven and at weaning.

Postnatal bodyweight gains were reduced in F_1 and F_2 pups at the 0.8% dose. Mean relative liver weights were significantly increased in F_1 male pups at the 0.8% dose and F_1 female pups at the 0.4% and 0.8% doses. Hepatic hypertrophy and eosinophilia were observed in F_1 and F_2 pups at the 0.4% and 0.8% doses. No developmental NOAEL could be identified due to decreased pup survival in the F_2 generation at the lowest dose tested (0.2%; 103–379 mg/kg bw/day).

In the second multigenerational study, there was a statistically significant reduction in F_2 pup mean body weights in males administered 0.4% of DIDP on postnatal day 14; in females administered 0.4% of DIDP on postnatal days 14 and 21; and in females administered 0.2% of DIDP on postnatal day 14. A statistically significant higher percentage of F_2 pups died on days one and four of lactation (0.2% and 0.4% doses) compared with controls and was outside the historical control range. There were no differences in anogenital distance or nipple retention. The age of preputial separation was increased in the highest dose F_2, but not F_1, pups. The developmental NOAEL was established at 0.06% (33–114 mg/kg bw/day). The LOAEL was 0.2% (114–352 mg/kg bw/day) based on decreased F_2 pup survival. The authors calculated the equivalent NOAEL dosage to be approximately 50 mg/kg bw/day, and indicated that this dose was the actual dose given to the dams at the time the effects occurred. Therefore, 50 mg/kg bw/day is considered to be the most relevant dose for this endpoint.

Prenatal developmental toxicity studies
In the study conducted by BASF (1995*; Hellwig et al. 1997), pregnant rats (Chbb:THOM; 7–10/dose) were administered DIDP by gavage at 0, 40, 200 or 1000 mg/kg bw/day on GD 6–15. Maternal toxicity was observed at 1000 mg/kg bw/day and included statistically significant reduced food consumption, and increased liver weights and vaginal haemorrhage. There was some evidence of increased foetal variations at the 200 and 1000 mg/kg bw/day doses. The main variations observed were increased rudimentary cervical ribs (6/10 litters versus

1/10 for controls) and/or accessory 14th ribs (8/10 litters versus 1/10 for controls) on a per litter basis (statistically significant only at 1000 mg/kg bw/day). An increased incidence of hydroureter and renal pelvic dilatation was observed in all treated animals and considered to be a sign of delay in maturation (ECHA 2013). The NOAEL for maternal toxicity was established at 200 mg/kg bw/day. The developmental NOAEL in the study was determined to be 40 mg/kg bw/day with a LOAEL of 200 mg/kg bw/day, based on increased foetal variations.

In the second study (Waterman et al. 1999), pregnant rats (Crl:CDBR; 25/dose) were administered DIDP by gavage at 0, 100, 500 or 1000 mg/kg bw/day from GD 6–15. Maternal toxicity was observed at the 1000 mg/kg bw/day dose and included reduced bodyweight gains and food consumption. However, these were not significantly different over the whole gestation period (GD 0–21). Similarly to the first study, DIDP did not affect the incidence of malformations, although there was evidence of increased foetal variations. The main variations observed were dose-related increases in rudimentary lumbar ribs and supernumerary cervical ribs at 500 mg/kg bw/day (statistically significant on a per foetus basis only), and 1000 mg/kg bw/day (statistically significant on a per litter and per foetus basis). The NOAEL for developmental effects in this study is considered to be 100 mg/kg bw/day.

ECB (2003a) and NTP (2003a) differ from Waterman et al. (1999) in identifying a NOAEL for developmental effects. In the EU risk assessment, the developmental NOAEL was 500 mg/kg bw /day, based on a significant increase in skeletal variations on a per litter basis at the highest dose of 1000 mg/kg bw/day. The NTP selected a developmental NOAEL of 100 mg/kg bw/day, based on the significant incidence of cervical and accessory 14th ribs per foetus at the 500 mg/kg bw/day dose. A litter is regarded as the preferred unit to statistically analyse developmental toxicity studies (ECB 2003a). According to the NTP, the study sponsor reanalysed the Waterman et al. data using a linearised model approach and generalised estimating equations (GEE) and obtained similar results. In addition, the sponsor also provided benchmark dose results. At the 5% excess risk level, the benchmark doses (and their 95% lower confidence limits estimated by bootstrap methods) were estimated as 188 (169), 258 (238), and 645 (515) mg/kg bw/day for rudimentary lumbar ribs, skeletal variants and supernumerary cervical ribs, respectively.

Summary of developmental effects
Based on pre-natal developmental studies in rats, in the absence of maternal toxicity a developmental NOAEL of 100 mg/kg bw/day was identified for skeletal variations.

In the two-generation reproductive/developmental studies in rats, decreased pup viability in the F_2 generation was reported and confirmed in a second two-generation study where F_2 pup mortality increased following exposure to 0.2% DIDP (103–379 mg/kg bw/day). However, there were no differences in anogenital distance or nipple retention when DIDP-treated animals were compared with the control group. The age of preputial separation was increased in the highest dose F_2, but not F_1, pups. The developmental NOAEL was established as 0.06% (calculated dose of approximately 50 mg/kg bw/day), based on decreased pup survival in the F_2 pups at the higher doses.

DnOP

Prenatal developmental toxicity studies
Singh et al. (1972) administered DnOP at 0, 4890, 9780 mg/kg bw/day to female SD rats (5/group) prenatally on GD five, 10 and 15 via intraperitoneal injection. A small, but significant, decrease in average foetal weight, and a significant increase in the incidence in gross foetal malformations (tail absence, absence of eye/s (anophthalmia), twisted hind legs and haematomas/haemangiomas) were observed in offspring. Details of maternal toxicity were not reported in the study.

DnOP had no effect on the AGD of foetuses following oral exposure (0, 250, 500 or 1000 mg/kg bw/day) to pregnant SD rats up to 1000 mg/kg/day. However, there was a significant increase in the incidence of cervical ribs in foetuses and litters at the same dose. The incidences of supernumerary lumbar ribs in foetuses (13, 35, 51 and 76%, respectively), and litters (corresponding to 21/15, 52/20, 69/19, 118/22 foetuses/litters) were significantly increased at all doses and in a dose dependent manner. The LOAEL for developmental toxicity was established at 250 mg/kg bw/day, based on the dose-dependent increased occurrence of supernumerary lumbar ribs (Saillenfait et al. 2011).

Administration of n-octanol, a precursor used in DnOP synthesis (~130, 650, 945, and 1300 mg/kg bw/day), by gavage to pregnant Wistar rats on GD 6–15 induced dose-related symptoms of maternal toxicity, with maternal

death seen at the two highest dose levels. However, no effects on foetal weight, viability, or incidence of malformations were seen (Hellwig & Jack 1997*).

Postnatal developmental toxicity studies
Hardin et al. (1987) administered DnOP via oral gavage to female CD-1 mice at 9780 mg/kg bw/day on GD 6–13. There was no effect on maternal weight. The test group varied from the concurrent control (vehicle treated) group only in an 11% reduction in numbers of liveborn pups per litter, and a 14% reduction in average pup weight gains on postnatal days 1–3 (both statistically significant). The authors reported that concurrent control values for these parameters were higher than other control groups from the same study, thus casting uncertainty on the biological significance of these changes.

Summary of developmental effects
Decreased foetal weight and increased malformations were noted in the offspring of rats given high doses of DnOP (up to 9780 mg/kg bw/day) by intraperitoneal injection. However, potentially confounding maternal effects, which may be expected at such high intraperitoneal injection doses were not reported. In a pre-natal study in mice, statistically significant decreases in pup viability and pup weight gains were also observed at very high doses (9780 mg/kg bw/day), but no developmental toxicity was observed in a continuous breeding multigenerational reproductive/developmental study in mice at concentrations up to 7500 mg/kg bw/day.

In contrast, in another recent prenatal developmental toxicity study in rats conducted with an appropriate study design, skeletal variations occurred at 250 mg/kg bw/day in a dose dependent manner and in the absence of maternal toxicity (Saillenfait et al. 2011).

Overall, there is limited information available to characterise the developmental toxicity of DnOP. Although the toxicological relevance of the incidence of skeletal variation (supernumerary ribs) as a malformation or a minor variation is questionable (CHAP 2014), a LOAEL of 250 mg/kg bw/day was determined. Considering that the incidence of skeletal variation is regarded as relevant to human risk assessment, the NOAEL for developmental toxicity is 83 mg/kg bw/day, based on a default uncertainty factor of three for LOAEL to NOAEL extrapolation (ECETOC 2003; Saillenfait et al. 2011).

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

DIDP

DIDP was negative for oestrogenic activity in a yeast two-hybrid assay (Nishihara et al. 2000) and in a recombinant yeast assay (Harris et al. 1997). Also, DIDP was not a competitive agonist at the oestrogen receptor in an *in vitro* competitive ligand-binding assay and did not induce oestrogen receptor-mediated gene expression in MCF-7 cells. *In vivo*, DIDP did not induce oestrogenic responses in uterotrophic and/or vaginal cornification assays using immature and mature ovariectomised rats (Zacharewski et al. 1998; Akahori et al. 2008).

DIDP did not show oestrogenic/antioestrogenic or androgenic/anti-androgenic activity (up to 10^{-5} M) when a receptor gene assay in Chinese hamster ovary (CHO) cells was used to characterise the activities of human ERα (oestrogen receptor α), human ERβ and human androgen (AR) receptors. In contrast, DEHP induced ER α-mediated oestrogenic activity, antagonised ERβ and was not active via AR (Takeuchi et al. 2005; Kruger et al. 2008). DIDP and DEHP induced weak aryl hydrocarbon receptor (AhR) activity (Kruger et al. 2008).

In a study to rank the anti-androgenic potencies of certain phthalates, including DIDP, rats were gavaged at doses of 0, 500, 750, 1000 or 1500 mg/kg bw/day on GD 14–18. *In utero* exposure to DIDP did not significantly change maternal body weight gain or foetal mortality. DIDP had no effect on *ex vivo* testicular testosterone (T) production and did not affect the gene expressions examined, which suggests that DIDP did not have anti-androgenic activity unlike some other phthalates, including dipentyl phthalate (DPeP), dihexyl phthalate (DHP), diisobutyl phthalate (DIBP), diheptyl phthalate (DHeP) and diisononyl phthalate (DINP) (Hannas et al. 2012).

DnOP

DnOP did not induce oestrogenic responses *in vivo* in a uterotrophic and vaginal cornification assay using immature and mature ovariectomised rats (Zacharewski et al. 1998). DnOP was negative for oestrogenic activity in a recombinant yeast assay (Harris et al. 1997). The chemical was also not a competitive agonist at the oestrogen receptor in an *in vitro* competitive ligand-binding assay and did not induce oestrogen receptor-mediated gene expression in MCF-7 cells (Zacharewski et al. 1998).

Phthalate-induced germ-cell detachment was examined *in vitro* in co-cultures of Sertoli and germ cells isolated from pubertal rats (Gray & Beamand 1984). Mono-*n*-octyl phthalate induced marked germ-cell detachment and disruption of the Sertoli-cell monolayer at 10^{-4} M, the magnitude of which exceeded that of the other eight monoesters tested.

DnOP (up to 10^{-3} M) showed no detectable binding to oestrogen receptor α or β *in vitro* (Toda et al. 2004). DnOP demonstrated neither agonistic nor antagonistic activity in *in vitro* reporter gene assays with CHO-K1 cells transfected with expression vectors for human oestrogen receptor α, and no anti-androgenic effects were reported (Takeuchi et al. 2005).

6.7 Summary

DIDP

Following oral administration, absorption of DIDP from the GIT is incomplete and decreases as the dose increases. Dermal absorption is found to be low and the bioavailability by dermal absorption is approximately 2–4% in humans (adults or children). Absorption of DIDP from the lung following inhalation exposure is approximately 73%; therefore, a worst-case bioavailability of 100% is considered appropriate for this exposure route for the purposes of this assessment.

DIDP is rapidly eliminated via urine and faeces. Following oral absorption, the major metabolites detected in urine are phthalic acid and oxidised monoester derivatives, while the parent compound, oxidised monoester derivatives and MIDP are detected in faeces.

DIDP has low acute oral, dermal and inhalation toxicity. It is a mild skin and eye irritant. It is not considered a skin sensitiser. The main effects following repeated exposure to DIDP are increased liver weights and lipid metabolism in the liver in the absence of associated pathology. Liver enlargement is due to hepatocyte hypertrophy. The major biochemical alterations consist of both peroxisomal (increased acyl-CoA oxidase) and microsomal (lauric acid 11- and 12-hydroxylases) induced fatty-acid-oxidising activities. The former is considered to be a specific marker of peroxisome proliferation. Current literature indicates that rodents, when compared with humans, are particularly susceptible to peroxisome proliferative effects. For systemic effects, the 90-day study conducted in rats with an NOAEL of 60 mg/kg bw/day is considered appropriate for risk assessment.

DIDP is considered not to be genotoxic, based on the results collected from *in vitro* bacterial mutation assays, *in vitro* mouse lymphoma assays and an *in vivo* mouse micronucleus assay.

Available animal carcinogenicity studies are insufficient to establish the carcinogenic potential of DIDP. Also, there are no *in vivo* carcinogenicity studies available for DIDP. One of two *in vitro* cell transformation assays is positive for transforming potential. The majority of phthalates have not been adequately tested for carcinogenicity (NICNAS 2008a) and so attempts to correlate carcinogenic potential with structural features are not possible.

In two, 2-generation reproduction studies with rats, DIDP caused increased liver and kidney weights in parental animals and reduced pup survival, which was more pronounced in the F_2 pup generation. There is no evidence to indicate that DIDP causes impairment of fertility. No testicular lesions were reported in repeated dose studies in rats at doses up to 2100 mg/kg bw/day. A NOAEL for fertility was determined as 0.8% (427–1424 mg/kg bw/day), the highest NOAEL from the two, 2-generation reproductive studies.

In the same two-generation studies, pup survival was reduced in the F_2 generations. The LOAEL for pup survival was 0.2% (114–352 mg/kg bw/day). The NOAEL was 0.06% (calculated to be approximately 50 mg/kg bw/day).

Increased incidence of foetal variations (rudimentary lumbar ribs and supernumerary cervical ribs) was seen in a rat developmental study. Although the finding of supernumerary ribs was commonly considered minor, in the absence of more profound signs of developmental toxicity, a developmental NOAEL of 100 mg/kg bw/day was determined based on increased skeletal variations and the absence of maternal toxicity at 200 mg/kg bw/day.

Table 6.6 lists the critical effects for DIDP, the specific effects observed and the effect levels selected for risk characterisation.

DnOP

DnOP is rapidly absorbed from the GIT following oral administration and metabolised predominantly to mono-*n*-octylphthalate and its oxidised metabolites. Elimination occurs via the urine, with MCPP levels exceeding MnOP after 24 hours.

DnOP has low acute oral toxicity. Information on dermal or inhalation toxicity is incomplete or unavailable. Data for other high molecular weight phthalates (NICNAS 2008b) suggest that dermal and inhalation toxicity would be expected to be low.

DnOP caused minimal skin and eye irritation in animals. Data are insufficient to determine the sensitisation potential of DnOP; however, it should be noted that phthalates, in general, have low skin sensitisation potential (NICNAS 2008b).

The liver appears to be the primary target organ on repeated exposure to DnOP. Liver toxicity (increased weights, histological or clinical chemistry changes) caused by DnOP was observed in several repeated dose studies. DnOP also induced ultrastructural changes in the thyroid and kidney. Overall, liver effects from DnOP did not appear to be associated with peroxisome proliferation. An LOAEL of 350 mg/kg bw/day was established based on histological changes in the liver and thyroid. The NOAEL was 37 mg/kg bw/day.

DnOP gave negative result in bacterial mutation and direct DNA-damage assays. Mixtures containing DnOP tested negative in bacterial and mammalian mutation assays. Based on available *in vitro* data, DnOP is considered non-genotoxic.

Limited data on carcinogenic potential indicated that DnOP may promote pre-neoplastic hepatic lesions in the rat via a non-peroxisome proliferative mechanism. A large increase in numbers of GGT-positive foci was observed in the livers of rats following initiation with diethylnitrosamine followed by 26 weeks' dietary administration of DnOP. GGT is often significantly increased in human tumours, and its role in tumour progression and invasion has been suggested. In another study, liver nodules were reported in rats after dietary administration of DnOP for 15 months. Current literature indicates that rodents are particularly susceptible to peroxisome proliferative effects and the resultant carcinogenicity compared with humans (NICNAS 2008b). However, peroxisome proliferation is not a notable effect in available repeated dose toxicity studies of DnOP. Overall, the data are insufficient to determine the carcinogenic potential of DnOP.

DnOP did not induce reproductive toxicity at the highest dose tested of 7500 mg/kg bw/day in a continuous breeding study in mice, or 350 mg/kg bw/day in a 13-week subchronic study in rats. *In vitro*, the potential for testicular effects is suggested from findings of mono-*n*-octyl phthalate-induced marked germ-cell detachment and disruption of Sertoli-cell monolayers in co-cultures of Sertoli-germ cells isolated from pubertal rats. However, testicular effects were not seen in subchronic studies in mice and rats. The NOAEL for fertility effects was established as 7500 mg/kg bw/day, the highest dose tested.

Decreased foetal weight and decreased pup viability, and increased visceral malformations were noted in rat and/or mice offspring given high doses (up to 9780 mg/kg bw/day) of DnOP post-gestation by intraperitoneal injection. However, the extent to which these may be attributable to maternal toxicity is not known. There are also uncertainties over the biological significance of these findings given the magnitude of concurrent control values.

In a recent pre-natal developmental study, dose-dependent skeletal variations (supernumerary lumbar ribs) were observed from a 250 mg/kg bw/day dose (LOAEL) in the absence of maternal toxicity. For human risk assessment, the NOAEL for developmental toxicity of 83 mg/kg bw/day is derived for DnOP by applying a factor of three for the LOAEL to NOAEL extrapolation.

Table 6.7 lists the critical effects for DnOP, the specific effects observed and the effect levels selected for risk characterisation.

Table 6.6: Endpoints selected for risk characterisation of DIDP

Toxicity	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day) and effects	Species	Reference
Systemic effects	60	120: ↑ liver weights	Rats	BASF 1969*
Developmental effects (skeletal variations)	100	200: ↑ skeletal variations at non-maternotoxic dose	Rats	Hellwig et al. 1997; Waterman et al. 199

↑ = increased; NOAEL = no observed adverse effect level; LOAEL = low observed adverse effect level.

Table 6.7: Endpoints selected for risk characterisation of DnOP

Toxicity	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day) and effects	Species	Reference
Systemic effects	37	350: Liver toxicity (↑ liver weights with histological or clinical chemistry changes)	Rats	Poon et al. 1997*
Developmental effects (skeletal variations)	83[a]	250 ↑ skeletal variations at non-maternotoxic dose	Rats	Saillenfait et al. 2011

↑ = decreased; NOAEL = no observed adverse effect level; LOAEL = low observed adverse effect level.

[a]Extrapolated from LOAEL.

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 2003b). The risk characterisation is conducted by comparing quantitative information on exposure to the NOAEL and deriving an MOE as follows:

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

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

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

7.2 Risk estimates

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

Risk estimates take into account the likelihood for adverse effects on liver and foetal 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 DIDP and DnOP doses in children (see Table 5.3) and the dose at which no adverse effect is observed for the critical health endpoints in laboratory animals, i.e. the NOAEL (see Table 6.6 for DIDP and Table 6.7 for DnOP).

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

Toxicity	NOAEL (mg/kg bw/day)	MOE for typical exposure scenario	MOE for worst-case exposure scenario
DIDP			
Systemic effects (liver toxicity)	60	1980	339
Developmental effects (skeletal variations)	100	3297	565
DnOP	37	1220	209
Systemic effects (liver toxicity)			
Developmental effects (skeletal variations)	83	2736	469

The risk estimates for the effects of DIDP on reproductive and developmental toxicity for both typical and worst-case exposure scenarios for toys used by children derive MOEs >500. The risk estimates of DIDP for liver toxicity in both typical and worst-case exposure scenarios for toys used by children, derive MOEs >300. Taken together, the overall risk estimates for the toxicity effects on the liver and development indicate a low risk of these adverse health effects under these conditions of exposure.

Similarly, the risk estimates of DnOP for liver toxicity and developmental effects in typical and worst-case scenarios of toy use by children derive MOEs >200 and >400, respectively, indicating a low risk of these adverse effects on the liver and foetal development.

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

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 DIDP and DnOP arise mainly from inadequate data and include the:

- absence of Australian-specific data on DIDP and DnOP 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 DIDP and DnOP from plastic matrices through the skin;
- significance of the observed toxicity in animals, particularly the systemic and reproductive/developmental effects, to the human population; and
- lack of adequate epidemiological studies for determining the health effects of DIDP and DnOP in children following repeated exposure.

Areas of concern

The risk estimates above do not indicate particular areas of concern for children exposed to DIDP and DnOP through handling and mouthing toys or childcare articles. Although the MOE of DIDP and DnOP for liver toxicity was reduced from 1980 and 1220 to 339 and 209, going from typical exposure to worst-case exposure respectively, the severity of liver effects was considered minor and the MOEs still provide an adequate safety margin. Liver toxicity was also seen in much higher doses in other animal species, and there were no studies in primate animal models for DIDP and DnOP. It should be noted that DIDP is a complex mixture of mainly C10 methyl-branched isomers and belongs to the HMW group of phthalates. MOEs derived from other HMW phthalates (DINP) for liver toxicity were comparable for DIDP and DnOP in both typical and worst-case exposure scenarios.

Risks for children from the cumulative exposure to DIDP and DnOP in toys and childcare articles, with or without the addition of DEHP at 1% (the maximum allowable concentration in Australia), together with co-exposure to DEP in cosmetics at a maximum of 0.5%* in body lotions, are comparable with the calculated cumulative MOEs of DINP (NICNAS 2012). They are, therefore, considered low as the cumulative MOEs of DIDP and DnOP for the systemic effects identified are all above 100 (Appendix A, tables A1.1, 1.2 and 1.3), indicating an adequate safety margin.

8 Public health risk management

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

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

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

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

This assessment does not provide evidence to support further regulatory action.

8.2 Public health risk standards—cosmetics

There was no information on the use of DIDP and DnOP in cosmetics from information provided by Australian industry. There is no available information to indicate the use of DIDP and DnOP in cosmetic products or any evidence to suggest that DIDP and DnOP are used in cosmetics in Australia or overseas.

There are currently no restrictions on the use of DIDP and DnOP in cosmetics in Australia, and this assessment does not provide evidence to support further regulatory action.

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

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

Determining risk from combined exposures to multiple phthalates takes into account any risk mitigation measures recommended in the individual PEC assessments for each phthalate. The cumulative risk estimates are 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 other phthalates operate by a similar mode of action for the endpoints (systemic effect) considered relevant to DIDP and DnOP 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, 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 together and a cumulative MOE determined. It should be noted that the HI for an individual chemical calculated in this way is the inverse of the MOE (i.e. HI = 1/MOE, refer to Section 7.1 Methodology). Equations for calculating the cumulative MOE are provided in *Appendix 4: Mixture risk assessment methodology—evaluating the health risk due to exposure to mixtures of chemicals* in the Sixth Framework Programme of the Health and Environment Integrated Methodology and Toolbox for Scenario Development (HEIMTSA) (Sarigiannis et al. 2010). This includes a number of different equations for determining cumulative risks; the choice of the most appropriate equation depends on the available input data. For the current calculations, the equation used is:

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

The calculations for toys are based on the MOE for each phthalate as a primary plasticiser, regardless of whether it is actually used in this way.

The cumulative risk calculations are undertaken for the following scenarios:

DIDP (Table A.1):

- The combined exposure to a primary plasticiser (DIDP 43%) in toys and DEP 0.5% in cosmetics.
- The combined exposure to a mixed phthalate plasticiser (DIDP 42% + DEHP 1%) in toys.
- The combined exposure to a mixed phthalate plasticiser (DIDP 42% + DEHP 1%) in toys and DEP 0.5 % in cosmetics.

DnOP (Table A.2):

- The combined exposure to a primary plasticiser (DnOP 43%) in toys and DEP 0.5% in cosmetics.
- The combined exposure to a mixed phthalate plasticiser (DnOP 42% + DEHP 1%) in toys.
- The combined exposure to a mixed phthalate plasticiser (DnOP 42% + DEHP 1%) in toys and DEP 0.5% in cosmetics.

An example of the calculation can be given for combined or additive systemic toxicity (increased liver weight) of DIDP or DnOP in toys and DEP in cosmetics. For this endpoint, DIDP and DnOP (NOAEL = 60 and 37 mg/kg bw/day, respectively) are more potent than that of DEP (NOAEL = 150 mg/kg bw/day). Hence, the MOEs for DIDP and DnOP (in toys) are 339 and 209, respectively, compared with 778 for DEP (in cosmetics), using the relevant exposure estimates (EHD) for a six-month-old infant (see below):

- $D_{int,\ oral\ +\ dermal}$ = 169.93 + 7.04 = 176.97 µg/kg bw/day (Table 5.3) for the primary phthalate (DIDP/DnOP) content of 43% from combined oral and dermal exposure.

- $D_{int, dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/day (Table 5.5 from DEP PEC assessment—NICNAS 2011) for DEP at 0.5% from dermal exposure to body lotion.

The relevant cumulative MOEs are calculated from the equations:

- For use of toys scenario:

  MOE cumulative = 1/[(42/MOE of DINP + 1/MOE of DEHP)/43].

- For combined scenario:

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

The estimated cumulative MOEs for the critical systemic effects indicate an adequate safety margin for children (Table A.1). These MOEs are specifically calculated for a six-month-old infant, the youngest age that demonstrates the maximum mouthing behaviour, because newborn babies are unlikely to use teethers or childcare articles, while the MOEs for older babies (e.g. 12-month-old infants) are expected to be higher, based on their lower surface area to body weight (SA/BW) ratio (DEP PEC Report, Table 5.5—NICNAS 2011).

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

Toxicity	Use of multiple phthalates[a] in children's toy and childcare articles (a mixed phthalate plasticiser at maximum 43 %[b])					Use of DEP[c] in body lotion (at maximum 0.5 %[d])		Cumulative MOE (combined scenarios)
	NOAEL	MOE	NOAEL	MOE	Cumulative MOE	NOAEL	MOE	
	DIDP 43 %					*DEP 0.5 %*		
Systemic toxicity	60	339				150	778	236
	DnOP 43 %							
Systemic toxicity	37	209				150	778	165
	DIDP 41.5 %		*DEHP 1 %*			*DEP 0.5 %*		
Systemic toxicity	60	339	28.9	163	331	150	778	232
	DnOP 41.5%		*DEHP 1 %*					
Systemic toxicity	37	209	28.9	163	208	150	778	164

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

a DIDP/DnOP = primary plasticiser; DEHP at >1 % is banned from use in plastic products intended to be placed in the mouth by children aged ≤36 months (ACCC 2011 <http://www.productsafety.gov.au>).

b For 'use of toys' scenario, the estimated human dose (EHD) or $D_{int,\ oral+dermal}$ = 169.93+7.04 = 176.97 µg/kg bw/day (Tables 5.3) for the total phthalate content of 43 % from combined oral and dermal exposure. Cumulative MOE = 1/[(42MOE of DIDP/DnOP + 1/MOE of DEHP)/43].

c DEP at >0.5 % are excluded from use in body lotion; DEHP is excluded from cosmetic use (SUSMP <http://www.comlaw.gov.au/Details/F2012L01685/Download>). DBP is recommended for exclusion from cosmetic use, similarly to DEHP, based on the NICNAS PEC assessments for DBP and DMEP.

d For 'use of cosmetics' scenario, the EHD or $D_{int,\ dermal}$ = 96.43 × 2 = 192.86 µg/kg bw/day (Table 5.5 from the PEC assessment of DEP, NICNAS 2011) for DEP at 0.5 % from dermal exposure to body lotion.

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