State of the Science Report

Phthalate Substance Grouping

Medium-Chain Phthalate Esters

Chemical Abstracts Service Registry Numbers

84-61-7; 84-64-0; 84-69-5; 523-31-9; 5334-09-8; 16883-83-3; 27215-22-1; 27987-25-3; 68515-40-2; 71888-89-6

Environment Canada
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Synopsis

The Minister of the Environment and the Minister of Health have prepared a state of the science report on ten phthalate esters part of the Phthalate Substance Grouping. The purpose of this report is to review the currently available science on medium-chain phthalates, so that the public has an opportunity to review, comment, and/or provide additional information for consideration prior to proposing conclusions through the publication of a draft screening assessment. A proposed approach for considering the cumulative risk of phthalates has also been prepared for public review and comment, and will be used in the development of the draft screening assessment. Key selection considerations for this group were based on similar potential health effects of concern; potential ecological effects of concern for some phthalates; potential exposure of consumers and children; potential to leverage/align with international activity; and potential risk assessment and risk management efficiencies and effectiveness.

While many phthalate substances have common structural features and similar functional uses, differences in the potential health hazard, as well as environmental fate and behaviour, have been taken into account through the establishment of subgroups. The primary basis for the subgroups from a health hazard perspective is a structure activity relationship (SAR) analysis using studies related to important events in the mode of action for phthalate-induced androgen insufficiency during male reproductive development in the rat. The effects of phthalate esters for these important events appear to be structure-dependent and highly related to the length and nature of their alkyl chain. Further information on the approach by which the substances in the Phthalate Substance Grouping were divided into three subgroupings from a health hazard perspective is provided in Health Canada (2015a). From an ecological perspective, subgrouping was based primarily on differences in log K_{ow} and water solubility, and their resulting effects on bioaccumulation and ecotoxicity. Further information on the ecological rationale for the subgroups is provided in an appendix to the draft approach for considering the cumulative risk of phthalates (Environment Canada and Health Canada 2015a).

The Chemical Abstracts Service Registry Number (CAS RN[1]), their Domestic Substances List (DSL) names and their common names and acronyms are listed in the table below.

Identity of ten medium-chain phthalate esters in the Phthalate Substance Grouping

[1] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the government when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

CAS RN	Domestic Substances List name	Common name (acronym)
84-61-7	1,2-Benzenedicarboxylic acid, dicyclohexyl ester	Dicyclohexyl phthalate (DCHP)
84-64-0	1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	Butyl cyclohexyl phthalate (BCHP)
84-69-5	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	Diisobutyl phthalate (DIBP)
523-31-9	1,2-Benzenedicarboxylic acid, bis(phenylmethyl) ester	Dibenzyl phthalate (DBzP)
5334-09-8	1,2-Benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester	Cyclohexyl isobutyl phthalate (CHIBP)
16883-83-3	1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester	Benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate (B84P)
27215-22-1	1,2-Benzenedicarboxylic acid, isooctyl phenylmethyl ester	Benzyl isooctyl phthalate (BIOP)
27987-25-3	1,2-Benzenedicarboxylic acid, bis(methylcyclohexyl) ester	Bis(methylcyclohexyl) phthalate (DMCHP)
68515-40-2	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	Benzyl octyl phthalate (B79P)
71888-89-6	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	Diisoheptyl phthalate (DIHepP)

The ten substances in the medium-chain phthalates subgroup do not occur naturally in the environment. Five substances, DIBP, DCHP, DIHepP, B79P and B84P, are known to be imported into Canada; import quantities for 2012 were less than 10 000 kg for DCHP and DIHepP, between 10 000 and 100 000 kg for DIBP, and between 100 000 and 1 000 000 kg for both B79P and B84P (Environment Canada 2014). The other five substances, CHIBP, BCHP, DMCHP, BIOP and DBzP, were not reported to be imported into Canada above the reporting threshold of 100 kg in 2012. None of the medium-chain phthalates are known to be manufactured in Canada above the reporting threshold of 100 kg. Major uses identified for DIBP, DCHP, DIHepP, B79P and B84P are in adhesives and sealants used in construction and/or in the automotive sector. Other applications of medium-chain phthalates in the automotive industry include their addition to automotive paints and coatings or to resins that are then molded into automobile parts. Most of these substances are also used as plasticizers in the production of plastic, and used in manufactured items such as electrical and electronics,

and children's toys. Import of B79P in raw material form for use in various applications was also reported.

Medium-chain phthalates are expected to be released primarily to water through wastewater effluents from industrial sources and through disperse releases from consumer products. In products, medium-chain phthalates are not bound within the matrix and are therefore subject to migration and environmental release. Consumer products disposed to wastewater treatment systems[2] are another potential source of environmental releases. When released to water, these substances are predicted to remain in water and to distribute to sediments, with the degree of partitioning driven by their molecular size and water solubility. Medium-chain phthalates are hydrophobic, capable of adsorption to soil particulates, and have limited potential for volatilization from water. Certain medium-chain phthalates were detected and measured in all environmental media (i.e., air, water, sediment and soil), including remote locations, wastewater and in biota.

These substances undergo relatively rapid biodegradation, particularly in aerobic conditions. However, at very low concentrations, biodegradation rates are slower. Abiotic degradation processes, such as hydrolysis, are slow. However, none of these substances are expected to persist in the environment.

Empirical and modelled data indicate that medium-chain phthalates have low to moderate bioaccumulation and biomagnification potential. However, DIBP and DIHepP have been measured in a variety of aquatic species, which confirms that these substances are bioavailable.

Based on high partition coefficients and low to moderate water solubilities, exposure of medium-chain phthalates to organisms will occur primarily through the diet. Results from standard laboratory tests suggest that most medium-chain phthalates have moderate to high hazard potential in aquatic species. DIHepP and B84P were not found to have adverse effects at concentrations up to and exceeding their water solubility limits. Results from an analysis of critical body residues (CBRs) conducted for aquatic organisms based on the solubility limit, determined that the maximum tissue

[2] In this assessment, the term "wastewater treatment system" refers to a system that collects domestic, commercial and/or institutional household sewage and possibly industrial wastewater (following discharge to the sewer), typically for treatment and eventual discharge to the environment. Unless otherwise stated, the term wastewater treatment system makes no distinction of ownership or operator type (municipal, provincial, federal, aboriginal, private, partnerships). Systems located at industrial operations and specifically designed to treat industrial effluents will be identified by the terms "on-site wastewater treatment systems" and/or "industrial wastewater treatment systems".

concentration of DIHepP and B84P will be much lower than levels associated with adverse acute or chronic lethality effects due to neutral narcosis.

Based on results from laboratory tests for DIBP and BBP, BCHP, CHIBP and DBzP are also expected to have low hazard potential in sediment dwelling organisms. A CBR analysis conducted for sediment organisms indicated that the maximum tissue concentration calculated from the saturation limit of DIHepP and its biota-sediment accumulation factor (BSAF) does not exceed minimum concentrations estimated to cause narcotic effects. Toxicity values for sediment-dwelling organisms were derived from aquatic toxicity results for DCHP, BIOP, B79P and DMCHP using the Equilibrium Partitioning method, generating moderate sediment toxicity values.

It should be noted that the CBR analysis does not consider the potential for adverse effects resulting from modes of action other than baseline narcosis. Secondary endpoints that may be mediated by endocrine activity and mechanisms of action other than narcosis are not well studied for medium-chain phthalates. Studies suggest that certain phthalates (such as BBP) have the potential for endocrine disruption; however, such studies have not been conducted for any of the substances in the medium-chain phthalates subgroup. The limited information on the estrogenic activity of medium-chain phthalates in aquatic organisms has not been demonstrated to result in population-level effects (such as growth, reproduction or survival).

Qualitative exposure scenarios were developed for B79P and B84P for the automotive sector to describe releases of these substances to water from facilities where they are used in applications such as automotive sealants and coatings. Calculations of the predicted environmental concentrations (PECs) were highly uncertain for B79P and B84P; therefore, monitoring or surveillance data were used for the purpose of developing PECs. Monitoring data were used to estimate potential exposure concentrations for DIBP and DCHP, whereas a critical body residue analysis was done for DIHepP, from the disperse uses of these substances. The calculated risk quotients (RQs) indicated that harm to aquatic organisms is unlikely. Given that CHIBP, BCHP, DMCHP, BIOP and DBzP were not reported to be imported into Canada above the reporting threshold of 100 kg, exposure scenarios were not developed for these substances.

For the general population in Canada, sources of exposure for medium-chain phthalates are from indoor air, dust, food and breast milk. Due to the information received indicating that a portion of these substances in manufactured items may come in contact with skin, exposure scenarios were identified to characterize dermal exposure for adults and infants. Finally, DIBP may also be present in children’s toys and articles; therefore, oral exposure from mouthing these products was also evaluated.

With regard to human health, the health effects data for medium-chain phthalates shows that there is evidence of effects in animal studies that include developmental, reproductive and systemic effects related to the liver and kidneys. Of these, depending on the phthalate in question, the critical effect for risk characterization is developmental

effects on males, as the available evidence is strongest for effects on the development of the reproductive system, such as alterations of feminization parameters and reproductive tract malformations, and effects on fertility related to a relatively well studied mode of action called the “rat phthalate syndrome” (RPS). This syndrome has been associated with the lowest levels of exposure to this subgroup of phthalates examined to date in animal studies.

Comparisons of estimates for exposure to seven of the medium-chain phthalates from various sources, such as environmental media, food, contact with plastic articles (PVC, polyurethane, polyester, etc.), toys and/or personal care products[3] as well as biomonitoring levels (if available) for all age groups with the appropriate critical effect levels, result in margins of exposures (MOEs) that are considered adequate to address uncertainties in the exposure and health effects databases. Further, these margins are also considered protective of potential reproductive effects not only in males at older life stages but also in females, in addition to effects in other organ systems.

Results of the section 71 industry survey indicate that CHIBP, BCHP and BIOP are not currently in use above the reporting threshold of 100 kg, and the likelihood of exposure to the general population in Canada is considered to be low. Hence, the potential risk to human health is considered to be low for these three substances.

Based on the information available, there is evidence that phthalates in the medium-chain subgrouping have a common mode of action, as they elicit effects on the developing male reproductive system indicative of RPS. Although the MOEs associated with the ten phthalates included in this report are currently considered adequate on an individual substance basis, these MOEs do not address potential risk from concurrent exposure to these phthalates.

Accordingly, a proposed cumulative risk assessment approach for certain phthalates is provided in a separate report (Environment Canada and Health Canada 2015a).

[3] For the purpose of this document, a personal care product is defined as a substance or mixture of substances in a product that is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada: cosmetics, drugs or natural health products.

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Tables and Figures

1. Introduction

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999), the Minister of the Environment and the Minister of Health conduct evaluations of substances to determine whether these substances present or may present a risk to the environment or to human health.

The Substance Groupings Initiative is a key element of the Government of Canada's Chemicals Management Plan (CMP). The Phthalates Substance Grouping consists of 14 substances that were identified as priorities for assessment, as they met the categorization criteria under section 73 of CEPA 1999 and/or were considered as a priority based on human health concerns (Environment Canada, Health Canada 2007). Certain substances within this Substance Grouping have been identified by other jurisdictions as a concern due to potential reproductive and developmental effects in humans. There are also potential ecological effects of concern for some phthalates. A survey conducted for phase 1 of the Domestic Substances List (DSL) Inventory Update identified that a subset of phthalates have a wide range of consumer applications that could result in exposure to humans, including children (Environment Canada 2012). Addressing these substances as a group allows for consideration of cumulative risk, where warranted.

This state of the science (SOS) report provides a summary and evaluation of the current available science intended to form the basis for a draft screening assessment scheduled for publication in 2016. The Government of Canada developed a series of SOS reports for the Phthalate Substance Grouping to provide an opportunity for early public comment on a proposed cumulative assessment approach for certain phthalates (Environment Canada and Health Canada 2015a), prior to that approach being used to propose conclusions on the substances in Phthalate Substance Grouping through publication of a draft screening assessment report.

This SOS report focuses on ten phthalate esters, listed in Table 1, that are referred to as the medium-chain phthalates subgroup based on the intermediate size of their functional side groups. These substances were identified in the categorization of the DSL under subsection 73(1) of CEPA 1999 as priority for assessment. These substances also met the categorization criteria for persistence but not for inherent toxicity of non-human organisms or bioaccumulation.

Table 1. Substances in the medium-chain phthalates subgroup

CAS RN	Substance name	Acronym
84-69-5	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	DIBP
84-64-0	1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	BCHP
5334-09-8	1,2-Benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester	CHIBP
84-61-7	1,2-Benzenedicarboxylic acid, dicyclohexyl ester	DCHP
27987-25-3	1,2-Benzenedicarboxylic acid, bis(methylcyclohexyl) ester	DMCHP
71888-89-6	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	DIHepP
523-31-9	1,2-Benzenedicarboxylic acid, bis(phenylmethyl) ester	DBzP
16883-83-3	1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester	B84P
27215-22-1	1,2-Benzenedicarboxylic acid, isooctyl phenylmethyl ester	BIOP
68515-40-2	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl ester	B79P

While phthalates have common structural features and similar functional uses, differences in their potential health hazard, environmental fate and behaviour have been taken into account through the establishment of subgroups. The primary basis for the subgroups from a health hazard perspective is a structure activity relationship (SAR) analysis using studies related to important events in the mode of action for phthalate-induced androgen insufficiency during male reproductive development in the rat. The effects of phthalate esters for these important events appear to be structure-dependent and highly related to the length and nature of their alkyl chain (Health Canada 2015a). From an ecological perspective, subgrouping was based primarily on differences in log K_{ow} and water solubility and their resulting effects on bioaccumulation and ecotoxicity (Environment Canada and Health Canada 2015a).

This SOS report includes consideration of information on chemical properties, environmental fate, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to December 2014 for the ecological portion and up to August 2014 for the health portion of the assessment. New hazard-related information was submitted after the literature cut-off date and will be incorporated in the next phase of the assessment process. Empirical data from key studies as well as some results from models were used. When available and relevant, information presented in assessments from other jurisdictions was considered.

The SOS report does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical and reliable studies and lines of evidence pertinent to development of a screening assessment in the future.

This SOS report was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada, and incorporates input from other programs within these departments. The ecological and human health portions of this report have undergone external written peer review and/or consultation. Comments on the technical portions relevant to the environment were received from Dr. Frank Gobas (Frank Gobas Environmental Consulting), Dr. Chris Metcalfe (Ambient Environmental Consulting, Inc.), Dr. Thomas Parkerton (ExxonMobil Biomedical Sciences, Inc.), and Dr. Charles Staples (Assessment Technologies, Inc.). Comments on the technical portions relevant to human health were received from Dr. Andreas Kortenkamp (Brunel University), Donna Vorhees (The Science Collaborative), Dr. Michael Dourson (Toxicology Excellence for Risk Assessment), and Dr. Raymond York (York & Associates). While external comments were taken into consideration, the final content and outcome of the report remain the responsibility of Health Canada and Environment Canada.

2. Identity of Substances

Phthalate esters are synthesized through the esterification of phthalic anhydride (1,2-Benzenedicarboxylic acid anhydride; CAS RN 85-44-9) with various alcohols (ACC 2001). The resulting phthalate esters are diesters of benzenedicarboxylic acid comprised of a benzene ring with two side-chain ester groups. Phthalates have the general structure outlined in Figure 1, where R1 and R2 represent ester side chains that can vary in length and structure (ACC 2001). The ester side groups can be the same or different and the nature of the side groups determines both the identity of the particular phthalate and its physical and toxicological properties. All substances in the Phthalate Substances Grouping are ortho-phthalates (*o*-phthalates), with their ester side chains situated adjacent to each other at the 1 and 2 positions of the benzene ring (refer to Figure 1; US EPA 2012).

The structural formula for phthalate esters is derived from the isomeric composition of the alcohol used in their manufacture (Parkerton and Winkelmann 2004). Dialkyl phthalates have ester groups of linear or branched alkyl chains containing from one to thirteen carbons, while benzyl phthalates generally contain a phenylmethyl group and an alkyl chain as ester side groups, and cyclohexyl phthalates contain a saturated benzene ring as an ester group (Parkerton and Winkelmann 2004).

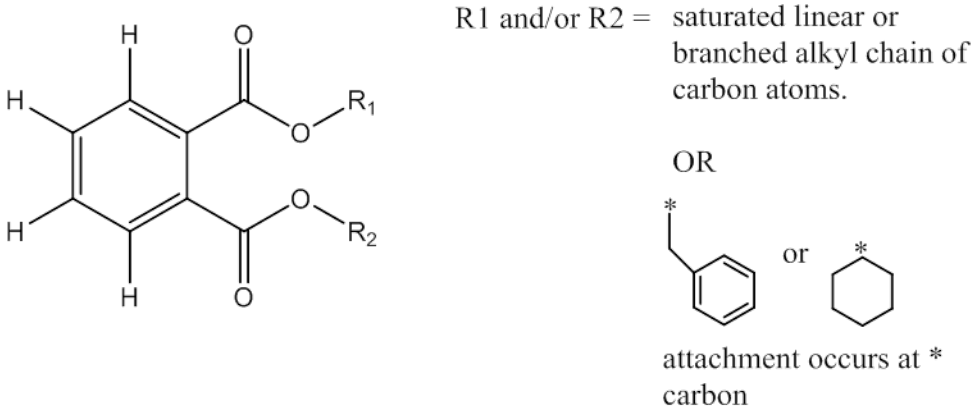
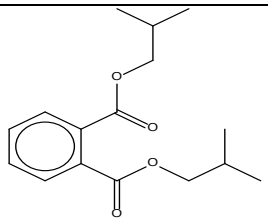


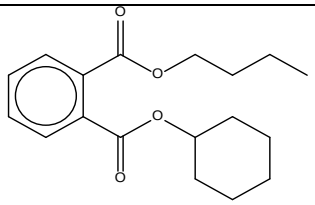
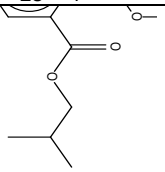
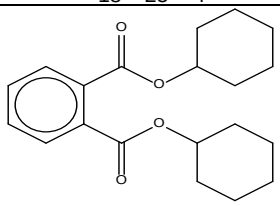
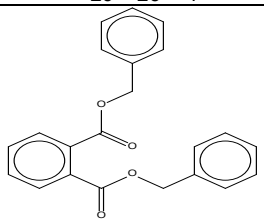
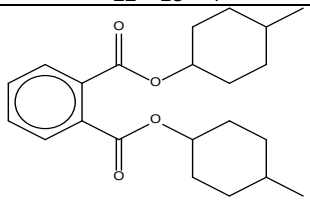
Figure 1. General structure of ortho-phthalates

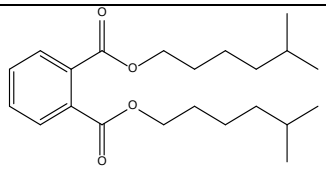
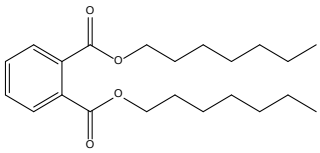
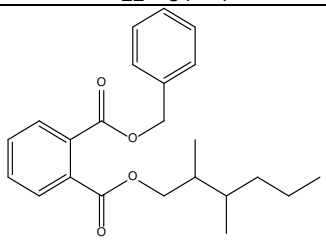
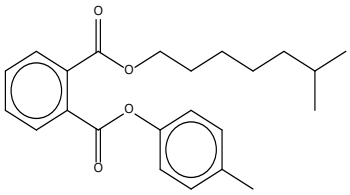
The ten substances of the Phthalate Substance Grouping that are the focus of this SOS report belong to the medium-chain phthalates subgroup and are characterized by ester side groups that mainly contain between 3 and 7 carbons, and do not exceed 9 carbons. Molecular weights of these substances range from 278.4 to 454.6 g/mol. The ester side groups, always in the *ortho*-position, occur in one of three side group combinations: as dialkyl phthalates, which are linear and/or branched alkyl chains; as phenyl or benzyl phthalates that have both an alkyl chain and a cyclic group; or as dicyclic phthalates. Substance identity information for the medium-chain phthalates subgroup is summarized in Table 2-1.

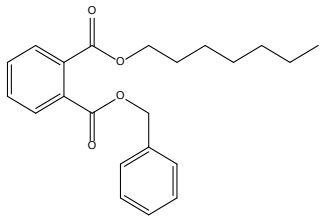
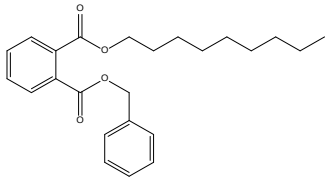
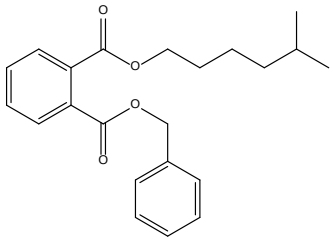
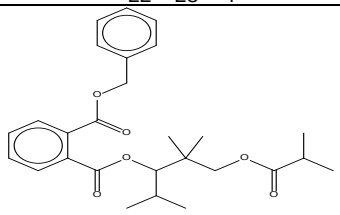
Two substances, DIHepP (CAS RN 71888-89-6) and BIOP (CAS RN 27215-22-1), are isomeric mixtures with alkyl chains that have a defined number of carbons, but can vary in branching. One substance, B79P (CAS RN 68515-40-2), is considered to be a substance of Unknown or Variable Composition, Complex Reaction Products or Biological Materials (UVCB), and it has alkyl chains that can vary in length from 7 to 9 carbons and in the degree of branching. The other seven substances are single constituent, discrete chemicals.

Table 2-1. Summary of substance identity information for the medium-chain phthalates subgroup

CAS RN acronym	**DSL name (common name)**	**Chemical structure and molecular formula**	**Molecular weight (g/mol)**
84-69-5 DIBP	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester (Diisobutyl phthalate)	 $C_{16}H_{22}O_4$	278.35

CAS RN acronym	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
84-64-0 BCHP	1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	 $C_{18}H_{25}O_4$	304.39
5334-09-8 CHIBP	1,2-Benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester	 $C_{18}H_{25}O_4$	304.39
84-61-7 DCHP	1,2-Benzenedicarboxylic acid, dicyclohexyl ester	 $C_{20}H_{26}O_4$	330.43
523-31-9 DBzP	1,2-Benzenedicarboxylic acid, bis(phenylmethyl) ester	 $C_{22}H_{18}O_4$	346.39
27987-25-3 DMCHP	1,2-Benzenedicarboxylic acid, bis(methylcyclohexyl) ester	 $C_{22}H_{30}O_4$	358.48

CAS RN acronym	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
71888-89-6 DIHepP[a]	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	 80%  20% $C_{22}H_{34}O_4$	362.51
27215-22-1 BIOP[a]	1,2-Benzenedicarboxylic acid, isooctyl phenylmethyl ester	 95%  5% $C_{23}H_{28}O_4$	368.48

CAS RN acronym	DSL name (common name)	Chemical structure and molecular formula	Molecular weight (g/mol)
68515-40-2 B79P[b]	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	 ~50%  ~50%  2% $C_{22}H_{28}O_4$	368.48
16883-83-3 B84P	1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester	 $C_{27}H_{34}O_6$	454.57

Abbreviations: CAS RN, Chemical Abstract Service Registry Number; DSL, Domestic Substances List

[a] The major component (i.e., the most prevalent component) is considered to be the representative structure for the isomeric mixture.

[b] A UVCB composed predominantly of three representative structures, where the two linear phthalate esters make up the majority of the substance and are considered to be representative structures of this substance.

2.1 Selection of analogues and use of (Q)SAR models

Guidance on the use of a read-across approach and Quantitative Structure-Activity Relationships or (Q)SAR models for filling data gaps has been prepared by various organizations, such as the Organisation for Economic Co-operation and Development (OECD). These methods have been applied in various regulatory programs, including the European Union's (EU) Existing Substances Programme. In this assessment, a read-across approach using data from analogues and the results of (Q)SAR models, where appropriate, has been used to inform the ecological and human health assessments. Analogues were selected that were structurally and/or functionally similar to substances within this subgroup (e.g., based on physical-chemical properties and toxicokinetics) and that had relevant empirical data that could be used to inform target substances for which limited empirical data was available. The applicability of (Q)SAR models was determined on a case-by-case basis.

2.1.1 Selection of Analogues for Ecological Assessment

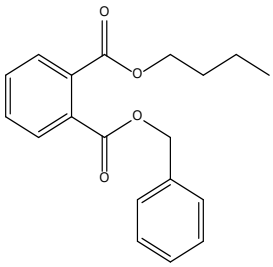
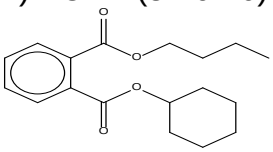
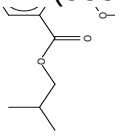
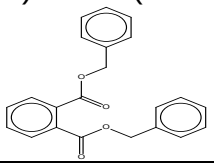
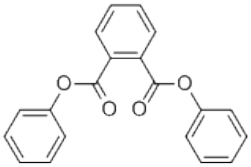
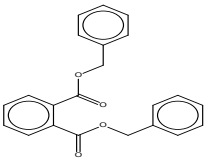
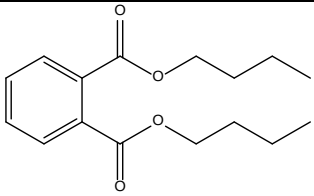
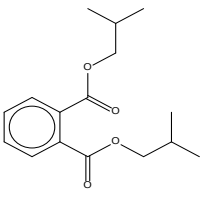
For the read-across approach to the ecological assessment, candidate analogues were selected using the OECD (Q)SAR Toolbox software (2012). Substances that were both structurally and functionally similar to the substances in the medium-chain phthalates subgroup with similarity indices of 80% and above were considered as a starting point. The selected analogues are phthalate esters with comparable molecular size and side groups, known to act through narcosis, and characterized by comparable physical-chemical properties, particularly water solubility and partition coefficients such as the K_{ow}, which influence the potential for environmental bioavailability.

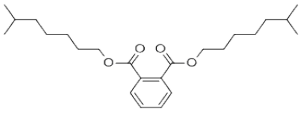
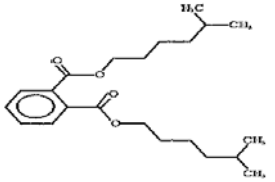
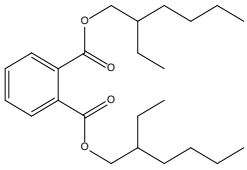
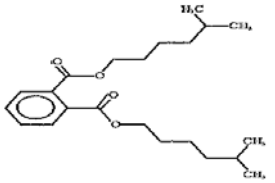
The following substances in the medium-chain phthalates subgroup have limited experimental fate and effects data: BCHP, CHIBP, DBzP, DIHepP and BIOP. A well-studied substance, butyl benzyl phthalate (BBP), characterized by a benzyl ester side group and a straight four-carbon alkyl side chain, is used as an analogue for BCHP, CHIBP and DBzP—each one containing at least one cyclic group and/or an alkyl chain. The substance diphenyl phthalate (DPhP), with two phenyl ester side groups, is used as an analogue for DBzP, which has two benzyl ester side groups. Diisooctyl phthalate (DIOP) and diethylhexyl phthalate (DEHP), characterized by two branched alkyl side chains of up to eight carbons, are used as analogues for DIHepP, which is predominantly composed of two seven-carbon branched alkyl side chains. In addition, the data-rich dibutyl phthalate (DBP), with its straight four-carbon alkyl side chains, can be used to fill data gaps for DIBP, which has branched 4-carbon alkyl side chains, although, it is noted that the available dataset for DIBP is extensive.

Analogues and their substance identity information are presented in Table 2-2. Additional substance identity information for the analogues is provided in Appendix A-1, and their physical chemical properties are summarized in Appendix A-2 and A-3. Table 2-4 provides a summary of the types of data sourced from the analogues.

Also, when appropriate, based on structural and functional similarities, information for data-rich substances in the subgroup is used to read-across for similar substances with limited or no data. Information available for DCHP is used to evaluate properties of DMCHP, and information available for B79P is used for BIOP. Structurally, these substances are quite similar. DCHP features two cyclohexanes as part of its ester side groups, and DMCHP has two methylcyclohexanes instead. B79P, a UVCB substance, has a benzyl ester side group, and a variable eight-carbon straight or branched alkyl ester side chain, whereas BIOP has an eight-carbon branched alkyl ester side chain and a methylphenyl ester side group. Substance names and structures are summarized in Table 2-3.

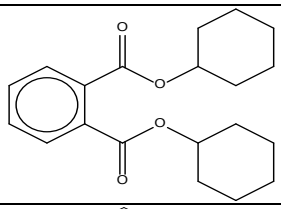
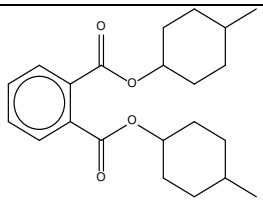
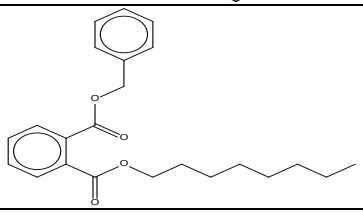
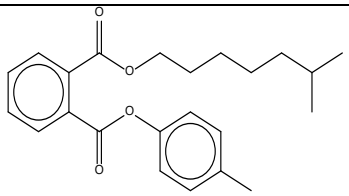
Table 2-2. Analogue identities for the medium-chain phthalates subgroup

Systematic name of analogue (CAS RN)	Common name or acronym of analogue	Analogue chemical structure, molecular formula and molecular weight (g/mol)	Target medium-chain subgroup substance
Butyl benzyl phthalate (85-68-7)	BBP	 $C_{19}H_{20}O_4$ 312.35	1) BCHP (84-64-0)  2) CHIBP (5334-09-8)  3) DBzP (523-31-9) 
Diphenyl phthalate (84-62-8)	DPhP	 $C_{20}H_{14}O_4$ 318.33	DBzP (523-31-9) 
Dibutyl phthalate (84-74-2)	DBP	 $C_{16}H_{22}O_4$ 278.34	DIBP (84-69-5) 

Systematic name of analogue (CAS RN)	Common name or acronym of analogue	Analogue chemical structure, molecular formula and molecular weight (g/mol)	Target medium-chain subgroup substance
Diisooctyl phthalate (27554-26-3)	DIOP	 $C_{24}H_{38}O_4$ 390.56	DIHepP (71888-89-6) 
Diethylhexyl phthalate (117-81-7)	DEHP	 $C_{24}H_{38}O_4$ 390.56	DIHepP (71888-89-6) 

Abbreviation: CAS RN = Chemical Abstract Service Registry Number

Table 2-3. Substances in the medium-chain phthalates subgroup identified for read-across approach

Common name or acronym of subgroup analogue (CAS RN)	Analogue chemical structure	Common name or acronym of subgroup target substance (CAS RN)	Chemical structure of target substance
DCHP (84-61-7)		DMCHP (27987-25-3)	
B79P (68515-40-2)		BIOP (27215-22-1)	

Abbreviation: CAS RN = Chemical Abstract Service Registry Number

Table 2-4. Read-across data used to inform various parameters evaluated in this assessment

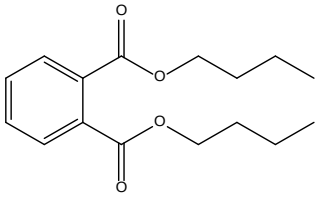
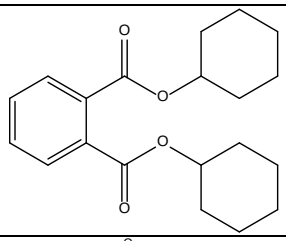
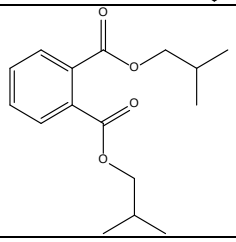
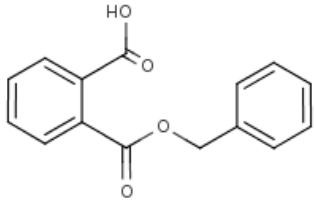
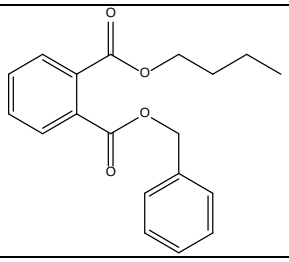
Analogue common name or acronym (CAS RN)	Persistence	Bioaccumulation	Ecotoxicity
BBP (85-68-7)	abiotic and biotic degradation studies	BCF, BAF, BSAF, BMF data	aquatic, soil and sediment toxicity studies
DPhP (84-62-8)	N/A	N/A	aquatic toxicity studies
DIOP (27554-26-3)	biotic degradation	N/A	aquatic toxicity studies
DEHP(117-81-7)	abiotic and biotic degradation studies	BAF, BSAF data	aquatic and sediment toxicity studies
DBP (84-74-2)	abiotic and biotic degradation studies	N/A	aquatic and sediment toxicity studies

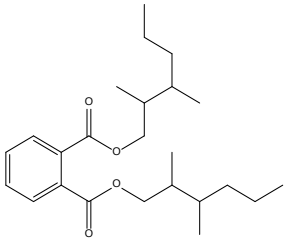
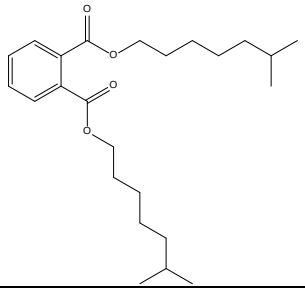
Abbreviations: CAS RN = Chemical Abstracts Service Registry Number; BCF = bioconcentration factor; BAF = bioaccumulation factor; BSAF = biota-sediment accumulation factor; BMF = biomagnification factor; N/A = data not available

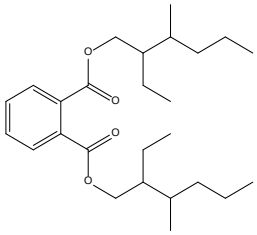
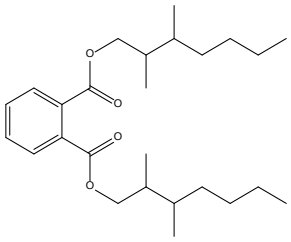
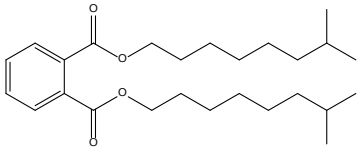
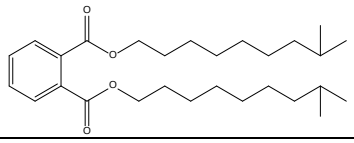
2.1.2 Selection of Analogues for Human Health Assessment

Based on the consideration of similarities in length and nature of the ester chains, several phthalates were identified as the “closest analogue(s)” for the phthalates of interest within its subgroup (Health Canada 2015a). See Table 2-5 for information on analogues within the medium-chain phthalates subgroup.

Table 2-5. Information on identity, chemical structure and branching of analogues used for read across

Analogue CAS RN	Analogue DSL name	Analogue common name (acronym)	Analogue chemical structure and molecular formula	Analogue branching (number of carbons in longest chain)	CMP2 phthalate (s) where analogue was used
84-74-2	1,2-Benzenedicarboxylic acid, dibutyl ester	Dibutyl phthalate (DBP)		Linear (4)	DIBP BCHP
84-61-7	1,2-Benzenedicarboxylic acid, dicyclohexyl ester	Dicyclohexyl phthalate (DCHP)		Cyclo (6)	DMCHP CHIBP BCHP
84-69-5	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	Diisobutyl phthalate (DIBP)		Branched (3)	CHIBP B84P
2528-16-7	1,2-Benzenedicarboxylic acid, mono(phenylmethyl) ester	Monobenzyl phthalate (MBzP)		Mono (4)	DBzP B84P BIOP B79P
85-68-7	1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester	Butyl benzyl phthalate (BBP)		Linear/Benzyl (4 benzyl)	B84P

Analogue CAS RN	**Analogue DSL name**	**Analogue common name (acronym)**	**Analogue chemical structure and molecular formula**	**Analogue branching (number of carbons in longest chain)**	**CMP2 phthalate (s) where analogue was used**
27554-26-3	1,2-Benzenedicarboxylic acid, diisooctyl esters	Diisooctyl phthalate (DIOP)	dimethyl hexyl ester groups (mixed isomers)  methyl heptyl ester groups (mixed isomers) 	Branched (6-7)	BIOP

Analogue CAS RN	Analogue DSL name	Analogue common name (acronym)	Analogue chemical structure and molecular formula	Analogue branching (number of carbons in longest chain)	CMP2 phthalate (s) where analogue was used
28553-12-0	1,2-Benzenedicarboxylic acid, diisononyl ester	diisononyl phthalate (DINP-1)	methylethyl hexyl ester groups  dimethyl heptyl ester groups  methyl octyl ester groups  isodecyl ester groups 	Branched (6*-9)	B79P

3. Physical and Chemical Properties

Physical and chemical properties determine the overall characteristics of a substance and are used to determine the suitability of different substances for different types of applications. Such properties also play a critical role in determining the environmental fate of substances (including their potential for long-range transport), as well as their toxicity to humans and non-human organisms.

Where experimental information was limited or not available, models based on quantitative structure-activity relationships (QSARs) were used to generate data. These models are mainly based on fragment addition methods and rely on the neutral form of a chemical as input. Phthalate esters in the medium-chain subgroup are considered amenable to model prediction using QSARs, as they are within the model domain of applicability (i.e., structural and/or property parameter domains are represented in the training set used for the models). These substances also occur as neutral (non-ionized) substances in the environment.

Experimental and modelled physical and chemical properties for the substances in the medium-chain subgroup are presented in ranges in Table 3-1. Key physical-chemical property data identified for the individual substances are presented in Appendix B. Median values were calculated for water solubility, log K_{ow} and log K_{oc} based on the estimates generated from various (Q)SAR models (see Appendix B-2). Representative experimental and/or modelled values chosen for key physical-chemical properties were checked for internal consistency using the three solubility approach described by Cole and Mackay (2000) and Schenker et al. (2005). Based on the results, the log K_{ow} values calculated from the model VCCLab (2005), rather than median values, were considered for DIHepP, BIOP and B84P.

Table 3-1. Range of experimental and predicted physical and chemical properties (at standard temperature) for phthalate esters in the medium-chain subgroup

Property	Range	Type of data	Reference
Physical state	Liquid	Experimental	US EPA 2010
Melting point (°C)	-64–66	Experimental	HSDB 1983–; Phys-Prop 2006; European Commission 2000
Boiling point (°C)	~205–390	Experimental	Haynes and Lide 2010; European Commission 2000
Boiling point (°C)	323–474	Modelled	EpiSuite 2012
Density (kg/m^3)	787–1076	Experimental	Haynes and Lide 2010; ECHA c2007–2014

Property	Range	Type of data	Reference
Vapour pressure (Pa)	3.8×10^{-6}–6.3×10^{-3}	Experimental	Daubert and Danner 1989; Werner 1952; European Commission 2000; Cousins and Mackay 2000; ECHA c2007–2014
Vapour pressure (Pa)	8.48×10^{-7}–0.322	Modelled	EPI Suite 2012
Water solubility (mg/L)	0.02–20.3	Experimental	Leyder and Boulanger 1983; Yalkowsky et al. 2010; HSDB 1983–; European Commission 2000; Letinksi et al. 2002; ECHA c2007–2014
Water solubility (mg/L)	0.001–5.0	Modelled	EPI Suite 2012; ACD/Percepta c1997–2012; VCCLab 2005
Henry's Law constant ($Pa \cdot m^3/mol$)[a]	1.03×10^{-6}–1.60×10^{2}	Modelled (bond estimate)	EPI Suite 2012
Log K_{ow} (dimensionless)[b]	4.11–5.5	Experimental	Leyder and Boulanger 1983; ECHA c2007–2014
Log K_{ow} (dimensionless)	4.46–7.41	Modelled	EPISuite 2012; ACD/Percepta c1997–2012; VCCLab 2005; ppLFER
Log K_{oc} (dimensionless)[a]	2.91–6.10	Modelled (average of MCI and log K_{ow} methods	EPI Suite 2012
Log K_{oa} (dimensionless)[a]	8.41–14.65	Modelled	EPI Suite 2012

Abbreviations: K_{ow} = octanol-water partition coefficient; K_{oc} = organic carbon-water partition coefficient; K_{oa} = octanol-air partition coefficient

[a] No experimental data were found.

[b] Range represents two experimental values.

Substances in the medium-chain phthalates subgroup are oily liquids at room temperature (US EPA 2010); however, some of the phthalates have the potential to exist as solids at low environmental temperatures (Cousins et al. 2003). They do not contain functional groups with ionizing potential and are therefore expected to exist as neutral chemicals at environmentally relevant pH (6–9).Their experimental melting points range from -64°C to 66°C. It is noted that melting point values and information regarding the physical state are inconsistent for BCHP and DBzP, and unknown for DMCHP. This introduces some uncertainty with respect the evaluation of their properties, in particular ecotoxicity, using the analogue BBP or the read-across

approach using DCHP. Melting points of phthalates cannot be predicted reliably using (Q)SAR models; therefore, these modelled values are not reported herein. Experimental boiling points ranged from approximately 205°C to 390°C, and modelled boiling points were in the range of 323°C to 474°C.

In general, both the vapour pressure and water solubility display an overall trend of decreasing values with increasing alkyl chain length, although this pattern is more pronounced for water solubility values (Appendix B-2). Medium-chain phthalates have low to moderate water solubilities and very low to low vapour pressures. The empirical and modelled log K_{ow} values were determined to be high, and the modelled log K_{oc} values were high to very high.

4. Sources

There is limited evidence showing that certain phthalate esters, DEHP, DBP and DIOP, can be synthesized by algae species, including red algae (*Bangia atropurpurea*) and brown algae (*Sargassum wightii*) (Chen 2004; Sastry and Rao 1995). The production process and the physiological role of phthalate esters in algae have not been defined. Similar studies have not been identified for the substances in the medium-chain phthalates subgroup; it is uncertain if they can occur naturally in the environment.

An industry survey, issued pursuant to section 71 of CEPA 1999, was conducted in 2013 to obtain information on quantities in commerce for substances in the Phthalate Substance Grouping in Canada (Canada 2013). Table 4-1 presents a summary of the total manufacture, import and export quantities reported for 2012 for the medium-chain phthalates subgroup. Due to the targeted nature of the survey, reported use quantities may not fully reflect all uses in Canada.

Results of a section 71 industry survey for the year 2012 (Environment Canada 2014) indicated that none of the ten substances in the medium-chain phthalates subgroup were manufactured in Canada, and that five of the substances, CHIBP, BCHP, DMCHP, BIOP and DBzP, were not imported into Canada above the reporting threshold of 100 kg. Five substances, DCHP, DIHepP, DIBP, B79P and B84P, were imported. Import quantities were less than 10 000 kg for DCHP and DIHepP, between 10 000 and 100 000 kg for DIBP, and between 100 000 and 1 000 000 kg for each of B79P and B84P (Environment Canada 2014; see Table 4-1).

Table 4-1. Summary of Canadian manufacturing, imports and exports of substances in the medium-chain phthalates subgroup for 2012

Common name	Total manufacture (kg)*	Total imports (kg)*	Total exports (kg)*
DIBP	0	10 000–100 000	0
BCHP	0	0	0
CHIBP	0	0	0
DCHP	0	< 10 000	0
DBzP	0	0	0
DMCHP	0	0	0
DIHepP	0	< 10 000	0
BIOP	0	0	0
B79P	0	100 000–1 000 000	> 100 000
B84P	0	100 000–1 000 000	> 100 000

* All information obtained from section 71 industry survey under CEPA 1999 (Environment Canada 2014).

Four of the medium-chain phthalates, DMCHP, B84P, DIHepP and DBzP, were previously included in phase 1 of the Domestic Substances List Inventory Update (DSL IU) initiative (Canada 2009), and their quantities in commerce were reported for 2008. Similar to the results of the section 71 industry survey for 2012 (Environment Canada 2014), DMCHP was not manufactured or imported in either 2008 or 2012. DIHepP was imported at higher quantities in 2008 in the range of 100 000 to 1 000 000 kg, compared to less than 10 000 kg in 2012. In 2008, less than 100 000 kg of DBzP was imported, and the substance was not imported above the reporting threshold of 100 kg in 2012. B84P was imported in the same range of 100 000 to 1 000 000 kg in 2008 as in 2012, and manufacturing below the reporting threshold of 100 kg was reported by three companies in 2008.

A summary of the combined production and use quantities for the medium-chain phthalates in the United States and the European Union is presented in Table 4-2. There have been no recent submissions under the United States Inventory Update Reporting (US EPA 2014a, b) or the European Union's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Initiative (ECHA c2007–2014a) for CHIBP, DBzP, DMCHP and BIOP. For BCHP, a low-use quantity was reported in the United States in 2002 but not in 2006, and there were no submissions through REACH. This suggests a similar commercial status to that in Canada, where these five substances do not appear to be in commerce above the reporting threshold of 100 kg. Furthermore, CHIBP, DBzP and BIOP were not identified as high- or low-production-

volume substances by the European Union Industry (ESIS 2014). DMPCHP, however, has been identified as a low-production-volume chemical in Europe (ESIS 2014).

In the United States, high quantities of DIHepP in production and use were reported both in 2002 and 2006, in the range of approximately 22 to 45 million kg (US EPA 2014ab). There were no submissions for DIHepP under REACH (ECHA c2007–2014a); however, this substance was previously identified as a high-production-volume chemical in Europe (ESIS 2014). Recent information indicates that DIHepP is no longer manufactured in North America and Europe (ECHA c2007–2014a; BASF Corporation 2011a; BASF Corporation 2011b).

Internationally, production and use have been reported for DIBP, DCHP, B79P and B84P in the United States and the European Union (US EPA 2014ab; ECHA c2007–2014a; refer to Table 4-2). In addition, these four substances have all been identified as high-production-volume chemicals in Europe (ESIS 2014).

Table 4-2. Summary of international production and use of substances in the medium-chain phthalates subgroup

Common name	United States 2002 (kg)[a]	United States 2006 (kg)[a]	European Union (kg)[b]
DIBP	> 227 000– 454 000	227 000– < 454 000	1 000 000– 10 000 000
BCHP	< 5000– < 227 000	NS	NS
CHIBP	NS	NS	NS
DCHP	> 227 000– 454 000	< 227 000	100 000–1 000 000
DBzP	NS	NS	NS
DMCHP	NS	NS	NS
DIHepP	> 22 680 000– 45 359 000	22 680 000– < 45 359 000	NS
BIOP	NS	NS	NS
B79P	> 453 000– < 4 536 000	> 453 000– < 4 536 000	10 000 000– 100 000 000
B84P	> 453 000– < 4 536 000	> 453 000– < 4 536 000	1 000 000– 10 000 000

Abbreviation: NS = no submissions reported in the United States or European Union.
[a] Production volumes in the US reported through Inventory Update Reporting (IUR) between 1986 and 2002 (US EPA 2014ab).
[b] Production volumes submitted to the European Union REACH Initiative (ECHA c2007–2014a).

5. Uses

The results of a section 71 industry survey (Environment Canada 2014) included information on the uses for DIBP, DCHP, DIHepP, B79P and B84P for 2012 (Environment Canada 2014).

Major uses identified are summarized in Table 5-1, based on responses to Section 8 of the industry survey (Environment Canada 2014). All five substances are used in adhesives and sealants that are used in construction and/or the automotive sector. Most of the substances are also used as plasticizers for applications in electrical and electronics, and children's toys. Import of B79P in raw material form for use in various applications was also reported (Environment Canada 2014).

Table 5-1. Summary of Canadian uses of five medium-chain phthalates

Major uses [a]	DIBP	DCHP	DIHepP	B79P	B84P
Adhesives and sealants	✓	✓	✓	✓	✓
Paints and coatings					✓
Electrical/electronics	✓		✓		
Automotive and transportation products		✓		✓	✓
Printing inks		✓			
Children's toys and articles	✓				
Plastic and rubber materials	✓				

[a] Based on consumer and commercial Domestic Substances List [DSL] codes that were reported in response to Section 8 of the section 71 industry survey

None of the ten substances included in this SOS report are listed in the Drug Products Database, the Therapeutic Product Directorate's internal Non-Medicinal Ingredients Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database as medicinal or non-medicinal ingredients present in final pharmaceutical products, veterinary drugs or natural health products in Canada (DPD 2014; NHPID 2014; LNHPD 2014; September 2014 email from the Therapeutic Products Directorate, Health Canada, to the Risk Management Bureau, Health Canada, unreferenced).

With the exception of DIBP, none of phthalates in this report are identified to be present in food packaging materials or incidental additives. DIBP has been identified as a plasticizer in polypropylene films used to package all types of food (September 2014 email from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada, unreferenced). However, DBzP and DCHP are present on the FDA's List of Indirect Additives Used in Food Contact Substances (US FDA 2014).

None of the ten phthalates are included on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may

contravene the general prohibition found in section 16 of the *Food and Drugs Act* or a provision of the *Cosmetic Regulations* (Health Canada 2007a). Based on notifications submitted under the Cosmetic Regulations to Health Canada none of the ten medium chain phthalates were notified to be present in (September 2014 email from the Consumer Product Safety Directorate (CPSD), Health Canada to Existing substances Risk Assessment Bureau (ESRAB), Health Canada).

A search of uses internationally was also conducted. No use information was identified for either CHIBP or BIOP, and while general uses were reported for BCHP, no specific product or article types were identified. Table 5-2 provides a summary of the general use information that was available for the remaining medium-chain phthalates in the subgroup.

Table 5-2. Summary of major uses of medium-chain phthalates identified internationally[a]

Major uses	Examples of uses	Substances
Automotive and transportation products	Caulks and sealants, glass insulation units, automotive paint, lacquers, varnishes, adhesive for automotive manufacture or repair, plastic articles, car mats, steering wheel covers	DIBP, DCHP, DIHepP, B79P, B84P
Coatings / adhesives / DIY products	Adhesives and binding agents; sealants, coatings, paints, thinners, paint removers, finger paints; acrylic coatings, lacquers and varnishes; fillers and filling agents, caulk, putties, plasters, modelling clay; process regulators, hardeners; polyvinyl acetate adhesives, polysulphide and castable polyurethane sealants, coatings and caulks; corrosion inhibitors; product used to detect surface flaws or cracks in vehicles parts, farm equipment, pipelines, non-metal surface treatment products, polishes, wax blends	DIBP, DCHP, DBzP, DIHepP, B79P, B84P
Inks / printing products	Screen printing inks; paper products, inks, toners; colouring agents; solvent for pressure-sensitive copying paper; plasticizer in printing inks; serigraphic printing paper/cardboard/paperboard; reprographic agents for publishing, printing and reproduction of recorded media	DCHP, DMCHP, DIHepP, B79P, B84P

Cables / wires / appliances / construction materials	Wire and cable insulation; electrical batteries and accumulators; vinyl flooring, tile and carpet backing; construction materials and specialized construction activities; artificial turfs, PVC with foam backing and cushioned PVC, PVC air mattresses	DIBP, DCHP, DMCHP, DIHepP, B79P, B84P
Clothing articles / furniture	Rubber and plastic articles such as belts, head phones, furniture, shoes, plastic sandals, balance balls	DIBP
Children's articles and toys	Nursing pillows, baby carriers, aprons for perambulators, baby mattresses, toys produced from foam plastic, erasers, plastic sandals and in childcare articles and children's toys, crayons	DIBP
Textiles	Urethane fabric coatings, fabrics, textiles, apparel; leather articles; textiles with decorative printings on the outer side of the fabric; textile dyes, and finishing and impregnating products, including bleaches and other processing aids; screen printing inks for textiles; plastisols in articles such as fabrics, textiles and apparel	DIBP, DCHP, B79P, B84P
Food packaging and processing	Food wrappers and labels; acrylic plastics when products are intended for food or drink contact; as a component in coated or uncoated food-contact surface of paper and paperboard used for all aspects of handling aqueous or fatty foods; as a component of adhesives for packaging in contact with food; in polymeric substances used in all aspects of food handling; in plastic film, foil, cellophane.	DIBP, DCHP, DBzP

[a] Uses listed in this table were identified through the following sources: SPIN 2014, ECHA c2007–2014a, US EPA 2014a, b, US CPSC 2010, US FDA 2014, SCCP 2007, HPD 2014.

6. Releases to the Environment

The presence of the substances in the medium-chain phthalates subgroup in the environment is mainly from anthropogenic sources..

Based on the use information regarding the medium-chain phthalates gathered from the section 71 industry survey and the related follow-up (Environment Canada 2014), aquatic systems are thought to be the major recipient of phthalate releases. Medium-chain phthalates are expected to be released primarily to the aquatic medium through wastewater effluents from industrial sources and through disperse releases from consumer products. Nonetheless, the degree of release into water and other environmental compartments is uncertain or largely unknown. At industrial sites, washing of phthalate-containing floors and wall-coverings may result in environmental releases. The general transport of phthalates can result in releases through reconditioning of transport containers and trucks. Consumer products disposed to wastewater treatment systems are another potential source of release.

In some cases, these phthalates can be transported to off-site facilities for disposal, where releases are possible via effluents. Releases to air were reported in some cases (Environment Canada 2014). The medium-chain phthalates are not reported on the National Pollutant Release Inventory (NPRI) Substance List (NPRI 1995–).

Phthalates are not chemically bound to the polymer matrix and therefore can migrate from plastic products, including those disposed of in landfills. Landfills that do not collect and treat their leachate may potentially release substances to soil and groundwater via leachate.

7. Environmental Fate and Behaviour

7.1 Environmental distribution

A summary of the mass-fraction distribution for substances in the medium-chain phthalates grouping based on individual steady-state emissions to air, water and soil is provided in tables 7-1, 7-2 and 7-3 below. Due to the range of physical-chemical properties and molecular weights of the substances in the medium-chain phthalates grouping, a wide range of distributions resulted, particularly in the air and water release scenarios. Substances with similar mass-fraction distribution predictions have been grouped together. The groups generally align with the molecular weight of the phthalates. The results in tables 7-1 to 7-3 represent the net effect of chemical partitioning, inter-media transport and loss by both advection (out of the modelled region) and degradation/transformation processes. The results of Level III fugacity modelling suggest that medium-chain phthalates can be expected to distribute into any of the four environmental compartments (air, water, soil and sediment), depending on the physical-chemical properties of the phthalate and the compartment of release.

Fugacity modelling results for individual substances in the grouping are presented in Appendix C.

Table 7-1. Summary of Level III fugacity modelling (New EQC 2011) for DIBP, BCHP and CHIBP, showing percent partitioning into each medium for three release scenarios

Substances released to	Air (%)	Water (%)	Soil (%)	Sediment (%)
Air (100%)	21–40	810	50–70	negligible
Water (100%)	negligible	93–98	negligible	2–7
Soil (100%)	negligible	negligible	100	negligible

Table 7-2. Summary of Level III fugacity modelling (New EQC 2011) for DCHP, DBzP, BIOP, B79P, DIHepP and DMCHP, showing percent partitioning into each medium for three release scenarios

Substances released to	Air (%)	Water (%)	Soil (%)	Sediment (%)
Air (100%)	0–10	4–7	79–94	2–8
Water (100%)	negligible	47–70	negligible	30–53
Soil (100%)	negligible	negligible	100	negligible

When released to air, DIHepP is an outlier, behaving more similarly to the substances in Table 7-1, with greater partitioning to air (22%) and lesser to soil (63%).

Table 7-3. Summary of Level III fugacity modelling (New EQC 2011) for B84P, showing percent partitioning into each medium for three release scenarios

Substances released to	Air (%)	Water (%)	Soil (%)	Sediment (%)
Air (100%)	negligible	3	85	12
Water (100%)	negligible	18	negligible	83
Soil (100%)	negligible	negligible	100	negligible

When released to air, medium-chain phthalates exhibit a trend of increasing partitioning to solid matrices as hydrophobicity increases, with a corresponding trend in decreasing partitioning to air. These trends align with the physical-chemical properties of the phthalates and the increasing capacity to adsorb to organic carbon and decreasing volatility as molecular weight increases.

When released to water, the lower-molecular-weight medium-chain phthalates are predicted to remain primarily in water, with a small proportion distributing into sediment. Medium-chain phthalates with an intermediate molecular weight are predicted to distribute more evenly between water and sediment, while B84P is predicted to distribute mainly into sediment with a lesser proportion remaining in the water.

The moderate to very high hydrophobicity of the medium-chain phthalates also influences their movement through soil. The hydrophobic nature of these substances results in their adsorption to soil particulates, thereby substantially reducing soil mobility

and delaying entry into groundwater and aquatic systems (CCME 1999). When medium-chain phthalates are released into soil, essentially all of the substance is predicted to remain within this environmental compartment.

The low Henry's Law constant values generated from models (Table 3-1) indicate that phthalates have little tendency to volatilize from water. In their trend analysis of Henry's Law constants for the phthalates, Cousins et al. (2003) noted that while lower-molecular-weight phthalates have fairly high vapour pressures and are therefore expected to volatilize readily in the pure state, their high solubility in water results in very low Henry's Law constants and therefore only slow volatilization from aqueous solution. For the higher-molecular-weight phthalates, water solubility has been observed to decrease more rapidly with increasing alkyl chain length than does vapour pressure (Staples et al. 1997; Cousins et al. 2003), leading to an apparent increase in the Henry's law constant. Therefore, higher-molecular-weight phthalates should evaporate more rapidly from water; however, this tendency is mitigated by an increase in sorption potential to suspended matter in the water column. The combined effects determine the overall distribution characteristics, although, in general, higher-molecular-weight phthalates volatilize only slowly from water (Cousins et al. 2003).

7.1.1 Long-range transport potential

Long-range transport (LRT) refers to the ability of a substance to be transported from its point of release in a mobile medium (usually air or water) over long distances. Following this movement, the substance can undergo a variety of fate processes, such as deposition from air into water and uptake in biota. Concentrations of DIBP have been measured far from any expected sources of release in sediment and biota along the eastern coast of Hudson's Bay (Morin 2003) and in air in the Norwegian Arctic (Xie et al. 2007). To investigate LRT as a potential explanation for these detected concentrations, the Transport and Persistence Level III Model (TaPL3 2000), developed by the Canadian Environmental Modelling Centre, and the OECD POPs Screening Tool, developed by the OECD Expert Group for Follow-up to the OECD/UNEP Workshop on Multimedia Models, were run for DIBP. Model inputs are available in Environment Canada (2015). The calculated Critical Travel Distance (CTD) in both models was very similar: 246 km and 269 km, respectively. This indicates that relatively little long-range atmospheric transport is expected.. This is consistent with what would be expected from the limited releases to air (described in section 6), the predicted partitioning (Table 7.1) and lack of persistence of DIBP (see section 7.2). Discussion of the concentrations of DIBP detected in the Arctic and possible explanations can be found in section 8.2.1. Some of the medium-chain phthalates have quite high log K_{oa} (i.e., 12), suggesting that they could sorb to fine particles and be transported though air; however, given their low persistence and limited releases to air, long-range transport is not expected.

7.2 Environmental persistence

Studies addressing environmental persistence of substances in the medium-chain subgroup are not available for most of these substances. However, degradation of

phthalate esters has been well characterized through studies focusing on a few phthalate ester substances with short, medium and long chain or cyclic side groups. Numerous studies have been conducted for these few substances. In general, these studies provide a relatively good understanding of biotic and, to a lesser extent, abiotic degradation pathways of phthalate esters, their typical behaviour in environmental media, and degradation rates. These studies can be used to characterize environmental persistence of the less studied substances, including those in the medium-chain phthalates subgroup. Biotic and abiotic degradation was best characterized for the analogue substances BBP and DEHP (Peterson and Staples 2003).

Phthalates can be degraded by abiotic and biotic processes. Abiotically, they undergo hydrolysis and photolysis, but these processes tend to be slow (Peterson and Staples 2003). It is the biodegradation by both micro-organisms and fungi in aerobic conditions, and less so, in anaerobic conditions, that contributes most to the breakdown of these substances in the environment. Studies have demonstrated that phthalates with shorter ester chains (such as BBP) can be readily biodegraded and mineralized, whereas phthalates with longer side chains (e.g., DEHP) tend to be less biodegradable (Liang et al. 2008). Moreover, the biodegradability differences among phthalates are attributed to the steric effects of the ester chains, where binding of hydrolytic enzymes is hindered, resulting in limited hydrolysis. Differences in phthalate isomers can also influence rates of degradation, as phthalate-hydrolyzing enzymes are structurally specific (Liang et al. 2008). In contrast, the degree of branching of the ester chains is thought to not play a significant role in limiting degradation (Ejlertsson et al. 1997). The medium-chain phthalates subgroup contains substances with diverse side chains of different lengths; therefore, their biodegradation rates are expected to be varied.

Empirical biodegradation data on persistence were available for three substances in the medium-chain phthalates subgroup, DIBP, DCHP and B79P. In contrast, such data and information on abiotic pathways were not found in the open literature and from unpublished sources for the rest of the phthalates in the medium-chain subgroup.

To characterize degradation potential for the data-poor medium-chain phthalates, data for the analogue substance BBP were used to inform BCHP, CHIBP and DBzP, and data for the analogue DEHP were used for DIHepP. Data for DBP were also used to fill data gaps for DIBP. Within the subgroup, data for DCHP were used to evaluate the properties of DMCHP, and data for B79P were used to evaluate BIOP and B84P. The medium-chain phthalates were found to be amenable to (Q)SAR model predictions. Therefore, hydrolysis rates, degradation by hydroxyl radicals, and primary and ultimate biodegradation were predicted using models EPI Suite 2012 (specifically HYDROWIN 2010, AOPWIN 2010 and the BIOWIN 2010 submodels) and CATALOGIC 2012.

Empirical biodegradation results for medium-chain phthalates and analogues are summarized in Table 7-2-2. Model results are summarized in tables 7-2-1, 7-2-3 and 7-2-4.

7.2.1 Abiotic degradation

Phthalate esters, including the medium-chain phthalates, tend to be relatively stable in the abiotic environment. Abiotic degradation processes, including hydrolysis and photolysis, occur very slowly and appear to be influenced by pH levels. Biodegradation studies that included controls in which organisms had been inactivated by sterilization indicate that losses of phthalate esters are limited to only a few percent of the initial concentration (Cheung et al. 2007; Kickham et al. 2012; Hashizume et al. 2002; Peng and Li 2012). The size and complexity of the phthalate ester side chains also impact rates of abiotic degradation, for example, DEHP degradation rates are observed to be much longer than those for BBP (Lertsirispon et al. 2009).

Hydrolysis rates of phthalate esters have been observed to decrease and the corresponding half-lives to increase with the length of the side chains (Staples et al. 1997), and to proceed at faster rates at higher pH levels (Wolfe et al. 1980). At pH 8, half-lives determined from second order kinetics varied from approximately months to a couple of years for a shorter-chain phthalate DBP, and 100 years for the medium-chain phthalate DEHP (Wolfe et al. 1980). Gledhill et al. (1980) estimated a hydrolysis half-life of > 100 days for BBP (an analogue to BCHP, CHIBP and DBzP). In 140-day tests at pH 5–9, degradation of DBP, BBP and DEHP by hydrolysis was found not to exceed 20%. DEHP did not hydrolyze at the neutral pH of 7 (Lertsirisopon et al. 2009). Modelled hydrolysis half-lives for the medium-chain phthalate subgroup ranged from 263 days for BIOP to 11.6 years for DMCHP at pH 7, and were considerably lower at pH 8, in the range of 26 days for BIOP to 1.1 years for DMCHP. Based on these observations, it can be concluded that hydrolysis is slow and unlikely to be an important fate process for phthalate esters under typical environmental conditions (Staples et al. 1997).

Photolysis is a more significant degradation pathway for phthalates, although it can also be a slow process in the aquatic environment at neutral pH (pH 7). Also, certain phthalates, such as DEHP, are less susceptible to photolysis. Exposure to sunlight conditions resulted in about 20% degradation of BBP and DBP over 140 days (Lertsirisopon et al. 2009). Photolysis was found to be considerably enhanced by acid- and alkali-catalyzed conditions (Lertsirisopon et al. 2009). Degradation half-lives of the phthalate esters DBP, BBP and DEHP were observed to decrease with pH and were fastest at the most extreme pH test conditions of 5 and 9, resulting in four- to eight-fold faster half-lives than those established at pH 7 (Lertsirisopon et al. 2009).

Degradation of medium-chain phthalates by hydroxyl radicals in air was investigated by using (Q)SAR models. Modelled half-lives ranged from 5.3 hours for DMCHP to 13.8 hours for DIBP (AOPWIN 2010), suggesting that when in air, these substances may be degraded relatively quickly by hydroxyl radicals.

(Q)SAR model predictions for atmospheric oxidation (AOPWIN 2010) and hydrolysis (HYDROWIN 2010) are summarized in Table 7-2-1 below. Degradation by ozone reaction could not be estimated for these substances.

Table 7-2-1. (Q)SAR model predictions for degradation of the medium-chain phthalates subgroup in air by hydroxyl radicals and through hydrolysis

Substance name	Extrapolated half-life in air (hours)	Estimated hydrolysis half-life	Reference
DIBP	13.8	194 days (pH 8); 5.3 years (pH 7)	AOPWIN 2010; HYDROWIN 2010
BCHP	7.6	193 days (pH 8); 5.3 years (pH7)	AOPWIN 2010; HYDROWIN 2010
CHIBP	7.7	267 days (pH 8); 7.3 years (pH 7)	AOPWIN 2010; HYDROWIN 2010
DCHP	5.3	1.1 years (pH 8); 11.6 years (pH7)	AOPWIN 2010; HYDROWIN 2010
DMCHP	5.3	1.1 years (pH 8); 11.6 years (pH7)	AOPWIN 2010; HYDROWIN 2010
DIHepP	7.2	125 days (pH 8); 3.4 years (pH7)	AOPWIN 2010; HYDROWIN 2010
DBzP	10	32 days (pH 8); 317 days (pH7)	AOPWIN 2010; HYDROWIN 2010
B84P	7.4	57 days (pH 8); 1.5 years (pH7)	AOPWIN 2010; HYDROWIN 2010
BIOP	8.8	26 days (pH 8); 263 days (pH7)	AOPWIN 2010; HYDROWIN 2010
B79P	7.4	55 days (pH 8); 1.4 years (pH7)	AOPWIN 2010; HYDROWIN 2010

7.2.2 Biodegradation

Biodegradation is the main route through which phthalate esters break down in the environment. It has been demonstrated that medium-chain phthalate esters with shorter ester chains, such as DBP or BBP, can be more easily biodegraded and mineralized, whereas those with longer ester chains, such as DEHP, tend to be less susceptible to biodegradation (Wang et al. 2000; Chang et al. 2004). This is likely due to the steric effect of ester side groups that hinder the hydrolytic enzymes from binding, thereby inhibiting hydrolysis. Also, phthalate-hydrolyzing enzymes are known to be structure-specific, with unique abilities to degrade phthalate isomers (Gu et al. 2005).

Phthalate esters can be biodegraded by aerobic and facultative anaerobic bacteria. However, fewer strains that are capable of degrading anaerobically have been isolated (Chang et al. 2005). In addition to bacteria, a few fungi species (Ganji et al. 1995; Sivamurthy et al. 1991; Engelhardt et al. 1977; Kim and Lee 2005; Lee et al. 2007; Kim et al. 2002, 2003, 2007) and green microalgae species (Yan and Pan 2004; Yan et al. 2002) can also degrade phthalate esters.

Microbial mineralization of phthalic acid esters in the environment involves a sequence of reactions common to all phthalates (Hashizume et al. 2002; Staples et al. 1997; Yuan

et al. 2002). This process requires diverse metabolic enzymes, such as esterases, dehydrogenases, decarboxylases and dioxygenases, and therefore a single organism is unlikely to be able to completely mineralize these complex organics (Staples et al. 1997; Liang et al. 2008). So far, only mixed cultures have been shown to completely mineralize phthalates (Chatterjee and Dutta 2008; Wang et al. 2004; Vega and Bastide 2003). Initially, the ester linkages between alkyl chains and the aromatic ring are hydrolyzed to form monoesters and then phthalic acid, while forming alcohols simultaneously (Amir et al. 2005). Secondary oxidation steps via the 3-oxoadipate pathway cleave the phthalic acid aromatic ring (Chatterjee and Karlovsky 2010). Biodegradation of phthalate esters may be preceded by a lag phase, and is thought to be related to the abundance of organisms with the specific ability to degrade phthalate isomers (Kleerebezem et al. 1999). Fungal degradation pathways of phthalates differ from bacterial degradation and are attributed to strong extracellular ligninolytic enzyme peroxidases and laccases (Kim et al. 2002; Liang et al. 2008). In addition, phytoplankton has also been shown to biodegrade phthalate esters, including DEHP, under sufficient nutrient and illumination conditions (Li et al. 2007).

The biodegradation of phthalate esters releases monoalkyl phthalate esters (MPEs) into the environment (McConnell 2007). Most studies suggest that biodegradation rates of MPEs proceed faster than those of phthalate esters (Peterson and Staples 2003). Moreover, studies on the biodegradation of short- and longer-chain MPEs, including mono-*n*-butyl-, mono-isobutyl-, mono-2-ethylhexyl phthalate-, mono-isononyl, mono-*n*-hexyl/*n*-octyl/*n*-decyl-, and mono-*n*-octyl/*n*-decyl- side chains, show that all these substances are readily biodegradable (Scholz 2003). The environmental fate of MPEs is largely unknown, but according to Peterson and Staples (2003), based on model evidence, MPEs partition more strongly to water than to solids in wastewater treatment systems given the differences in hydrophobicity. In sediments, MPE biodegradation rates are not affected by sorption because monoesters are largely ionized at environmental pH levels; sediment half-lives of various MPEs, including MEHP and MBP, were determined to be in the range of 0.34 to 2 days (Otton et al. 2008; Kickham et al. 2012). McConnell (2007) investigated the distribution of MPEs in a marine ecosystem, and levels of MPEs were detected in both water and sediment samples. It has been observed that MPEs degrade at a common rate, that is to say, the structure of the functional side group does not affect the rate of biodegradation.

At low concentrations, biodegradation rates of phthalate esters have been observed to be very slow, in other words, biodegradation occurs until levels fall to the order of parts per billion (ppb) and then biodegradation ceases, resulting in ubiquitous background levels of phthalates (Rubin et al. 1982; Boethling and Alexander 1979). This phenomenon has been attributed to the general inability of bacteria to produce metabolic enzymes at low concentrations (Peterson and Staples 2003) and to the characteristics of the bacteria capable of chemical biodegradation. This is true of the eutrophs, capable of growing at a high concentration of a chemical but with low capacity for its degradation at low concentrations, and the oligotrophs, which can degrade chemicals at low concentrations but are less specific to the target chemical (Rubin et al. 1982). Boethling and Alexander (1979) hypothesized that the energy obtained from

oxidizing chemicals at low concentrations may be insufficient to meet the energy demands of the microorganisms, limiting the proliferation of the organisms to levels needed to cause appreciable loss of the chemical. Other explanations included the lack of bioavailability for biodegradation due to particle adsorption and, simply, contamination of laboratory equipment (Peterson and Staples 2003). Despite their inherent biodegradability, phthalate esters exhibit long half-lives in sediments due to the high degree of sorpion driven by their hydrophobicity (Kickham et al. 2012).

7.2.2.1 Inherent and ready biodegradation by sludge microorganisms

Most phthalate esters are biodegradable by micoorganisms, and first-order kinetics is frequently used to describe their biodegradation (Liang et al. 2008). Numerous inherent and ready biodegradation studies have been conducted using microorganisms found in activated sludge and, in some studies, pre-adapted sludge and varying concentrations of the test substances, to determine the biodegradation potential of phthalate esters in water.

In addition to published studies, the unpublished industry studies summarized for the EU Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH) were considered; study summaries were available from ECHA (c2007–2014a).

Table 7-2-2. Summary of key empirical data for biodegradation of medium-chain phthalates and analogue substances in water

Common name	Fate process	Degradation value	Degradation endpoint/units	Test method; date	Reference
DIBP	Aerobic biodegradation 28 days (activated sludge)	98	% BOD	OECD Guideline 302C (Inherent Biodegradability: Modified MITI Test (II)); study report dated 2002	ECHA c2007–2014b
DIBP	Aerobic biodegradation 28 days (non-adapted sludge)	66–70	% BOD	OECD Guideline 301D (Inherent Biodegradability: Closed Bottle Test); study report dated 2007	ECHA c2007–2014b
DIBP	Aerobic biodegradation (activated sludge) 28 days	98	% BOD	OECD Guideline 301C (Ready Biodegradability: Modified MITI Test (I)); study report dated 2002	ECHA c2007–2014b
DIBP	Aerobic biodegradation 14 or 28 days	42	% degradation measured as CO_2 evolution	OECD Guideline 301B (Ready Biodegradability: CO_2 Evolution Test); study report dated 2010	ECHA c2007–2014b

DIBP	Aerobic biodegradation (activated sludge) 14 days; 28 days	60–70 70–80	% CO_2 evolution	OECD Guideline 301B (Ready Biodegradability: CO_2 Evolution Test); report dated 2007	ECHA c2007–2014b
DCHP	Aerobic biodegradation 28 days	68.5; 91	% BOD; % degradation	Not specified; study performed from 1976 to 1977	ECHA c2007–2014c
B79P	Aerobic biodegradation 24 hours (activated sludge)	57–81	% degradation	OECD Guideline 302A (Inherent Biodegradability: Modified SCAS Test); 1981	ECHA c2007–2014d
B79P	Aerobic biodegradation 28 days (pre-adapted activated sludge)	83	% degradation	ASTM shake flask procedure; 1979	ECHA c2007–2014d
BBP (analogue to BCHP, CHIBP, DBzP)	Aerobic biodegradation 14 days (activated sludge)	81	% BOD	OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I)); 1992	ECHA c2007–2014e
BBP (analogue to BCHP, CHIBP, DBzP)	Aerobic biodegradation 27 days (activated sludge)	93	% CO_2 evolution	Analytical Chemistry Method 71-42 (SCAS test); 1976	ECHA c2007–2014e
BBP (analogue to BCHP, CHIBP, DBzP)	Aerobic biodegradation 27 days (acclimated bacteria)	96	% CO_2 evolution	Thompson-Duthie-Sturm procedure; 1976	ECHA c2007–2014e
BBP (analogue to BCHP, CHIBP, DBzP)	Aerobic biodegradation 2 days (activated sludge)	50	% degradation	River Die-Away Procedure; 1976	ECHA c2007–2014e
BBP (analogue to BCHP, CHIBP, DBzP)	Aerobic biodegradation (activated sludge) 24 hours; 48 days	99; 93–99	% degradation	Primary biodegradation	Graham 1973; Saeger and Tucker 1976
DIOP	Aerobic biodegradation (activated sludge) 24 hours; 4 days	84.5; > 90	% degradation	Combined SCAS and activated sludge die-away procedure	O'Grady et al. 1985

DEHP (analogue to DIHepP)	Aerobic biodegradation 29 days (activated sludge from a region where DEHP is produced)	82	% CO_2 evolution	OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test); 1994	ECHA c2007–2014f
DEHP (analogue to DIHepP)	Aerobic biodegradation 28 days (activated sludge)	4–5	% CO_2 evolution	OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test); 1990	Struijs and Stoltenkamp 1990; ECHA c2007–2014f
DEHP (analogue to DIHepP)	Aerobic biodegradation 28 days (activated sludge from industrial source)	60–70	% BOD	EU Method C.5 (Degradation: Biochemical Oxygen Demand) from EG-guideline 79/831; 1984	ECHA c2007–2014f
DEHP (analogue to DIHepP)	Aerobic biodegradation 28 days (activated sludge)	63	% BOD	OECD Guideline 301 F (Ready Biodegradability: Manometric Respirometry Test); 1995	ECHA c2007–2014f

Abbreviations: BOD = biological oxygen demand; SCAS = Semi-Continuous Activated Sludge procedure; OECD = Organisation for Economic Co-operation and Development

Data from biodegradation studies using activated sludge were available for DCHP, DIOP, DIBP, B79P, BBP and DEHP. Inconsistent results were reported in some cases, for example for DEHP. These differences in biodegradation rates can be attributed to differences in experimental protocols and concentrations of the test substance and the substrate.

For DCHP, a single biodegradation study was summarized on ECHA (c2007–2014c). The study was performed between August 1976 and January 1977. Degradation of 25 µg/L of DCHP was followed for 28 days. The percentage of biological oxygen demand (BOD) was measured as 68.5, and the substance was found to be 91% degraded, as measured by gas chromatography. Results indicated that under the test conditions, DCHP was readily degradable. Given the structural similarities between DCHP and DMCHP, it is expected that DMCHP is also readily degradable.

Several mineralization biodegradation studies for DIBP, conducted between 2002 and 2010 according to various OECD protocols, were summarized on ECHA (c2007–2014b). In three studies, biodegradation of DIBP was determined by percent BOD over 28 days. The test results ranged between 66 and 98% BOD, indicating that DIBP is readily biodegradable. Similar results suggesting ready biodegradation of DIBP were obtained in two studies that measured CO_2 evolution as an indication of biodegradation. In the 2007 study, at least 60% biodegradation was observed in 14 days and up to 80%

in 28 days, whereas the 2010 study indicated only 40% biodegradation of DIBP. The 2010 study summary is unclear with respect to the length of the study, as the final percent degradation is provided based on a 28-day duration. However, it is also indicated that the study was terminated after 14 days. This implies that 40% degradation occurred over 14 days, rather than 28 days. Overall, the majority of the available studies suggest that DIBP is readily biodegradable.

Two studies, a 24-hour study and a 28-day study, to determine biodegradation of B79P were summarized in ECHA (c2007–2014d). Study details were limited, and the results were provided only as percent degradation. B79P was found to be both inherently and readily biodegradable under the test conditions of both the 24-hour study and the 28-day study, respectively. The percent degradation reported was as high as 83% in 28 days. It is noted that in the 28-day study (ECHA c2007–2014d), pre-adapted activated sludge was used, whereas the condition of the activated sludge was not specified in the 24-hour study. Given that up to 80% biodegradation of B79P was observed in 24 hours, it is possible that pre-adapted sludge was also used in this study.

Three biodegradation studies for BBP, conducted in the 1970s and in 1992, were summarized on ECHA (c2007–2013e). The substance was observed to be readily biodegradable, based on percent BOD (81% BOD in 14 days) (ECHA c2007–2013e) and percent CO_2 evolution (over 90% CO_2 evolution in 27 days) (ECHA c2007–2013 e, f). In another study (ECHA c2007–2013e), also measuring percent CO_2 evolution as an indication of biodegradation, it was found that BBP degraded by 50% in 2 days. Graham (1973) reported 99% biodegradation in 48 hours in activated sludge, with similar results (93–99% biodegradation in 24 hours) also reported by Saeger and Tucker (1976).

Several biodegradation studies were also available for DEHP (ECHA c2007–2014f). Two ready CO_2 evolution biodegradation studies, conducted according to the same protocol (i.e., OCED 301B) in the 1990s, showed contradictory results. In one study from 1992, DEHP was shown to be readily biodegradable in 28 days, with observed 82% CO_2 evolution (ECHA c2007–2014f). In contrast, in the 1990 study, only 4–5% CO_2 evolution was observed after 28 days (Struijs and Stoltenkamp 1990; ECHA c2007–2014f). Both studies used activated sludge, but in the 1994 study, sludge from a sewage treatment plant located in a region with major producers of DEHP was used. Therefore, it is possible that microorganisms used in the 1994 study may have been pre-adapted to DEHP from local manufacturing activities. In another earlier study from 1984, using sludge from an industrial source, also likely pre-adapted to DEHP, between 60 and 70% BOD was observed after 28 days (ECHA c2007–2014f). Ready biodegradation, measured as 63% BOD, was observed in a 1994 manometric respirometry study (ECHA c2007–2013l). In this study, an eight-day lag-phase that preceded biodegradation of DEHP was reported. Rapid primary biodegradation of DEHP in activated sludge was reported by Graham (1973) and O'Grady et al. (1985), were 91% biodegradation in 48 hours and 81.5% biodegradation in 24 hours were observed in each study, respectively, and over 90% biodegradation was achieved between 2 and 5 days (O'Grady et al.1985). O'Grady (1995) also reported rapid primary

biodegradation for DIOP, where nearly 85% of the substance was found to biodegrade in 24 hours and over 90% in 4 days.

In summary, medium-chain phthalates are readily biodegradable by microorganisms found in activated sludge. Rates of biodegradation for DCHP, DIOP, DIBP, B79P, BBP and DEHP were generally rapid, but some variability was observed, likely due to non-standard experimental conditions. For example, the use of pre-adapted sludge may have accelerated or aided biodegradation of B79P. However, these results are similar to the majority of degradation values observed for other medium-chain phthalates, where activated sludge was used as substrate rather that pre-adapted sludge. Given that the medium-chain phthalates are generally structurally similar, they are considered both inherently and readily degradable.

Modelled primary and ready biodegradation

(Q)SAR models EPI Suite 2012 and CATALOGIC 2012 were also used to evaluate inherent and ultimate biodegradation potential of the medium-chain phthalates. SMILES and, when available, physical chemical properties, such as water solubility and log K_{ow}, were used as model inputs. Medium-chain phthalates were found to be amenable to model predictions, with the exception of two substances, B84P and BIOP, determined to be outside of the model domain of the model CATALOGIC (2012). However, since the CATALOGIC (2012) results for B84P and BIOP were consistent with the results generated for all substances, they were considered to be acceptable and were included in the assessment.

The (Q)SAR-determined biodegradation rates for substances in the medium-chain subgroup were relatively rapid. Results for DIBP, BCHP, CHIBP, DCHP, DMCHP, DIHepP and BIOP based on BIOWIN submodels 3, 4, 5 and 6 universally showed fast biodegradation rates; primary biodegradation based on submodel 4 was estimated to be in the range of days to weeks, and the ultimate degradation half-lives calculated based on CATALOGIC (2012) were between 11 to 37 days. It is noted that the calculated half-life for DIHepP was the longest among the medium-chain phthalates, which was expected for a phthalate ester of a larger molecular size. However, its nearly linear side chains may be amenable to fast biodegradation as suggested by BIOWIN submodels. Model results are summarized in Table 7-2-3.

Slightly slower biodegradation rates were determined for DBzP, B84P and B79P. These results are consistent with the observation that phthalates with longer and more complex ester side groups are less biodegradable. B84P is the largest phthalate in the medium-chain phthalate subgroup. The primary biodegradation for DBzP, B84P and B79P was determined to be in the order of weeks, whereas results from the ultimate biodegradation models varied, with BIOWIN submodel 3 suggesting biodegradation rates in the order of weeks to months, and BIOWIN submodel 6 indicating that these substances were not readily biodegradable. Half-lives calculated based on CATALOGIC (2012) results ranged from 14 to 21 days. Model results are summarized in Table 7-2-4.

Overall, the model results indicate that substances in the medium-chain phthalate subgroup are readily biodegradable and are in agreement with the experimental biodegradation data, including that for the analogue phthalate esters BBP and DEHP. Based on the model results, the following ranking for rates of biodegradation of the medium-chain phthalates is proposed:

DIBP > BCHP, CHIBP, DBzP, DCHP, DMCHP > B79P, BIOP, B84P > DIHepP

DIBP, the smallest and simplest phthalate in the medium-chain subgroup, is expected to be most easily degradable. DIHepP is expected to be the least degradable, which is consistent with the experimental data available for its analogue substance DEHP showing lowest biodegradation rates.

Table 7-2-3. Summary of modelled primary and ultimate biodegradation data for DIBP, BCHP, CHIBP, DCHP, DMCHP and DIHepP

Fate process	Degradation endpoint or prediction	Test method or model basis	Model-assigned or calculated half-life ($t_{1/2}$ = days)	Reference
Primary aerobic degradation	3.1–4.1 (biodegrades fast; "days–weeks")	Submodel 4: Expert Survey (qualitative)	n/a	BIOWIN 2010
Ultimate aerobic degradation	2.7–3.1[a] (biodegrades fast; "weeks to months")	Submodel 3: Expert Survey (qualitative)	n/a	BIOWIN 2010
Ultimate aerobic degradation	0.5–0.7[b] (biodegrades fast)	Submodel 5: MITI linear probability	n/a	BIOWIN 2010
Ultimate aerobic degradation	0.3–0.8[b] (biodegrades fast)	Submodel 6: MITI non-linear probability	n/a	BIOWIN 2010
Ultimate aerobic degradation	40–80 (biodegrades fast)	% BOD	11–37[c]	CATALOGIC 2012

Abbreviation: BOD = biological oxygen demand
[a] Output is a numerical score from 0 to 5.
[b] Output is a probability score.
[c] Calculated based on first-order kinetics.

Table 7-2-4. Summary of modelled primary and ultimate biodegradation data for DBzP, B84P, B79P and BIOP

Fate process	Degradation endpoint or prediction	Test method or model basis	Model-assigned or calculated[c] half-life ($t_{1/2}$ = days)	Reference
Primary aerobic degradation	3.7–3.8 (biodegrades fast, "weeks")	Submodel 4: Expert Survey (qualitative)	n/a	BIOWIN 2010
Ultimate aerobic degradation	2.4–2.7[a] (biodegrades fast, "months")	Submodel 3: Expert Survey (qualitative)	n/a	BIOWIN 2010
Ultimate aerobic degradation	0.3–0.6[b] (biodegrades fast)	Submodel 5: MITI linear probability	n/a	BIOWIN 2010
Ultimate aerobic degradation	0.1–0.2[b] (biodegrades slowly)	Submodel 6: MITI non-linear probability	n/a	BIOWIN 2010
Ultimate aerobic degradation	50–70 (biodegrades fast)	% BOD	$t_{1/2}$ = 14 – 21[c]	CATALOGIC 2012

Abbreviation: BOD = biological oxygen demand
[a] Output is a numerical score from 0 to 5.
[b] Output is a probability score.
[c] Calculated based on first-order kinetics.

7.2.2.2 Biodegradation in surface waters and sediments

Phthalate esters have been detected in freshwater worldwide and tend to adsorb to sediments (Chang et al. 2005). Most phthalate esters are readily biodegradable in surface waters (Furtmann 1994). Both aerobic and anaerobic microorganisms found in sediments can degrade phthalate esters (Hashizume et al. 2002; Chang et al. 2004; Kim et al. 2008), although they are not as abundant as isolates from activated sludge or soil. Abiotic biodegradation rates for phthalate esters with longer side chains tend to be slow (Lertsirisopon et al. 2006).

Furtmann (1994) reported that DIBP and DCHP in samples of Rhine, Ruhr and Emscher river water from Germany were subject to rapid primary degradation at 20°C. At 4°C, the degradation was delayed by as much as 3 to 4 days. The addition of sodium azide (bacteriostatic poison of cytochrome oxidase in mitochondria) stopped the degradation processes. Hashizume et al. (2002) observed complete biodegradation of DIBP over 7 days in river water samples collected from urban Japan.

Both phthalate esters and their primary metabolites, monoalkyl phthalate esters, have the capacity to be quickly degraded by microbes in sediments. However, their

biodegradation rates decrease with increasing sorption, and this can result in long sediment half-lives for those phthalates with higher K_{oc} values (Kickham et al. 2012).

Monoalkyl phthalate esters were shown to be quickly degraded in natural sediments (Otton et al. 2008). In this study, biodegradation rates measured at 22ºC did not differ between marine and freshwater sediments, and no apparent relationship between the degradation half-life and the length or extent of branching of the monoester alkyl-chain was observed. Half-lives of eight monoalkyl esters tested (characterized by ethyl-, butyl-; benzyl-; *iso*-hexyl-; ethylhexyl-; *n*-octyl; *iso*-nonyl-; iso-decyl- alkyl side chain) ranged from 16 to 39 hours at 22ºC in freshwater and marine sediments, and were somewhat longer, up to 200 hours at 5ºC in freshwater sediments (Otton et al. 2008). Lower temperatures cause a lower microbial activity, thereby limiting biodegradation.

Yuan et al. (2002) studied biodegradation of eight phthalates, including DEHP, in river sediment in Taiwan. Average aerobic half-lives ranged from 2.5 to 14.8 days, with anaerobic half-lives being longer, in the range of 14.4 days to 34.7 days. Yuwatini et al. (2006) estimated the biodegradation half-life of DEHP in sediment to be about 14 days.

Anaerobic biodegradation in sediments of DBP (similar to DIBP), BBP and DEHP was studied by Lertsirisopon et al. (2006). DBP and BBP were degraded in a few days (average half-lives for DBP and BBP were 1.4 and 1.8 days, respectively) and were preceded by short lag phases (up to 0.7 days for DBP and 1.4 days for BBP). DEHP, characterized by longer alkyl chains, was degraded with a 5-day lag phase and an average half-life of 252 days. Kickham et al. (2012) determined sediment half-lives for BBP and for DEHP and DINP to be 2.9 and 347 days, respectively.

7.2.2.3 Biodegradation in soils

The pathways and rates of biodegradation for phthalate esters in different types of soils were studied. Soil biodegradation was identified for DIBP (Ferreira and Morita 2012), but not for the remaining phthalates in the medium-chain subgroup. In contrast, numerous data were available for the analogue substance DEHP (Gejlsberg et al. 2001; Scheunert et al. 1987; Wang et al. 2009; Schmitzer et al. 1988; Madsen et al. 1999). DEHP is considered to be a good analogue to DIHepP. However, the findings from the numerous studies on DEHP can also be applied generally to the medium-chain phthalate subgroup. DEHP tends to be most slowly biodegraded of the medium-chain phthalates and, therefore, biodegradation rates for the substances in the medium-chain phthalates subgroup are expected to not exceed or to be equal to those of DEHP.

The patterns for biodegradation rates of phthalate esters in soil are very similar to those in water (Peterson and Staples 2003). Both the length and the branching of the ester side group affect biodegradation rates. Short and linear phthalates tend to be degraded faster, whereas slower biodegradation rates were observed for phthalates with longer and branched side groups (Zeng et al. 2004). Increased temperature appears to speed up soil biodegradation rates (Rüdel et al. 1993; Chen et al. 1997; Chang et al. 2009). Madsen et al. (1999) noted that doubling temperature resulted in the doubling of the

degradation rate for DEHP. Soil moisture also affects the degradation rates of phthalate esters, where higher soil moisture contributes to greater rates of biodegradation and mineralization (Peterson and Staples 2003). Finally, aerobic conditions are expected to result in faster biodegradation rates in soil. For DEHP, slower biodegradation rates were observed in anaerobic conditions (Madsen et al. 1999; Sheunert et al. 1987).

Biodegradation of DIBP in bioremediated soil from an industrial site in São Paulo, Brazil, was investigated by Ferreira and Morita (2012). Using a first-order kinetics equation (half-life = ln2/k) and the degradation rate constant (k) of 0.01 provided in Ferreira and Morita (2012), the half-life of DIBP can be calculated as 69.3 days. Reported half-lives (calculated using first order kinetics) for DEHP in different types of soil range from 2 days in loam soil to 69.3 days in sand (Rüdel et al. 1993; Shanker et al. 1985; Roslev et al. 1998; Peterson and Staples 2003) and up to 77 days in bioremediated soil from the industrial site in Brazil (Ferreira and Morita 2012).

The mineralization of DEHP in soil starts with a lag phase (observed in some studies) and then follows two distinct kinetic phases: the initial phase over approximately 30 days that follows first-order kinetics, followed by a slower late phase (Dörfler et al. 1996; Peterson and Staples 2003). The phenomenon known as “sequestration,” whereby a hydrophobic chemical penetrates into solid particles and is no longer surface-adsorbed and available to extraction solvents, was put forward by Peterson and Staples (2003) as a possible explanation for the slow degradation phase of DEHP. The DEHP half-life for the initial phase was calculated as 58 days, and 147 days for the late phase (Dörfler et al. 1996). Similarly, in a soil study by Wang et al. (2009), there was a lag phase of approximately 5 days for degradation of DEHP at all concentrations tested (ranging from 10 to 1000 mg/kg), followed by rapid degradation in the first 30 days to as low as 10% of the initial concentration at the lowest test concentration of 10 mg/kg. In this study, degradation past 30 days remained stable with no further appreciable decreases in concentration until the end of experiments at 55 days. The extent of DEHP biodegradation was shown to be dependent on the initial substance concentration, as at 55 days DEHP biodegraded to less than 10% in the lowest 10 mg/kg treatment, and to over 20 to 35% in the 50 to 1000 mg/kg treatments, respectively. The dependence of DEHP biodegradation rates on the initial concentrations was also shown by Fairbanks et al. (1985), where half-lives were two- to four-fold longer at higher concentrations, and by Dörfler et al. (1996), where higher initial substance concentrations resulted in slower biodegradation.

Environmental conditions, such as temperature, soil moisture and oxygen levels, as well as initial substance concentration and the type of soil all have an impact on the biodegradation rate of phthalate esters. Biodegradation of phthalate esters is also known to be affected by the length and complexity of the ester side groups. Biodegradation of DEHP seems to proceeds in two phases, a rapid biodegradation phase and a slow phase, which can be preceded by a lag phase. This may or may not be the case for the substances in the medium-chain phthalate subgroup, in particular the initial lag phase, since similar degradation studies have not been conducted for these substances. It is considered, however, that the soil half-lives determined for

DEHP, ranging from 2 to up to approximately 77 days, can be representative of the medium-chain phthalate grouping. The soil half-life for DIBP was determined to be 69.3 days.

7.3 Potential for bioaccumulation

The discussion on the potential for bioaccumulation considers several potential parameters, including the substance properties (i.e., log K_{ow}, log K_{oa}), bioconcentration factor (BCF), biomagnification factor (BMF), food web magnification factor (FWMF) and bioaccumulation factor (BAF). The role of metabolism in determining bioaccumulation potential is also examined.

Empirical bioaccumulation data were available for two substances in the medium-chain phthalate subgroup, DIBP and DIHepP. Data-rich BBP will be used as an analogue for BCHP, CHIBP and DBzP, and DEHP will be used as an analogue for DIHepP where data on the target compounds are not available (i.e., BCF). Refer to Section 2.1 for the analogue selection rationale. Modelling data are used to inform the bioaccumulation evaluation of the remaining medium-chain phthalates.

The log K_{ow} values for the medium-chain phthalates range from 4.11 to 6.92, suggesting that they can partition to biota from water and other media. Results from the laboratory studies discussed below indicate that other factors come into play that influence the bioaccumulation of phthalates, such as metabolism.

7.3.1 Bioconcentration factor (BCF)

Bioconcentration data are only available for the analogue substances BBP and DEHP, which are being used as read-across for BCHP, CHIBP, DBzP and DIHepP (refer to Section 2.1 for analogue selection rationale). Studies show that BCFs range from 188 to 1890, with a median value of 663, using calculations based on total and dissolved concentrations (Table D-1 in Appendix D).

Ratzlaff (2004) performed bioconcentration studies on several phthalates to determine how BCF values are affected when different analytical methods are used to measure phthalate concentrations in water. With their moderate to high K_{ow}, it is expected that some of the medium-chain phthalates would be associated with organic matter, thereby reducing their bioavailability. Measured water concentrations that include the fraction sorbed to organic matter would be expected to overestimate the amount of dissolved phthalates in the system and underestimate the BCF. Measuring the freely dissolved concentrations would include only this bioavailable fraction that can be absorbed via the respiratory surface of fish and, therefore, bioconcentrated. Ratzlaff (2004) exposed rainbow trout to BBP for 61 days, and BCFs were calculated based on both the total water concentrations (including fraction associated with organic matter) and the operationally defined freely dissolved water concentrations. As some phthalates were sorbed to small-diameter (< 0.45 µm) particulate matter and were still measured in the

operationally defined freely dissolved concentration, a model was also used to predict the freely dissolved concentrations based on the three-phase sorption model using the K_{ow}, K_{oc}, organic carbon content, concentration of small suspended matter and degree of chemical disequilibrium between the small-diameter suspended matter and the water. Generally, BCFs increased over the duration of the uptake period and then reached a maximum value by day 21, indicating that steady state was reached. As expected, the freely dissolved water concentrations of BBP were lower than total water concentrations. The corresponding BCFs using the operational freely dissolved water concentration were higher (BCF 1890) than those calculated using the total water concentration (BCF 918). The BCF based on the predicted freely dissolved concentration was much higher, with a predicted value of 11500.

Carr et al. (1997) exposed bluegill sunfish to 0.034 mg/L of BBP over 3 days and measured BBP in the fish. An exposure duration of 3 days was selected based on a previous study (Monsanto, unpublished) that had shown that equilibrium in bluegill tissues was reached after 3 days (Carr et al. 1997). This is significantly less than the 21 days identified by Ratzlaff (2004) required to achieve steady state in rainbow trout. Experiments that use short exposure times have a tendency to underestimate the BCF, since steady state conditions may not be achieved (Staples 2003). In fact, by measuring BBP in bluegill sunfish tissues, Carr et al. (1997) calculated a $BCF_{whole\ fish}$ of 9.4, which is lower than the BCF of 918 obtained by Ratzlaff with the longer exposure, based on total BBP concentration. Carr et al. (1997) also calculated the BCF using radiolabelled BBP and obtained a BBP equivalent $BCF_{whole\ fish}$ of 194, which is in line with results from earlier tests that measured total radioactivity and would have included metabolites in the measurement.

Studies that measure C-14 labelled BBP are available. However, it has been noted by Carr et al. (1997) that these calculations overestimate bioconcentration, since metabolites cannot be distinguished from the parent substance. An unpublished BCF study is summarized in detail in the ECHA database (ECHA c2007–2013), which involved a flow-through test using radiolabelled BBP at exposure concentrations of 0.002 mg/L over 21 days. It was found that BBP has a low potential to bioconcentrate in bluegill sunfish, with a BCF of 188 for the whole body. Concentrations were also measured in the muscle and viscera, and were found to concentrate more in the viscera than the muscle (BCF values of 1693 compared to 29).

Barrows et al. (1980) exposed bluegill sunfish to C-14 labelled BBP in flow-through conditions. Fish and water samples were collected throughout the test for 21 days, when equilibrium was reached. With an average water concentration of 0.0097 mg/L, a whole body BCF of 663 was calculated. Following the exposure phase, the fish were placed in a clean aquarium so that depuration could be monitored.

The empirical bioconcentration data indicate that BBP is quickly metabolized by fish. Carr et al. (1997) compared intact BBP measurements to radioactivity in tissue, and calculated that more than 90% of the radiolabelled compounds in the fish tissue were metabolites of BBP. The reduction of intact BBP in fish tissue was determined to be

influenced by metabolism of BBP and the exposure of BBP degradation products directly from water and subsequent metabolism, as the concentration of BBP in solution was observed to decrease over the 3-day exposure period.

Ratzlaff (2004) measured the BBP monoester metabolite monobenzyl phthalate in fish that were exposed to BBP; however, it was not detected. It was noted that the MDL was quite high (31.3 ng/g) due to the relative insensitivity of the new analytical technique.

McConnell (2007) measured phthalate ester metabolites in biota in False Creek Harbour, British Columbia, in 2005. The metabolite of DIHepP, monoheptyl phthalate (referred to as MC7P), was detected in samples of blue mussel, softshell Cclam, dungeness crab and juvenile shiner perch in concentrations ranging from 6.9 to 350 ng/g lipid equivalent, but was not detected in the higher trophic level white spotted greenling or spiny dogfish (where the MDL ranged from 0.018 to 41 ng/g wet weight [ww]). In most cases, the DIHepP concentration was greater than the metabolite concentration. The metabolite of the analogue BBP, monobenzyl phthalate (MBzP), was found only in blue mussel and juvenile Shiner Perch, and BBP was detected in higher concentrations than MBzP.

A study by Mayer (1976) calculated BCFs for DEHP using both C-14 labelled DEHP and concentrations of the parent compound measured by gas chromatography. Reported BCF values in the fathead minnow based on total reactivity ranged from 155 to 886 over a 56-day exposure period, while the BCF values based on actual DEHP concentrations ranged from 91 to 569. Fish were exposed to concentrations of C-14 labelled DEHP ranging from 0.0019 to 0.062 mg/L, the lower concentrations being within the range of solubility for DEHP (0.003 mg/L). The BCFs were found to decrease with increasing exposure concentrations, and the authors suggest that this may be due to the induction of detoxification enzymes in the liver and an increase in the DEHP degradation and elimination. These values suggest that DIHepP would also have a low potential for bioaccumulation.

BCF estimates were generated using a modified three-trophic-level version of the Arnot-Gobas mass balance model (Arnot and Gobas 2003) for a middle-trophic-evel fish weighing 184 g. The modelled data are considered to be reliable, as the medium-chain phthalates fall within the parametric and metabolism domains of the model. Table D-2 in Appendix D lists the BCF predictions for each of the medium-chain phthalates, which range from 29 to 237 L/kg ww and include biotransformation rate estimates (k_M). The experimental BCF data for BBP, the analogue for BCHP, CHIBP and DBzP, ranges from 9.4 to 1890. The BCFBAF models predict a BCF in the range of 17 to 112 L/kg for these substances, indicating that the k_M in the model is perhaps overestimated at 3.4, 3.8 and 25. The metabolic biotransformation rate constant database from Arnot et al. (2008a) contains k_Ms for higher-molecular-weight phthalates, with values for diisoheptyl phthalate of 1.17/day and diisononyl phthalate of 3.52/day, which suggest that particularly the k_Ms of 25 for DBzP and B84P are overestimated. Using the k_M of 3.52/day generates a BCF estimate of 96 L/kg and 45 L/kg for DBzP and B84P, respectively (Arnot et al. 2008b). Nevertheless, the model and experimental

bioconcentration data and measurement of metabolites in aquatic organisms suggest that the medium-chain phthalates are subject to metabolism and thus do not tend to significantly bioconcentrate.

7.3.2 Bioaccumulation factor (BAF)

Bioaccumulation factors are measured under field conditions as the ratio of the whole body burden of chemical taken up from all exposures to that of the ambient water concentrations. Measures of BAF are a preferred metric for assessing the bioaccumulation potential of substances because it incorporates all chemical exposures, including diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003). BAF studies were not found in the published literature for the medium-chain phthalates; however, a thesis by Mackintosh (2002) calculated BAFs for DIBP, DIHepP, DEHP and BBP, among other phthalates, in 18 organisms in a marine food web. The mean BAF values for DIBP, DIHepP, DEHP and BBP in green algae, sculpin and dogfish muscle can be found in Table D-3, in Appendix D, and are expected to represent three levels of the False Creek food web (1st, 3rd and 4th trophic levels, respectively). Ranges and medians obtained by Mackintosh (2002) are presented in Table 7-4.

Table 7-4. Summary of bioaccumulation factors for medium-chain phthalates

Substance	Endpoint	Range of values (L/kg)	Median (L/kg)	Reference
DIBP	BAF, ww[1]	34–776	143	Mackintosh 2002
DIHepP	BAF, ww[1]	12–3236	125	Mackintosh 2002
BBP	BAF, ww[1]	186–8709	717	Mackintosh 2002
DEHP	BAF, ww[1]	4.9–1097	38	Mackintosh 2002

[1] BAF calculations are based on total water concentrations (including phthalates bound to large- and small-diameter suspended matter and freely dissolved) and have been converted from their log BAF values reported in the study.

Mean BAF values calculated by Mackintosh (2002) indicate that medium-chain phthalates have a low potential for bioaccumulation, with most BAFs reported below 1000 and almost all BAFs below 3000. An exception was the BAF of 8709 L/kg that was calculated for BBP in the surf scoter, based on liver sample analysis only. The location of the samples and differences in foraging area may also contribute to these differences in BAF, as the surf scoter occupies a larger foraging area and is more mobile than the other organisms in the study.

The steady-state middle-trophic-level bioaccumulation model published by Arnot and Gobas (2003) predicts BAFs for the medium-chain phthalates in the range of 1.48 to 2.6 L/kg ww using the same k_Ms as the BCF predictions and a dietary uptake efficiency of 1% for each phthalate to account for gut metabolism (Table D-2 in Appendix D). Studies with DBP, BBP and DEHP in staghorn sculpin have demonstrated that these substances are very effectively transformed in the gut with no significant accumulation

from dietary exposure, indicating very low (< 0.01) assimilation efficiencies (Webster et al. 2003). All BCF and BAF predictions are below 1000, suggesting that the medium-chain phthalates have a low potential to bioaccumulate. Experimental BAF values in sculpin for DIBP and BBP of 78 and 631 L/kg are higher than the modelled BAF values, with predictions of 34.31 for DIBP and 117, 104 and 17 for BCHP, CHIBP and DBzP, respectively. Differences could be due to the assumptions used in the model.

7.3.3 Biota-sediment accumulation factor (BSAF)

BSAF is a parameter describing bioaccumulation of sediment-associated compounds into tissues of ecological receptors (Burkhard 2009). Because of the different sorptive capacities of lipid and organic carbon, equilibrium is represented by a value of three, as the sorptive capacity of organic carbon is 0.35 times that of octanol (lipid). A BSAF greater than three is therefore an indication of more chemical in biota compared to sediment (Morin 2003). Alternatively, ASTM (1997) recommends a “cut-off” value of 1.7 to represent equilibrium conditions. BSAFs that exceed approximately 1.7 to 3 (on a normalized basis) indicate more uptake than can be explained by partitioning theory alone (bioaccumulation is occurring).

In a review of the bioaccumulation of phthalate esters in aquatic food webs, Gobas et al. (2003) describe a disequilibrium that occurs between sediment pore water and overlying water for all phthalate esters, to varying degrees. They found that sediment pore water concentrations were higher than overlying water concentrations, which would result in a higher degree of direct exposure to a sediment-burying invertebrate than to epibenthic organisms that inhabit the epilimnion. Mackintosh (2002) calculated the BSAF values of phthalate esters in 18 organisms in the marine food web by dividing the mean lipid normalized biota concentration by the mean organic carbon normalized sediment concentration. Calculated BSAFs for DIBP, DIHepP, BBP and DEHP were below 1.7 (values can be found in Table D-3 in Appendix D), even for sediment-burying invertebrates like the Geoduck Clam and the Manila Clam.

In a study on the distribution of phthalate esters (including DIBP and BBP) in mammals, fish, sediment and air in Hudson’s Bay, Morin (2003) calculated BSAF values of phthalate esters in the beluga whale and Arctic Cod. Sediment is considered a source of dietary exposure for the beluga whale, as it uses suction while scavenging for benthic organisms and could ingest sediment (Morin 2003). In Arctic cod, BSAF values are reported as 2.75 and 3.45 kg OC/kg lipid, for DIBP and BBP, respectively. Beluga whale BSAFs were 4.19 and 3.71 kg OC/kg lipid for DIBP and BBP, respectively (Morin 2003). Beluga whale BSAFs are similar to Arctic cod BSAFs and are close to unity, suggesting that sediment is not a major source of DIBP for the beluga whale. These BSAF values are higher than those measured in False Creek Harbour by Mackintosh (2002). Morin (2003) measured higher biota concentrations and lower sediment concentrations of DIBP in the Arctic. A discussion on possible explanations for higher concentrations in biota in the Arctic can be found in Section 8.2.1.5.

7.3.4 Biomagnification

Biomagnification describes the process in which the concentration of a chemical in an organism reaches a level that is higher than that in the organism's diet due to dietary absorption (Gobas and Morrison 2000). A biomagnification factor (BMF) greater than 1 indicates that biomagnification is potentially occurring. Food web magnification factors (FWMFs) are another measure of the degree of biomagnification in the food web, representing the average increase in lipid-equivalent chemical concentration for a unit increase in trophic position (Mackintosh et al. 2004). An FWMF greater than 1 indicates chemical biomagnification in the food web, while an FWMF less than 1 indicates trophic dilution. Few studies measured biomagnification of medium-chain phthalates and the analogue BBP.

Morin (2003) examined DIBP and BBP in adult beluga whale and Arctic cod tissues, and calculated lipid-equivalent biomagnification factors of 1.52 (cod to beluga; DIBP) and 1.07 (cod to beluga; BBP). These values suggest limited ability of these phthalates to biomagnify, as the values are close to unity (Morin 2003).

Field studies were conducted to determine the occurrence of biomagnification or trophic dilution for a variety of phthalate esters, including DIBP, BBP and DIHepP (identified as di-iso-heptyl, and referred to as C7 in the studies) (Mackintosh et al. 2004; McConnell 2007). The studies calculated FWMFs in a marine food web in False Creek Harbour, in British Columbia. Samples were taken from four trophic levels, and FWMFs were calculated using the phthalate concentrations in biota and the ratio of $^{15}N/^{14}N$, which has been shown to increase with trophic level (Mackintosh et al. 2004). Mackintosh et al. (2004) and McConnell (2007) calculated FWMFs for DIBP, BBP and DIHepP in the range of 0.38 to 0.94, indicating that biomagnification is not taking place (see tables D-4 and D-5 in Appendix D for all values). DIHepP was not detected in the muscle of the top predator, dogfish, which may reduce the power to detect statistically significant trends in the food web. Lipid-equivalent concentrations of DIBP, BBP and DIHepP appeared to decline slightly with increasing trophic position in the food web; however, the correlation was not statistically significant, suggesting that a small amount of trophic dilution may take place (Mackintosh et al. 2004).

McConnell (2007) also calculated FWMFs for the metabolite of DIHepP, MC7P, which was found to be 0.22 (McConnell 2007). It would be expected that the metabolites of the medium-chain phthalates would not biomagnify as they are more water soluble and more rapidly metabolized in the organisms.

The available biomagnification data are limited to just a few of the medium-chain phthalates and suggest that dietary exposure may not significantly contribute to trophic transfer and food web accumulation in the environment. This is consistent with the low to moderate BCF/BAF calculations and the observation that the medium-chain phthalates are metabolized by fish.

7.4 Summary of environmental fate

The medium-chain phthalates are expected to be released primarily to the aquatic medium through wastewatereffluents originating from industrial sources and through disperse releases from consumer products .Within the medium-chain phthalates subgroup, as the molecular weight of the phthalates increases, there is an increasing tendency to sorb to the solid phase in various media. Therefore, some medium-chain phthalates will tend to reside in sediments and in sludges, whereby they could also be transferred to soil from their application to agricultural lands. Medium-chain phthalates are not expected to undergo long-range transport based on modelled results. Nonetheless, DIBP, characterized by the lowest molecular weight in the subgroup, has been detected far from release sources, likely due to particle transport, a phenomenon that is not presently captured by (Q)SAR modelling. Abiotc and biotic degradation processes have been relatively well characterized for phthalate esters. Medium-chain phthalates are susceptible to degradation through abiotic processes, although these processes are very slow in the environment and are influenced by environmental conditions, such as pH and the presence of oxygen. In contrast, biodegradation processes can be relatively fast; however, substance-specific biodegradation rates and the degree of mineralization vary depending on the size and complexity of ester side groups, with the more complex and larger molecules having longer residence time in the environment. Biodegradation rates in soils and sediments are similar to those in water. Lower-molecular-weight medium-chain phthalates are more water soluble and are therefore more bioavailable to aquatic organisms. Bioaccumulation data were only available for a small subset of the subgroup, primarily for the substances that have lower molecular weights (i.e., DIBP and the analogue BBP) and suggest that the medium-chain phthalates have low to moderate potential for bioaccumulation. Bioconcentration studies suggest that these substances can be metabolized. Food web field studies indicate that bioaccumulation potential is not significant in the food web, as the medium-chain phthalates are not found to biomagnify in the food web.

8. Potential to Cause Ecological Harm

8.1 Ecological effects

Empirical aquatic toxicity data were available for the following medium-chain phthalates: DIBP, DCHP, B84P and B79P. These data were sourced from both published and unpublished studies. The unpublished industry studies were summarized for the EU Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemical Substances (REACH), and study summaries were available from the European Chemicals Agency website (ECHA c2007–2014a). Since limited study details were provided in some of the study summaries, multiple studies were used to compare the results.

Empirical data for DIBP, DCHP, B84P and B79P as well as information available for analogue substances BBP, DPhP and DIOP, along with (Q)SAR model data, were used to evaluate BCHP, CHIBP, DBzP, DMCHP and DIHepP.

It has been proposed that the lower-molecular-weight phthalates, including DBP and BBP (with molecular weights ranging from 278.34 to 312.35 g/mol), likely act through non-polar narcosis, based on the positive correlation of toxicity data to the K_{ow} values (Oehlmann et al. 2009). Adams et al. (1995) also described that lower-molecular-weight phthalates have higher toxicity relative to neutral organic non-specific narcotics, which would suggest that they would be classified as either polar narcotics or compounds having an "unspecified reactivity" mode of action. For higher-molecular-weight compounds (molecular weights greater than 312.35 g/mol), Rhodes et al. (1995) suggest that their data support a "solubility cutoff" mode of action, wherein aqueous solubility declines with increasing molecular weight, such that critical body burdens eliciting adverse effects cannot be achieved.

The potential for the medium-chain phthalates to cause effects on the endocrine system is well studied in mammals, but data on aquatic organisms is scarce. The ability to extrapolate the data obtained from these mammalian studies to other vertebrates or invertebrates is uncertain. Christiansen et al. (2000) point out that teleost fish, as compared with mammalian species, have lower xenobiotic metabolizing abilities, different hormonal control and sexual differentiation, and certain steroid hormone receptors that are specific to teleosts. The section on ecological effects is limited to the evaluation of aquatic toxicity studies, while the section on human health (Section 9.2) provides an evaluation of the mammalian data. Limited data on secondary endpoints (measured at the molecular, biochemical, cellular, tissue, blood or organ level) suggest that certain phthalates (such as BBP) may have the potential to cause endocrine effects; however, studies on primary endpoints (including development and reproduction) show no evidence of effects on the endocrine system . Studies on secondary endpoints that may be mediated by endocrine activity have not been conducted for any of the substances in the medium-chain phthalates subgroup. The use of an analogue for the evaluation of these effects, which are substance-specific and structure-dependent, is highly uncertain for aquatic organisms. They have therefore not been used as read-across or in the calculation of assessment factors for the medium-chain phthalates.

The ecological effects of the medium-chain phthalates are discussed below in the sections for each environmental compartment, namely water, sediment and soil.

In brief, available empirical toxicity information indicates that the medium-chain phthalates are highly to moderately toxic to aquatic organisms (with median lethal concentration [LC_{50}] values ranging from less than 1 to 10 mg/L). Aquatic toxicity data are compiled in Appendix E, in Tables E-1 and E-2.

Most aquatic toxicity studies with medium-chain phthalates measure primary endpoints, including survival, growth, development and reproduction. Secondary endpoints that may be mediated by endocrine activity and mechanisms of action other than narcosis are discussed in subsection 8.1.1.3 of the water compartment section. Available results are summarized in Appendix E in Table E-4.

While there is no information on potential effects in wildlife species, a number of studies examine toxicity in rodents (see Section 9.2). Chronic oral exposure to low levels of medium-chain phthalates, for example, through the ingestion of food, is a possible scenario of concern for wildlife. A detailed consideration of potential impacts in mammalian species is provided in the Health Effects Assessment (Section 9.2).

Monoester metabolites appear to exhibit less toxicity to aquatic organisms than their parent compounds. The effects are discussed in subsection 8.1.1.4.

Sediment and soil toxicity data are extremely limited for the medium-chain phthalates. The limited data available on analogues are presented in subsections 8.1.2 and 8.1.3, and suggest that the medium-chain phthalates would have low toxicity to sediment and soil-dwelling organisms (LC_{50} > 100 mg/kg dry weight [dw]).

8.1.1 Water

Empirically determined aquatic toxicity

Ecotoxicological experiments on medium-chain phthalates have been conducted using a variety of aquatic organisms, with several toxicological responses observed depending on the organisms and the particular substances that were studied. Available empirical toxicity information for the medium-chain phthalates indicates that these substances are highly to moderately toxic to aquatic organisms (median lethal concentration [LC_{50}] values ranging from less than 1 to 10 mg/L]) (refer to tables E-1 and E-2 in Appendix E).

Bradlee and Thomas (2003) describe a solubility cut-off (threshold) for phthalates, where solubility decreases below 1 mg/L when the carbon chain length on the alkyl side chains increases above 6 carbons. They suggest that in terms of aquatic toxicological properties, phthalates can be classified as “lower phthalates,” with ester chains of less than C6, and “higher phthalates,” with ester chains of C6 or greater. They indicate that higher phthalates do not pose intrinsic toxicity to aquatic organisms, as the rapid metabolism and low water solubility prevent their critical body burden for toxicity from being reached (Bradlee and Thomas 2003). They also note that the higher phthalates form stable emulsions that lead to artificial toxicity in laboratory tests, where daphnids become entrapped. DBzP, DCHP, DMCHP, B84P, B79P, BIOP and DIHepP are all phthalates in the medium-chain subgroup where both ester chains have 6 or more carbons. Many of the ecotoxicological studies described below for these substances were conducted above the water solubility limit of the substance and comment on the presence of a surface layer. When solubility is exceeded in a toxicity test, a stressor (i.e., undissolved test chemical) is present in the test that under normal circumstances (i.e., in the absence of spills) cannot occur in the environment. Hence, the toxicity results are not applicable to normal environmental situations. This includes the results from toxicity tests, where part of the exposure concentrations is above and the other part is below the solubility. In these cases, it is possible to create an apparent but “false” dose-response curve, as the dosing concentrations above the solubility include the

undissolved chemical stressor, while the dosing concentrations below the solubility do not include the undissolved chemical stressor (personal communication, external science review to Ecological Assessment Division (Environment Canada), dated November 5, 2014, unreferenced). In most cases, studies were carried out within the water solubility limit.

DIBP is the most studied phthalate in the medium-chain phthalate group, with studies available for fish, invertebrates and algae. It also has the lowest molecular weight and, therefore, is the most water-soluble and bioavailable of the medium-chain phthalates. In a well-documented acute toxicity study summary on the fathead minnow, a non-guideline study that was not specified as conforming to good laboratory practices (GLP) resulted in behavioural abnormalities at low concentrations of DIBP, generating a 96-hour EC_{50} of 0.73 mg/L (ECHA c2007–2014b). The study was conducted within the range of solubility of DIBP. *Daphnia magna* were also found to exhibit chronic reproductive effects, with a 21-day NOEC of 0.27 mg/L. However, details of the guidelines followed for this study were not available (ECHA c2007–2014b). A very well-documented summary of a study on algae indicated that DIBP is highly toxic to algae, with a 72-hour EC_{50} of 0.56 mg/L, based on reductions in biomass (ECHA c2007–2014b). In this study, concentrations of test solutions were based on measurements made at the beginning of the test. The empirical data indicate that DIBP is highly toxic to fish, invertebrates and algae, with effects observed between 0.27 and 4.8 mg/L (see Table E-1 in Appendix E).

Most aquatic toxicity studies on B84P were conducted at concentrations exceeding the water solubility limit (0.81 mg/L). B84P is a substance with ester chains that exceed 6 carbons in length. A confidential study of acute toxicity on *Daphnia* was conducted using nominal concentrations in the range of 1 to 10 mg/L, and generated a 48-hour LC_{50} of 7.5 mg/L (Study Submission 2014a). Acetone was used as a vehicle in this test up to a concentration of 1 mL per 200 mL of water in the beaker. There was no indication if a surface film was present or if *Daphnia* were entrapped. Summaries of fish studies consistently show no effects at concentrations near the water solubility limit or exceeding the water solubility limit. LC_{50} is reported to exceed 0.3, 5 and 1000 mg/L. None of the summaries of the fish studies provide sufficient detail to evaluate the study. A 96-hour fathead minnow test conducted according to OECD Guideline 203 and following GLP resulted in an LC_{50} greater than 0.3 mg/L, although no further details are provided (ECHA c2007–2014g). These data indicate that *Daphnia* are more sensitive to B84P than fish, as *Daphnia* mortality is observed at 7.5 mg/L and no effects have been observed in fish studies.

DCHP toxicity has been studied in fish, invertebrates, algae and amphibians. Due to its structural similarity and similar physical chemical properties to DMCHP, it will also be used as read-across for DMCHP, which is data-poor. DCHP and DMCHP have ester chains equal to or exceeding a length of 6 carbons (C6 and C7, respectively), which has been described as the limit where emulsions start to be formed in water when solubility is exceeded. Water solubility measurements of DCHP range from 0.2 to 4 mg/L and are estimated to be 0.275 mg/L for DMCHP. Two *Daphnia* studies were available where

testing occurred at concentrations near the limits of water solubility so that emulsion effects would not be expected. An acute *Daphnia* study with nominal concentrations ranging from 0.2 to 2 mg/L resulted in no loss of mobility over 48 hours at any concentration (ECHA c2007–2014c). However, a 21-day study, with measured concentrations (nominal concentrations were not reported), generated an EC_{50} of 0.679 mg/L and a NOEC of 0.181 mg/L (ECHA c2007–2014c). The summary provided very little details, but was considered reliable given that it was reported to be carried out following OECD guidelines. Available fish and algae studies were not considered reliable as both tests were conducted at concentrations well above the water solubility limits (10–100mg/L and 2 mg/L, respectively) (ECHA c2007–2014c).

De Solla and Langlois (2014) used the Frog Embryo Teratogenesis Assay – *Xenopus* (ASTM, 1998) as a rapid test to identify potential developmental toxicity. In a progress report on ongoing work, they reported that in 72-hour acute toxicity tests, exposure to DCHP was observed to lead to mortality, malformations and developmental delays in western clawed frog tadpoles in concentrations above the water solubility limit. DCHP was observed to significantly induce mortality relative to controls in western clawed frog tadpoles at measured concentrations above 4.1 mg/L (corresponding to nominal concentrations of 23 mg/L). In the same lethal range, DCHP increased the presence of malformations in tadpoles, including edemas and heart and gill abnormalities. All DCHP concentrations augmented the rate of underdeveloped tadpoles when compared to the control, although this was significant only at 4.1 and 19 mg/L. Below 4.1 mg/L, sublethal effects, such as alterations to gene expression, were observed, suggesting that DCHP-induced cellular stress perhaps contributes to the malformations and developmental effects observed at concentrations above 4.1 mg/L. These results indicate that DCHP and DMCHP are highly toxic to aquatic invertebrates and moderately toxic to amphibians.

Aquatic toxicity of B79P has been determined in algae, *Daphnia* and fish (see Table E-1 in Appendix E). Based on the structural similarities between B79P and BIOP and similar aquatic bioavailability, and given the lack of data for BIOP, effects data for B79P can be used to evaluate BIOP. Several summaries for studies on B79P using fish, *Daphnia* and algae studies were available (ECHA c2007–2014d). The algae studies were conducted above the water solubility limit and with a solvent; EC_{50} in the range of 521 to 674 mg/L was observed, although details were lacking on the study (ExxonMobil 2006). Two studies for *D. magna* are available (Study Submission 2014b; ECHA c2007–2014d). A study exposing daphnids to nominal concentrations of 1 to 10 mg/L of B79P in acetone generated a 48-hour LC_{50} of 4.5 mg/L. There are limitations to this study, however, as the submitting company notes that the composition of B79P at the time of testing was different than that of the product currently on the market. The test was carried out on a substance that was largely formed from C8 alcohols, while it is currently predominantly made from C9-rich alcohol. Furthermore, entrapment of *Daphnia* was observed at the 1 and 1.8 mg/L concentrations of B79P (Study Submission 2014b). A study summary provided a 48-hour EC_{50} for B79P of 0.3 mg/L, which was determined according to OECD Guideline 202, although further study details, including the nominal concentrations used in the test, are lacking (ECHA c2007–2014d). Fish studies were

conducted at concentrations exceeding water solubility (0.3 mg/L), and effects were not observed (ExxonMobil 2006). Brown et al. (1998) tested the chronic effects of di-heptyl/nonyl phthalate and other phthalate esters on *Daphnia magna* in the presence of a chemical dispersant. The study followed OECD test guidelines and included analytical confirmation. At a nominal concentration of 1 mg/L, no chronic effects were observed on daphnid survival or reproduction. The study summary indicates that BIOP and B79P exhibited high to moderate toxicity to *Daphnia* at concentrations within the water solubility limit.

Key studies that were available for the medium-chain phthalates and considered in choosing a critical toxicity value are summarized in Table 8-1. The key studies were critically reviewed and found to be reliable for use as a critical toxicity value (Environment Canada 2015).

Table 8-1. Key aquatic toxicity studies for medium-chain phthalates considered in choosing a critical toxicity value for water

Substance name	Test organism	Endpoint	Value (mg/L)	Reference
DIBP	Fathead minnow, *Pimephales promelas*	96 h EC_{50}	0.73	ECHA c2007–2014b
DIBP	Water flea, *Daphnia magna*	21 d NOEC Reproduction	0.27	ECHA c2007–2014b
DIBP	Green algae, *Pseudokirchneriella subcapitata*	72 h EC_{50} Biomass	0.56	ECHA c2007–2014b
DCHP	Water flea, *Daphnia magna*	21 d NOEC	0.181	ECHA c2007–2014c

B79P and BIOP did not have any aquatic toxicity studies available that were considered reliable for use as a critical toxicity value, therefore modelled results were used for the critical toxicity value, as discussed in Section 8.1.1.2.

BCHP and CHIBP did not have empirical data available, but BBP is considered a close structural analogue with similar physical-chemical properties and bioavailability, as shown in Appendix A, and will be used as read-across for these two substances. Fish, invertebrate and algal studies indicate that these substances have a high acute toxicity, with toxicity values less than 1 mg/L (see Table E-2 in Appendix E for all values). Adams et al. (1995) conducted a study on 14 phthalate esters and found that BBP was acutely toxic to both fish and algae. In the study by Adams et al. (1995), many aquatic organisms were tested, and algae was the most sensitive species to the acute effects of BBP, with a 96-hour EC_{50} of 0.21 mg/L and a NOEC below the lowest tested concentration (< 0.1 mg/L). Fish were less sensitive, but still exhibited LC_{50} between 0.82 and 1.7 mg/L. In many of the species examined, insufficient mortality was observed at the highest BBP concentration tested to calculate an LC_{50}. The values

reported by Adams et al. (1995) are based on concentrations measured on the first and last days of the study. The authors also make reference to BBP values reported by Gledhill et al. (1980), where a 96-hour NOEC for the bluegill was observed at 0.36 mg/L. While EC_{50} values for *Daphnia* could not be calculated in the Adams et al. (1995) study, toxicity to *Daphnia* was observed by Rhodes et al. (1995), where a 21-day study resulted in a LOEC of 1.4 mg/L and a NOEC of 0.28 mg/L. The latter study also showed that fish were less sensitive than daphnids, with no effects observed in fish at the highest concentration tested (0.2 mg/L). The Adams et al. (1995) study and the Rhodes et al. (1995) study both tested 14 phthalates and noted that many of the tests had to be repeated due to the presence of a microlayer of test chemical on the surface of the water. In both studies, BBP was the exception, showing no signs of the test chemical floating on the surface, as the test was conducted at measured concentrations below the water solubility limit (measured exposure concentrations reported by Rhodes et al. [1995] indicate that all exposure concentrations were below the water solubility limit of 2.96 mg/L). A 28-day flow-through test was conducted with mysid shrimp in saltwater with mean measured exposure concentrations of radiolabelled BBP ranging between 0.024 and 0.75 mg/L (corresponding to nominal concentrations ranging from 0.031 to 0.5 mg/L; mean measured concentrations were 62–68% of nominal in most treatment levels). NOECs calculated based on survival, reproduction and growth were found to be 0.17, 0.075 and 0.075 mg/L, respectively (Study Submission 2014c).

A 2-generation fathead minnow study was conducted to measure the potential effects of BBP on development, growth and reproduction (Study Submission 2014d). The study was conducted in a flow-through system according to GLP and multiple guidelines. The study involved two phases, where phase 1 lasted 21 days and assessed the survival and reproductive performance of adults, and phase 2 lasted 126 days and assessed the performance of the embryos from phase 1. BBP was tested at measured concentrations of 0.018 and 0.064–0.067 mg/L (from 0.025 and 0.1 mg/L nominal, respectively) with 100 µL/L of the vehicle triethylene glycol. In phase 1, effects on adult survival, number of eggs, number of spawns, number of eggs per spawn, percent fertility and hatchability were not found to be significantly affected by BBP. In phase 2, effects on fry survival, adult survival, female length and weight, male length and weight, and female and male vitellogenin were not found to be significantly affected by BBP (Study Submission 2014d).

The toxicity of BBP to sediment-dwelling organisms in water-only tests has been examined in two studies. Santicizer 160 (BBP) was tested on the sediment organism *Chironomus tentans* over 48 hours at nominal concentrations ranging from 1.25 to 20 mg/L and generated a 48-hour LC_{50} of 1.64 mg/L. A NOEC of 1.25 mg/L was observed (ECHA c2007–2013). The study was conducted prior to the implementation of GLP and was described as “closely following” a guideline from Mosher et al. (1982) and a US EPA guideline (1975). Call et al. (2001a) studied the effects of BBP on *H. azteca, C. tentans* and *L. variegatus* over 10 days in a water-only toxicity test with mean measured concentrations ranging from 0.036 to 1.76 mg/L and a 90% spike recovery from water. LC_{50} values were 0.46, > 1.76 and 1.23 mg/L, respectively. These data indicate that BCHP and CHIBP can also be moderately to highly toxic to aquatic

organisms and sediment-dwelling organisms presumably exposed to the test substances via pore water.

There are no empirical toxicity data for DBzP, but an acute toxicity study on DPhP will be used as read-across. This is because these two substances differ by only two carbon atoms and have very comparable water solubility and log K_{ow} estimates (Appendix A), with DBzP expected to be slightly less bioavailable due to lower water solubility (0.51 mg/L) and higher log K_{ow} (5.1) compared to DPhP (2.47 mg/L and 4.1). A study by Geiger et al. (1985) generated an acute LC_{50} of 0.08 mg/L to fathead minnow, which is below the water solubility limit of DBzP (0.51 mg/L) and DPhP (3.039 mg/L). The study tested a range of nominal concentrations from 0.1 to 0.48 mg/L (corresponding to measured concentrations in the range of 0.069 to 0.48 mg/L), which were all below the water solubility limit of DPhP. This can be considered a worst case toxicity estimate for DBzP, which is expected to be less bioavailable than the analogue.

Since only one aquatic toxicity study was available for DIHepP, toxicity data for DIOP was also used as read-across. DIOP has the same basic structure as DIHepP, with one extra carbon in each of the alkyl side chains. Brown et al. (1998) tested the chronic effects of DIHepP (identified as di-iso heptyl phthalate) and other phthalate esters on *Daphnia magna* in the presence of a chemical dispersant. The study followed OECD test guidelines and included analytical confirmation. At a nominal concentration of 1 mg/L, no chronic effects were observed on daphnid survival or reproduction. DIOP has been studied in two well-documented articles. Since phthalates with side chains exceeding 6 carbons tend to exist as surface film in concentrations above their water solubility, Adams et al. (1995) conducted an acute toxicity study using a bottom drain in a flask to transfer the stock solution to the test beakers so that any floating test chemical remained in the flask. Even with these precautions, the DIOP study had to be repeated, as *Daphnia* were entrapped at the surface in the first test. The test solutions were analyzed at the beginning and end of the study. Of the14 chemicals studied, the final test concentrations in the static tests were frequently 50% of the initial concentration, and mean measured concentrations were used in the EC_{50} calculation. It was hypothesized that this is likely due to adsorption to the test vessel. The findings are based on daphnid immobility and not entrapment. The 48-hour EC_{50} for *Daphnia* to DIOP was greater than the highest concentration tested (0.16 mg/L), which is also above its water solubility limit (0.09 mg/L). Adams et al. (1995) tested other aquatic organisms (fish, other invertebrates and algae) and, in all cases, the LC_{50} and EC_{50} values were above the highest concentration tested (in both static and flow-through tests). Rhodes et al. (1995) examined the chronic toxicity of 14 phthalates to *Daphnia magna*. Test concentrations were measured at 7-day intervals throughout the 21-day test. While no visible film of DIOP was observed on the surface, test organisms were observed floating on the surface at the LOEC of 0.14 mg/L. A NOEC of 0.062 mg/L was observed. Rhodes et al. (1995) looked at the most sensitive endpoints of the *Daphnia* studies and observed that survival and reproduction were equally sensitive endpoints for DIOP. They note that it is common in daphnid chronic toxicity studies for reproduction to be the most sensitive endpoint. However, of the 14 phthalates tested, reproduction was never the most sensitive endpoint. They postulated that this was

because mortality was due to physical effects. It appears that immobilization of *Daphnia* is the primary mechanism of toxicity for DIOP and DIHepP, even at concentrations near the water solubility limit (DIHepP water solubility is 0.02 mg/L and DIOP water solubility is 0.09 mg/L [HSDB 2014]).

Key studies for analogues of BCHP, CHIBP and DBzP considered in choosing a critical toxicity value in water are summarized in Table 8-2. Key studies were critically reviewed and found to be reliable for use as a critical toxicity value (Environment Canada 2015).

Table 8-2. Key aquatic toxicity studies for analogues of BCHP, CHIBP and DBzP considered in choosing a critical toxicity value for water

Substance name	Test organism	Endpoint	Value (mg/L)	Reference
BBP	Rainbow trout, *Salmo mykiss*	96 h LC_{50}	0.82	Adams et al. 1995
BBP	Mysid shrimp, *Mysidopsis bahia*	28 d NOEC	0.075	Study Submission 2014c
BBP	Water flea, *Daphnia magna*	21 d NOEC	0.28	Rhodes et al. 1995
BBP	Green algae, *Pseudokirchneriella subcapitata*	96 h EC_{50}	0.21	Adams et al. 1995
BBP	Green algae, *Pseudokirchneriella subcapitata*	96 h NOEC	< 0.1	Adams et al. 1995
DPhP	Fathead minnow, *Pimephales promelas*	96 h LC_{50}	0.08	Geiger et al. 1985

Modelling aquatic toxicity

For many of the medium-chain phthalates, there are no experimental toxicity data available, and the assessments are being informed by read-across data. The (Q)SAR program (ECOSAR 2012) was run using the ester structure activity relationships to build on the weight of evidence. Some of the predictions for CHIBP, DMCHP, DIHepP and BIOP included flags that the chemical may not be soluble at the predicted effect concentration for acute exposures. Upon further examination, the predicted effect concentrations are above the water solubility values for only DBzP and DIHepP; therefore, the modelled effect concentrations will only be retained for the evaluation of toxicity for the remaining medium-chain phthalates. The ranges predicted by ECOSAR (2012) (Table 8-3) are in agreement with the experimental data, which suggest that the medium-chain phthalates are highly to moderately toxic to aquatic organisms. The complete predictions are summarized in Table E-3 of Appendix E.

Table 8-3. Ranges of predicted aquatic toxicity endpoints generated by ECOSAR v1.00 for medium-chain phthalates

Organism	Duration (hr)	Endpoint	Range of predictions (mg/L)
Fish	96	LC_{50}	0.049–1.48
Daphnid	48	LC_{50}	0.05–2.2
Green algae	96	EC_{50}	0.012–0.72

Key aquatic toxicity studies could not be identified for B79P or BIOP, therefore modelled predictions were considered in choosing a critical toxicity value in water. In addition to ECOSAR v1.00, the models AIEPS v2.05 and the OASIS sub-model CPOPs (2008) were run for B79P and BIOP. The model results are summarized in Table 8-4 and the complete predictions are provided in Table E-3 of Appendix E. It was found that AIEPS v2.05, which uses fragments to generate predictions, had good structural coverage in the training set (>70%), but produced results that exceeded the water solubility limits in almost all cases. The OASIS-CPOPs (2008) model predictions were higher than the ECOSAR v1.00 predictions by approximately one order of magnitude, and in both cases, algae was the most sensitive species. These substances were considered out of the domain for the OASIS-CPOPs (2008) model as their log K_{ow}'s exceed 5. Therefore, the algal 96 hr EC_{50} values calculated by the esters SAR in ECOSAR (2012) were selected as the critical values for both B79P and BIOP (with values of 0.012 and 0.032 mg/L, respectively). These modelled critical toxicity values are within an order of magnitude of the experimental critical toxicity values for the other medium-chain phthalates (shown in Table 8-5).

Table 8-4. Summary of model results for B79P and BIOP

Substance name	Organism	Endpoint	Prediction (mg/L)	Reference
B79P	Fish	96hr LC_{50}	0.0045 – 0.763	ECOSAR 2012; TOPKAT 2001; AIEPS 2003–2007; CPOPs 2008
B79P	Daphnid	48hr LC_{50}	0.05 – 31.11	ECOSAR 2012; AIEPS 2003–2007; CPOPs 2008
B79P	Algae	72hr and 96hr EC_{50}	0.012 – 1.36	ECOSAR 2012; AIEPS 2003–2007; CPOPs 2008
BIOP	Fish	96hr LC_{50}	0.108 – 0.504	ECOSAR 2012; AIEPS 2003–2007; CPOPs 2008
BIOP	Daphnid	48hr LC_{50}	0.122 – 13.89	ECOSAR 2012; AIEPS 2003–2007; CPOPs 2008
BIOP	Algae	72hr and 96hr EC_{50}	0.032 – 1.75	ECOSAR 2012; AIEPS 2003–2007; CPOPs 2008

Derivation of the predicted no-effect concentration (PNEC)

In order to determine a predicted no-effect concentration (PNEC) for the medium-chain phthalates, the most sensitive (reliable) endpoint was chosen as a critical toxicity value (CTV) in considering the acceptability of available studies. The CTV was then divided by an assessment factor to account for such factors as inter- and intra-species variability, short-term to long-term effects, and the extent of species covered by the dataset to give a PNEC value for each of the substances in the medium-chain phthalate subgroup. The CTVs, assessment factors and corresponding PNECs are presented in Table 8-5. Although there is uncertainty caused by the limited coverage of species in the dataset, inter- and intra-species variability and extrapolation of short-term to long-term effects, an assessment factor of 30 was used in the case of DBzP because the analogue used to derive the CTV is expected to be more bioavailable than DBzP.

Table 8-5. PNECs derived for medium-chain phthalates

Substance name	Test organism	Endpoint	CTV (mg/L)	Reference	AF	PNEC (mg/L)
DCHP	Water flea, *Daphnia magna*	21 d NOEC	0.181	ECHA c2007–2014c	3	0.06
DIBP	Green algae, *Pseudokirchneriella subcapitata*	72 h EC_{50} Biomass	0.56	ECHA c2007–2014b	3	0.19
BIOP	Algae	96 h EC_{50}	0.032	ECOSAR v1.00	10	0.0032
B79P	Algae	96 h EC_{50}	0.012	ECOSAR v1.00	10	0.0012
BCHP[1]	Mysid Shrimp, *Mysidopsis bahia*	28 d NOEC	0.075	Study Submission 2014c	3	0.025
DBzP[2]	Fathead Minnow, *Pimephales promelas*	96 h LC_{50}	0.08	Geiger et al. 1985	30	0.003
CHIBP[1]	Mysid Shrimp, *Mysidopsis bahia*	28 d NOEC	0.075	Study Submission 2014c	3	0.025
DMCHP[3]	Water Flea, *Daphnia magna*	21 d NOEC	0.181	ECHA c2007–2014c	3	0.06

Abbreviations: CTV = critical toxicity value; AF = assessment factor; PNEC = predicted no-effect concentration
[1] Data are from analogue BBP
[2] Data are from analogue DPhP
[3] Data are from analogue DCHP

No evidence of chemical toxicity was seen in standard aquatic toxicity testing with DIHepP or B84P up to their water solubility limits, although mortality was observed in

Daphnia at 0.14 and 7.5 mg/L, respectively. In the absence of a definitive lowest observed adverse effect concentration (LOAEC), a PNEC cannot be derived.

The low water solubility (ranging from 0.001 to 0.81 mg/L) and high hydrophobicity (log K_{ow} 6.15 to 6.76) of DIHepP and B84P suggest that dietary exposure could be a more relevant route of uptake for organisms, rather than uptake from the surrounding medium. For this reason, endpoint values derived from water concentrations may not fully describe the potential for effects. The toxic potential of substances that are taken up primarily through diet is better captured by examining whole-body residues (internal concentrations) of the substance in an organism. Critical body residues (CBRs) can then be calculated in order to estimate the potential for the substance to reach internal concentrations that are sufficiently high to cause effects through baseline narcosis (McCarty and Mackay 1993; McCarty et al. 2013).

CBRs were calculated for DIHepP and B84P using the McCarty and Mackay (1993) equation:

CBR = BAF × WS / MW

where:

CBR = the critical body residue (mmol/kg)
BAF = fish bioaccumulation factor (L/kg); normalized to 5% body lipid
WS = water solubility of the substance (mg/L)
MW = molecular weight of the substance (g/mol)

Input values to the equation for DIHepP and B84P and the outputs are summarized in Table 8-5 below. Using maximum water solubility in the calculation of CBR represents a conservative but realistic scenario. Experimental BAF data are not available for the calculation of the CBR for B84P; however, a general trend was noticed with the other medium-chain phthalates that the BAF predictions obtained using the Arnot and Gobas (2003) approach with a 1% dietary uptake efficiency were lower than the experimental values. Therefore, CBR calculations were also completed using the higher BAF prediction obtained using the BCFBAF model (v3.01) (Table 8-6).

Table 8-6. CBR equation input and output values for DIHepP and B84P

Substance name	BAF (L/kg)	Water solubility (mg/L)	Molecular weight (g/mol)	CBR (mmol/kg)
DIHepP	115 (fish; Mackintosh 2002)	0.017 (Letinski et al. 2002)	362.51	5.39×10^{-3}
DIHepP	427 (mussel; Mackintosh 2002)	0.017 (Letinski et al. 2002)	362.51	0.02

B84P	54 (fish; Arnot and Gobas 2003)	0.81 (European Commission 2000)	454.57	0.1
B84P	71 (fish; BCFBAF v3.01)	0.81 (European Commission 2000)	454.57	0.13

McCarty and Mackay (1993) determined that CBRs associated with acutely lethal baseline neutral narcosis in small aquatic organisms typically range from about 2 to 8 mmol/kg, while those for chronic exposures range from 0.2 to 0.8 mmol/kg. The CBR values calculated for DIHepP and B84P are lower than these, indicating that internal concentrations are unlikely to reach levels sufficient to elicit acute or chronic effects through a neutral narcosis mode of toxic action.

Secondary endpoints in aquatic organisms

Secondary endpoints at lower levels of organization (e.g., the molecular, biochemical, cellular, tissue or organ level) are useful measurements to support the assessment of mode of toxicological action (Staples et al. 2011). A search of the literature revealed that none of the medium-chain phthalates have data on secondary endpoints that would suggest effects on the endocrine system in fish. Limited data for DCHP and DIHepP are available on the amphibian thyroid system, where DCHP and DIHepP have been studied for their potential to alter genes involved in reproduction and thyroid-hormone homeostasis in frogs (De Solla and Langlois 2014; Sugiyama et al. 2005). Numerous secondary endpoints, both *in vivo* an *in vitro*, have been determined for BBP and DEHP – substances used as analogues for certain medium chain phthalates (see Table2-4 for the summary of the read-across approach).

DCHP and DIHepP are being studied for their potential to alter gene expression in the Western Clawed Frog, particularly looking at genes involved in reproduction, thyroid-hormone (TH) homeostasis and cellular stress (De Solla and Langlois 2014). While DIHepP was not found to alter the expression of the targeted genes in frog embryos, DCHP disrupted gene expression from the sex steroid, TH and cellular axes. DCHP increased the expression of reproduction-related genes and TH-related genes in frogs exposed to concentrations ranging from 0.3 to 4.1 mg/L. Disruption of sex steroid-related gene expression may affect later life events, such as sex differentiation and reproduction, while effects on active TH levels could potentially delay tadpole development (De Solla and Langlois 2014). Data are presented in Table E-4 of Appendix E.

Sugiyama et al. (2005) conducted *in vitro* tests to screen phthalates, including DCHP, BBP and DEHP, for potential interference with the amphibian thyroid system and compared those with results from *in vivo* tests with tadpoles. They observed that DCHP was the most potent antagonist to the TH, triiodothyronine (T_3), with an IC_{50} of 0.43 mg/L, followed by BBP and DEHP (IC_{50} = 12.5 mg/L and > 19.53 mg/L, respectively). The phthalates were also found to inhibit the expression of the TH nuclear

receptor β by > 50% for BBP (at 1.25 mg/L), 42% for DCHP (at 6.6 mg/L) and 29% for DEHP (at 19.53 mg/L). In a 5-day *in vivo* test with tadpoles, only BBP was found to inhibit the increase in the amount of TRβ transcript by 48% (at 1.25 mg/L).

For BBP, secondary endpoints have been examined *in vivo* in the fathead minnow (Study Submission 2014d; Harries et al. 2000; Christiansen et al. 2000) and *in vitro* in the rainbow trout (Chen et al. 2014; Jobling et al. 1995; Knudsen and Pottinger 1999; Tollefsen 2002).The effects on the endocrine system of DEHP has been extensively studied *in vivo* (Kim et al. 2002; Caunter et al. 2004; Carnevali et al. 2010; Wang et al. 2013; Ye et al. 2014) and *in vitro* (Sugiyama et al. 2005), although many of these studies are performed at concentrations above the water solubility limit of DEHP.

In the rainbow trout, BBP has been observed to displace estradiol (E2) from the hepatic estrogen receptor (ER) (effects observed at 0.3 mg/L, Jobling et al. 1995; 51.5 mg/L, Knudsen and Pottinger 1999) and from the sex steroid binding protein (1124 mg/L, Tollefsen 2002). BBP has also been observed to inhibit binding to the African clawed frog ER by 50% at 7.4 mg/L (Suzuki et al. 2004). Upon binding to the ERs, phthalates can alter the production of vitellogenin (VTG) in aquatic species (Mathieu-Denoncourt et al. 2015). In one study, BBP has been found to increase VTG in the rainbow trout following intra-peritoneal (IP) injection (500 mg/kg, Christiansen et al. 2000), while in studies on the fathead minnow, no changes were observed (0.0675 mg/L, Study Submission 2014d; 0.071 mg/L, Harries et al. 2000). At IP injection levels of 50 mg/kg, Knudsen et al. (1998) observed no effects on the induction of zona radiata proteins in the rainbow trout, which would be induced at lower concentrations of estrogen than necessary to induce VTG. In a study on the adult male clawed frog, VTG was not found to increase after exposure to concentrations of BBP as high as 31 mg/L (Nomura et al. 2006).

Effects were observed in what appears to be a novel test for estrogen activity, where Chen et al. (2014) used transgenic medaka (*Oryzias melastigma*) eleutheroembryos and their green fluorescence reporter gene signal to test estrogen responsiveness to BBP and other phthalates. At a concentration of 1.5 mg/L, BBP induced a fluorescent signal in the liver of the exposed eleutheroembryos, with an intensity reading close to that of medaka exposed to 17β-estradiol (E2) at 0.002 mg/L (2 ppb). Chen et al. (2014) concluded that BBP possesses estrogenic activity.

Qualitative histopathologic observations were made on male and female fathead minnow tissues exposed to BBP at 0.018 and 0.067 mg/L (Study Submission 2014d). At both concentrations, the only effects observed were impacts on the gonadal histology of the fish, including increased incidence and severity of spermatogonia (minimal to moderate) in the testes of males, characterized by the visual impression of the proportion of spermatogonia relative to spermatocytes and spermatids expected for a given stage. In females, a slight increased incidence of oocyte atresia (minimal to severe) was observed. In the high treatment group, altered gonadal stage scores were observed in both males and females (Study Submission 2014d).

Mankidy et al. (2013) investigated the molecular mechanisms of action of BBP and DEHP by assessing transcriptional changes in developing fathead minnow embryos exposed to the phthalates until 96 hours post fertilization. The concentrations used in the tests were above the water solubility limit of DEHP. Exposure to 1 mg/L BBP and 1 mg/L DEHP caused two-fold greater lipid peroxidation in membranes of developing embryos. Neither phthalate altered the expression of mRNA of the ER (α or β); however, BBP exhibited a small, yet significant increase in the expression of mRNA of the androgen receptor (AR) in developing fish embryos at 1 mg/L, while DEHP caused only a slight increase in expression of mRNA of the AR at 1 mg/L. Fathead minnow embryotoxicity tests showed that DEHP was more potent than BBP, with 30% mortality observed at 1 mg/L. Given the significantly greater products of lipid peroxidation observed in membranes of the developing embryos exposed to DEHP and the lack of up-regulation in the expression of mRNA of the enzymes involved in mitigating oxidative stress, the authors concluded that oxidative stress is the critical mechanism of toxic action for DEHP (Mankidy et al. 2013).

DEHP has been found to increase VTG in the zebrafish (effects observed at 5000 mg/kg, Uren-Webster et al. 2010; 2×10^{-5} mg/L, Carnevali et al. 2010), the Chinese rare minnow (0.0128 mg/L in females and 0.0394 mg/L in males, Wang et al. 2013) and the marine medaka (0.1 mg/L, Ye et al. 2013). In a study on juvenile Atlantic salmon, VTG was not detected in blood plasma after IP injection with DEHP (160 mg/kg, Norrgren et al. 1999). VTG levels were not found to statistically increase in male fathead minnow exposed to DEHP via both water (0.005 mg/L) and food (125 or 500 mg/kg), but increased in females at the high dose (ECHA c2007–2014f).

Changes in sex hormone levels in fish following exposure to DEHP have been reported in several papers. In male fish, T levels have been found to increase at 0.039 mg/L DEHP (Wang et al. 2013), while E2 levels have been found to significantly increase after exposure to 0.039 and 0.1 mg/L (Wang et al. 2013; Ye et al. 2013). T levels were not found to change significantly in male fish from two studies (at DEHP concentrations of 0.5 mg/L, Ye et al. 2013; 0.012 mg/L, Crago and Klaper 2012). Crago and Klaper (2012) observed a significant decrease in plasma E2 concentrations at exposures of 0.012 mg/L DEHP. In female fish, T levels were observed to increase at exposures of 0.1 mg/L DEHP (Wang et al. 2013; Ye et al. 2013), while E2 levels have been found to both decrease (0.013 mg/L, Wang et al. 2013) and increase (0.1 mg/L, Ye et al. 2013). In all cases, the exposure concentrations were above the water solubility limit of DEHP.

The gonadal-somatic index (GSI) is usually used as a biomarker in aquatic wildlife to assess exposure to environmental estrogens (Wang et al. 2013). The GSI of DEHP has been calculated by several authors, with mixed results. Increased GSI was found in male Chinese rare minnow exposed to 0.118 mg/L DEHP (Wang et al. 2013), and in female fish exposed to 2×10^{-5} mg/L and 0.118 mg/L DEHP (Carnevali et al. 2010; Wang et al. 2013). GSI was found to decrease in female Japanese medaka following exposure to 0.01 and 0.05 mg/L (Kim et al. 2002), while no effects were observed in males at 0.012 and 0.05 mg/L (Crago and Klaper 2012; Kim et al. 2002). The hepatosomatic index (HSI) of the male Chinese rare minnow was increased significantly

at 0.013 mg/L, but no differences were observed for the females (Wang et al. 2013). Uren-Webster et al. (2010) also observed an increase in the HSI in male zebrafish exposed to 5000 mg/kg DEHP via IP-injection.

Reports of histological changes following exposure to DEHP have also been reported. Exposure of DEHP to marine medaka at 0.1 and 0.5 mg/L resulted in a reduced number of spermatozoa in the testes and an increased number of atretic follicles in the ovaries (Ye et al. 2013). In female Japanese medaka, retardation of oocyte development has been observed, with 37, 0 and 22% of female fish having mature oocytes in their ovaries at 0.001, 0.01 and 0.05 mg/L, compared to 54% of female fish in the control. No deformation of the testes in males was observed (Kim et al. 2002). Histological examination of the gonads from Atlantic salmon exposed to 1500 mg/kg DEHP via diet showed a small but significant incidence (3%) of intersex fish, but no complete sex reversal resulting in skewed sex ratios were found (Norman et al. 2007). Uren-Webster et al. (2010) observed that after ten days of exposure to 0.5, 50 and 5000 mg/kg DEHP via IP injection, there was no evidence of DEHP-induced sperm DNA damage in male Zebrafish; however, at 50 mg/kg, there was a decrease in the proportion of spermatozoa and an increase in the proportion of spermatocytes.

Staples et al. (2011) assessed if primary endpoints at the whole-body level and the population level were integrating secondary endpoints for phthalate esters by comparing the primary and secondary endpoints that were both measured within studies. They found that for the low-molecular-weight phthalate esters (C1 to C4), primary and secondary NOECs did not span the same ranges, and concluded that secondary endpoints provided limited benefit in practical ecological risk assessment to aquatic species. However, the number of secondary endpoints available to compare to primary endpoints was quite limited. An analysis of medium-chain phthalates from C5 to C7 was not provided. A comparison between the primary and secondary endpoints for DEHP could not be completed, as Staples et al. (2011) indicate that DEHP was not reported to have adverse effects for either primary or secondary endpoints consistent with solubility constraints. Indeed, many of the studies on DEHP are conducted at concentrations above the water solubility limit; however, two studies that looked at primary and secondary endpoints have recently been conducted within the water solubility limits of DEHP. Carnevali et al. (2010) found a significant reduction in fecundity of female Zebrafish exposed to nominal DEHP concentrations ranging from 2×10^{-5} to 0.40 mg/L. By measuring several key regulators of oocyte maturation and ovulation, they concluded that DEHP affected signals involved in oocyte growth, maturation and ovulation, which impaired ovarian functions and embryo production. Furthermore, Corradetti et al. (2013) found that exposure to 2×10^{-4} mg/L DEHP impaired reproduction in Zebrafish by inducing a mitotic arrest during spermatogenesis, increasing DNA fragmentation in sperm cells and reducing embryo production (up to 90%).

Mammalian data, however, point to androgen insufficiency as a mode of action, which is discussed in detail in the Health Effects Assessment (Section 9.2). This has not been studied in aquatic organisms for the medium-chain phthalates or the analogue BBP, and

is considered a data gap, although a multi-generational fathead minnow study on BBP shows no effects on phase 2 embryos (Study Submission 2014d). The data available for the analogue DEHP suggest an estrogenic mode of action (Norrgren et al. 1999; Norman et al. 2007; Carnevali et al. 2010; Corradetti et al. 2013), while some data indicate the anti-androgenic mode of action that occurs in mammals may also be involved in aquatic species (Wang et al. 2013, Ye et al. 2014).

Aquatic toxicity of phthalate ester metabolites

Given the rapid degradation of the medium-chain phthalate esters to monoesters and phthalic acid, the aquatic toxicity of these degradation products was examined. While not all metabolites of the medium-chain phthalates have been studied, Scholz (2003) found that the short-chain monoesters are considerably less toxic to aquatic organisms than the short-chain diesters. Acute toxicity tests on mono-isobutyl phthalate, the degradation product of DIBP, with fish and *Daphnia* result in LC_{50} values of 125 and 141 mg/L, respectively (Scholz 2003). A study by Jonsson and Baun (2003) examined the toxicity of the analogue BBP and its metabolite, monobenzyl phthalate (MBzP), to algae and *Daphnia magna*. They noted that the monoesters can be expected to be more water soluble, more hydrophilic and less volatile from aqueous solution than their corresponding diesters. In a 72-hour algal toxicity test, they found that BBP had an EC_{50} of 0.96 mg/L, which is consistent with what is found in the literature, and that its degradation product MBzP had an EC_{50} of 28.6 mg/L and phthalic acid had an EC_{50} of 2270 mg/L. Similarly, the 48-hour *Daphnia magna* test resulted in a BBP EC_{50} of 2.43 mg/L, a MBzP EC_{50} greater than 274 mg/L and a phthalic acid EC_{50} of 103 mg/L. This trend was consistent in all of the tested diester phthalates and their monoesters, where the diester showed greater toxicity than the monoester. It is therefore expected that the diesters would be of primary concern in the aquatic compartment.

8.1.2 Sediment

No published data on sediment toxicity have been identified for the medium-chain phthalates. Two studies were found that examined sediment toxicity to DBP and DEHP, which are phthalate esters that also have chain lengths below 6 carbons (Call et al. 2001b; Brown et al. 1996).

Call et al. (2001b) indicate that previous benthic invertebrate testing with other chemicals has shown that benthic invertebrates exhibit a similar range of species sensitivities as pelagic or planktonic invertebrates and that water-only test data for benthic species can be used with equilibrium partitioning (EqP) to predict the effects of phthalates in spiked-sediment laboratory tests. Call et al. (2001b) conducted sediment toxicity tests with DBP (the straight chain isomer of DIBP) to compare with toxicity predictions derived from EqP theory. The overlying water concentrations were found to be much lower than the pore water concentrations and are therefore expected to have negligible impact on the LC_{50} determination. The empirical sediment toxicity results showed that DBP exposures reduced survival and weight of *C. tentans* at all sediment organic carbon levels, with 10-day LC_{50} ranging from 826 to 4730 mg/kg dw. *H. azteca*

was less sensitive, with LC_{50} greater than the highest exposure concentration of 71,900 mg/kg dw, perhaps due to the avoidance of the higher concentrations in sediment and migration to the overlying water (Call et al. 2001b). Call et al. (2001b) used the EqP theory with the aqueous toxicity values for DBP from their previous study (Call et al. 2001a) to predict its acute toxicity in spiked sediment laboratory tests. They found that it accurately predicts the acute toxicity of phthalate esters in sediment to benthic invertebrates when the concentrations are stable in the sediment and pore water, and when animal behaviour patterns are such that they receive a continuous exposure. Call et al. (2001a) calculated aqueous LC_{50} for BBP. Given the similar aqueous toxicity values of DBP and BBP obtained in the 2001a study and their similar K_{oc} values, it would be expected that BBP would also have sediment LC_{50} in the range of 826 to 4730 mg/kg dw. No adverse effects on either survival or growth based on dry weight were observed at pore water concentrations between 0.273 and 0.382 mg/L or bulk sediment concentrations between 3070 and 3170 mg/kg dw for the analogue DEHP.

Brown et al. (1996) examined the toxicity of DEHP and DIDP on *Chironomus riparius* at 100, 1000 and 10000 mg/kg dw over 28 days. Test concentrations were measured at the start and finish of the study and were consistent with the nominal concentrations. From the results on emergence and sex distribution, they concluded that there were no effects from either phthalate on survival, development or emergence of *C. riparius* at any of the concentrations tested. The study also measured the tissue concentration from ^{14}C activity in the midges, and demonstrated quite high body burdens (from 70 to 14 000 mg/kg), which did not appear to be affecting the health of the midges.

The maximum saturation of phthalates in sediment can be determined using the following relationship:

$$C_s = C_w \times K_{oc} \times f_{oc}$$

where:
C_s = maximum saturation of the substance in sediment (mg/kg dw)
C_w = water solubility of the substance (mg/L)
K_{oc} = organic carbon-water partition coefficient of the substance (L/kg OC)
f_{oc} = fraction of organic carbon (OC) in the sediment (kg OC/kg)

Maximum saturation reflects the theoretical maximum thermodynamic saturation of a compound in a given medium at equilibrium. It cannot be exceeded according to thermodynamic principles. In surface waters, the presence of co-solvents or surfactants can create conditions that allow for an “apparent solubility” that exceeds the maximum solubility. In solid phases, such as sediments and soils, maximum saturation is a direct function of the amount of organic carbon present in the matrix if it is assumed that only hydrophobic interactions with organic matter occur. Sediment organic carbon content can vary from location to location, and often average carbon contents are used for calculating maximum saturation in sediments. The apparent solubility in water, and saturation in sediment or soil, can increase or decrease the bioavailability of a

compound. The values calculated using the above equation therefore represent the theoretical saturation limit, which, for the purposes of bioavailability, may be exceeded under some circumstances. For example, it is difficult to be certain that only hydrophobic interactions are responsible for defining the maximum theoretical saturation limit in solid phases. These circumstances cannot be easily predicted without specific information regarding the nature of release and the characteristics of the receiving environment. Given the very high hydrophobicity of the long-chain phthalates, hydrophobic interactions are likely to be the major factor influencing the maximum saturation limit.

The maximum saturation of the medium-chain phthalates is summarized in Table 8-7, using a default f_{oc} value of 0.04 (default value for average Canadian sediment OC content).

Table 8-7. Maximum saturation in sediment input and output values for medium-chain phthalates

Substance name	C_w (mg/L)	K_{oc} (L/kg OC)	Calculated C_s (mg/kg dw)
DIBP	20.3	977	793.52
BCHP	3.76	4898	736.63
CHIBP	4.82	4266	822.45
DCHP	0.2	6166	49.33
DBzP	0.51	13490	275.19
BIOP	0.22	45709	402.24
B79P	0.3	15849	190.19
DMCHP	0.275	40738	448.12
DIHepP	0.017	48978	33.30
B84P	0.81	239883	7772.22

Derivation of the predicted no-effect concentration (PNEC)

There is a significant lack of data available on sediment toxicity relating to the medium-chain phthalates. Based on the available data, the 10-day LC_{50} of 1664 mg/kg dw in *C. tentans* will be selected as a conservative CTV, based on the effects of DBP (and used as read-across for DIBP and BBP) in sediments with an organic carbon content of 4.8%. The CTV was then divided by an assessment factor of 100 to account for inter- and intra-species variability and to extrapolate to long-term effects in order to give a PNEC value of 16.64 mg/kg dw. This PNEC applies to DIBP and the analogues of BBP, BCHP, CHIBP and DBzP. This PNEC value is below the calculated maximum saturation in sediment for each of the substances shown in Table 8-7. Since no effects were observed in sediment toxicity testing with DEHP, a PNEC cannot be calculated for DIHepP. The BSAF value of 0.526 kg OC/kg lipid that was reported for DIHepP in the Pacific staghorn sculpin (Mackintosh 2002) can be used in a CBR analysis to determine the potential for adverse effects.

Applying the CBR relationship to DIHepP in sediment,

$CBR = BSAF \times S_S / MW$

where:

CBR = the critical body residue (mmol/kg)
BSAF = biota-sediment accumulation factor (kg/kg); normalized to 5% body lipid
S_S = saturation limit of the substance in sediment (mg/kg)
MW = molecular weight of the substance (g/mol)

Input values to the equation were: BSAF 0.526 kg/kg (Mackintosh 2002 for Pacific staghorn sculpin; see Appendix D, Table D-3), saturation limit of DIHepP in sediment 33.3 mg/kg (assuming 4% OC content for average Canadian sediment; see Table 8-7) and molecular weight 362.51 g/mol (Table 2-1).

Using the maximum saturation in the calculation of CBR represents a conservative but realistic scenario.

Based on these input values, the calculated CBR is 0.05 mmol/kg. This suggests that tissue levels of DIHepP in sediment-dwelling organisms will remain below those predicted to result in acute or chronic effects due to baseline narcosis.

PNECs for DCHP, DMCHP, BIOP and B79P in sediment can be derived using the Equilibrium Partitioning method (Redman et al. 2014) by multiplying the aquatic PNEC by the substances' K_{oc} values and using a default sediment organic carbon content to present the values on a dry weight basis. Using the equation from Call et al. (2001b):

$C_s/f_{oc} = K_{oc} \times C_d$

where:

C_s = bulk sediment concentration (mg/kg dw)

f_{oc} = organic carbon content of the sediment (kg OC/kg dry)

K_{oc} = sediment organic carbon-water partition coefficient (L/kg OC)

C_d = free dissolved concentration (mg/L)

An organic carbon content of 4% was assumed in the calculation. The resulting calculated PNECs in sediment ($PNEC_{sediment}$) range from 0.76 to 97.8 mg/kg dw as shown in Table 8-8. These PNECs are all below the maximum saturation in sediment values calculated in Table 8-7.

Table 8-8. Sediment PNEC input and output values for DCHP, BIOP, B79P and DMCHP

Substance	K_{oc} (L/kg OC)	C_d (mg/L) (from $PNEC_{aquatic}$)	Calculated C_s (mg/kg dw) ($PNEC_{sediment}$)
DCHP	6,166	0.06	14.8
BIOP	45,709	0.0032	5.85
B79P	15,849	0.0012	0.76
DMCHP	40,738	0.06	97.8

A PNEC cannot be determined for B84P, as sediment studies have not been conducted and aquatic PNECs could not be calculated. BSAFs have not been reported for B84P; therefore, a CBR analysis cannot be conducted.

8.1.3 Soil

No published data on soil toxicity have been identified for the medium-chain phthalates. One study summary is available on the analogue BBP.

In a summary of an unpublished study, earthworms (*Eisenia fetida*) were exposed to nominal concentrations of 95 to 1000 mg/kg dw of BBP in artificial soil, following OECD Guideline 207. The weight and survival was recorded after 7 and 14 days. After 14 days, no effects were observed at the highest concentration (1000 mg/kg dw). There were no marked differences in weight changes between the test and control groups (ECHA c2007–2013).

Due to the lack of data, and the lack of effects observed in the study summary that is available, a PNEC for soil cannot be calculated.

8.2 Ecological exposure

8.2.1 Measured concentrations in environmental media and wastewater

The discussion on the measured environmental concentrations of the medium-chain phthalate esters considers several media, including air, water, sediment, soil and biota. Measured data are primarily available for DIBP, and to a lesser extent DCHP and DIHepP in water, sediment and biota in urban areas. Results can be found in Environment Canada (2015). Measured environmental concentrations are not available for B79P or B84P, the two medium-chain phthalates that have been reported to be in commerce in the highest quantities in Canada. Measured concentrations are also not available for the medium-chain phthalates that were not reported to be in commerce (CHIBP, DMCHP, BIOP, DBzP and BCHP).

Phthalate esters are commonly found as background concentrations in both sampling and analytical equipment, as well as in laboratory air and reagents (McConnell 2007).

Reducing and determining the background contamination of samples and properly cleaning field equipment is crucial for ensuring that environmental measurements on phthalate esters are acceptable, accurate and of high quality (Lin et al. 2003).

Measured concentrations in air

No monitoring data for concentrations of the medium-chain phthalates in air could be found in Canada. Internationally, DIBP and DCHP have been detected in outdoor air, the results for which can be found in Environment Canada (2015). Rudel et al. (2010) measured DIBP in more than 90% of air samples at concentrations ranging from 1.4 to 18 ng/m^3. Lower concentrations have been measured in Sweden, with the maximum air concentration of 2.6 ng/m^3 measured near industrial sites (Cousins et al. 2007). Concentrations have also been measured in the Norwegian Arctic, ranging from 0.096 to 0.549 ng/m^3 (Xie et al. 2007). DCHP has been monitored at industrial and rural sites in California, where the method reporting limit was 1 ng/m^3, with no concentrations detected in most samples (Rudel et al. 2010).

Measured concentrations in water

A range of concentrations of medium-chain phthalates have been measured in surface waters in Canada (Environment Canada 2015). Data were available for surface waters in Alberta and British Columbia, predominantly for DIBP. In urbanized areas such as False Creek Harbour in British Columbia, mean concentrations of DIBP of approximately 5 ng/L have been detected (McConnell 2007; Mackintosh et al. 2006), although these concentrations are near the detection limits (6.4–7.9 ng/L). Sosiak and Hebben (2005) measured median concentrations of 2.85 ng/L downstream of wastewater treatment plants in Alberta using detection limits ranging from 0.01 to 5.7 ng/L. DIHepP has been detected in higher concentrations in False Creek Harbour, ranging from 2.91 to 153 ng/L, with an average of 21.1 ng/L (Mackintosh et al. 2006).

DIBP concentrations in urban environments in other countries have been measured at higher concentrations than those reported in Canada. Concentrations are listed in Environment Canada (2015). In Germany and China, median concentrations were as high as 56 ng/L in the early 1990s and 430 ng/L in 2005, respectively (Furtman 1994 and Zeng 2008).

Measured concentrations of DCHP in the environment are only available for other countries. A monitoring study in the Netherlands found a median surface water concentration of 8 ng/L, while the median concentration in wastewater effluents was slightly higher at 15 ng/L (Vethaak et al. 2005). DCHP has also been measured in Germany and China, with median concentrations below 0.03 and 76 ng/L (Furtman 1994 and Zeng 2008). It would be expected that DCHP concentrations in Canada would be far below those found in China, based on DIBP measured concentrations, which were found to be much higher in China than in Canada.

Degradation products of DIBP and DIHepP were measured by Sosiak and Hebben (2005) in wastewater treatment plant effluents and receiving rivers in Alberta. In all cases, mono-butyl phthalate and the mixture of mono C7 isomers were not detected. This was consistent with what has been measured in Japan, where MIBP was not detected in the Tama River (with a method detection limit of 12 ng/L) (Suzuki et al. 2001). Blair et al. (2009) measured the concentration of the isomeric mixture mono-*iso*-heptyl phthalate in False Creek Harbour, and measured between 2.71 and 6.61 ng/L in all ten samples.

BBP and DBP have been measured in biosolids in Vancouver, British Columbia, in the range of < 0.02 to 1.3 µg/g (Bright and Healy 2003). Biosolids monitoring data are not available for substances in the medium-chain phthalate subgroup.

Measured concentrations in sediment

DIBP and DIHepP have been detected in sediment in False Creek Harbour, with mean concentrations ranging from 4 to 5.6 ng/g dw, and 27 to 60.8 ng/g, respectively (Mackintosh et al. 2006; McConnell 2007). DIHepP is known to have a significantly lower commercial involvement than DIBP (Environment Canada 2014). Its higher concentrations in sediment could therefore be attributed to its more hydrophobic nature. Mackintosh et al. (2006) found that concentrations of the phthalates in bottom sediments were significantly lower than those in suspended sediments. For example, the concentration of DIBP in suspended sediments was 1190 ng/g dw compared to 4 ng/g dw in bottom sediment. DIBP has been measured in more remote areas of Hudson's Bay and found to have a lower mean concentration (0.22 ng/g) (Morin 2003). A complete list of concentrations in sediment can be found in Environment Canada (2015).

Concentrations in the Netherlands have been measured at a maximum of 11 ng/g, but most samples are below the detection limit of 2 ng/g (Vethaak et al. 2005).

Measured concentrations in soil

No monitoring data for concentrations of the medium-chain phthalates in soil could be found in Canada. DIBP and DCHP were detected in soils in China (Environment Canada 2015). Residential areas in China had DIBP concentrations ranging from 40 to 1420 ng/g (Zeng et al. 2009; Hongjun et al. 2013). DCHP levels in the soil of residential areas were lower, with concentrations of approximately 71 ng/g and a greater number of samples with concentrations below the detection limits (Zeng et al. 2009). Based on trends found in comparing water and sediment samples from Canada to those from China, it would be expected that soil in Canada would also have lower concentrations.

Measured concentrations in biota

A series of studies on the distribution of dialkyl phthalate esters in a marine environment have been conducted in False Creek Harbour. Environment Canada (2015) lists the

lipid equivalent concentrations found in biota in False Creek Harbour. Samples from 1999 and 2005 show that DIBP was detected in at least four levels of the aquatic food chain: algae, bivalves, fish and the Surf Scoter (Mackintosh et al. 2004; McConnell 2007). Bivalves and fish exhibited the highest concentrations, ranging from 32.4 to 160 ng/g lipid weight (lw) and 7 to 162 ng/g lw, respectively. While DIBP and other medium-chain phthalates are expected to be metabolized by aquatic organisms, a continuous exposure in these urban areas could be responsible for the concentrations measured in biota.

A study in Hudson's Bay measured the concentrations of DIBP in the Arctic cod and beluga whale, and found concentrations in both organisms. Morin (2003) compared the measured fish concentrations in the Arctic with those measured by Mackintosh et al. (2004) in urban areas. Comparisons were made between the Pacific staghorn sculpin (*Leptocottus armatus*) and the Arctic cod, as they hold a similar trophic level in the food web. Mackintosh et al. (2004) measured approximately 145 ng/g lw of DIBP in the sculpin in False Creek Harbour, while Morin (2003) measured a significantly higher concentration ($p < 0.05$) of 413 ng/g lw in the Arctic. Morin noted DIBP was the only phthalate that exhibited this significant increase in the Arctic. Median concentrations in the beluga whale were higher, at approximately 544 ng/g lw.

Long range transport is not expected to occur with the medium-chain phthalates, as discussed in section 7.1.1, and the high measurements of DIBP in biota in the Arctic are unexpected. The low measured concentration of 0.22 ng/g in sediment in the Arctic (Morin 2003), as compared to the higher measurements of 27 to 60.8 ng/g DIBP in False Creek Harbour (Mackintosh et al. 2006 and McConnell 2007), are consistent with the long-range transport predictions. DIBP concentrations in water were not measured in the Arctic. Nevertheless, Morin (2003) noted that the results indicate that phthalate esters are being transported northwards from mid-latitudes, as concentrations in the different ecosystems are similar, and emissions from sources in the Arctic would be minimal (e.g., small landfills). The source of the exposure is a key uncertainty of the data. While DIBP sources in the Arctic are expected to be minimal, it is possible that the Arctic cod and beluga whale were exposed to DIBP in another area of their migration. The Eastern Hudson Bay population of beluga whales are described by Morin (2003) as being permanent residents of the North. They have been found to leave Eastern Hudson Bay in the fall and go into Ungava Bay and as far as Nain, Newfoundland and Labrador, in the winter (COSEWIC 2004). Another possible source is from prey that could have been exposed to DIBP in their migration. The migration patterns of Arctic cod could not be found in the literature.

Contamination during field sampling or laboratory analysis is another possible reason for the high biota concentrations measured in the Arctic, although this is unlikely, as steps were taken to reduce the potential for contamination. The Arctic study was carried out by the same research group at Simon Fraser University that conducted the False Creek Harbour studies reported by McConnell (2007) and Mackintosh et al. (2004).

The measurements from the Morin study (2003) are the only data available in the literature for medium-chain phthalate concentrations in biota in the Arctic. Further work is needed in this area to determine if these measurements can be repeated, given the unexpected nature of the results.

8.2.2 Exposure scenario for B79P and B84P

Measured environmental concentrations are not available for B79P or B84P, the two medium-chain phthalates that have been reported to be in commerce in the highest quantities per industrial site in Canada (Environment Canada 2014). These substances are used in applications of automotive sealants and coatings in automobile and light-duty motor vehicle manufacturing. Through section 71 submissions and related communication with the automotive industry (Environment Canada 2014), it was learned that B84P and B79P are contained within automotive adhesives and sealers, which are applied in the body shop, in the paint shop and in general assembly at automobile and light-duty motor vehicle manufacturing plants. Body shop adhesives are applied between vehicle body panels, whereas body shop automotive sealers are applied as a weld sealer when vehicle bodies are assembled in the plant's body shop from sheet metal parts. The weld sealers are typically used for seam sealing, waterproofing and dust-proofing, and are applied to seams and joints directly on the metal. In the body shop, adhesives and sealers are pumped directly from their containers (typically lined 55 gallons drums) and applied to the body frame and panels using robots.

In the paint shop, sealers are supplied in lined 55 gallon drums and 300 gallon magna drums, and are pumped directly to the point of use. Most paint shop sealers are applied by robots directly to the vehicle body, depending on where the materials are needed. For example, some paint shop sealers are used for sound deadening and are applied to the inside of the vehicle floor and other inside panels where acoustical controls are needed. Other sealers are typically applied along the floor boards, the inside of the trunk and other interior cavities of the frame of the vehicle. These are not typically visible after vehicle assembly is complete. For certain areas in the vehicle, sealers may be applied manually by an operator, or by using a wand. In general assembly, urethane adhesive is used for windshield installation and is contained in lined 55 gallon drums. The material is applied by a robot.

In addition, some repair paints contain phthalates. Repair paints are used for quality control and are applied in very limited quantities (typically a few millilitres per vehicle) manually in a controlled area with air filtration system.

Among these applications, there are some possibilities for B84P and B79P to enter a wastewater stream at the facility of use. For example, the automotive industry specified that after the body shop weld sealant application, prior to painting, the vehicle frame known as the "Body in White" enters the wash and rinse stages to remove any oil, grease and dirt from the metal surfaces for quality control (Environment Canada 2014). There is therefore a theoretical potential for some sealer and phthalates to be transferred to an on-site wastewater treatment system during the cleaning process

(phosphating). However, no information is available on the amounts of weld sealants and their constituents that could potentially be lost to wastewater during the phosphating or cleaning process. Also, the automotive industry pointed out that if some sealers are removed during the wash and rinse stages, they will settle as solids at the bottom of the sludge tank and are removed during a prescribed cleaning schedule (at least once per year) (Environment Canada 2014). Phthalates are not chemically bound to the polymer, meaning that a migration of phthalates from the sealant solids at the bottom of the sludge tank is theoretically possible over the course of one year. This is a large uncertainty for this exposure assessment. Consequently, the quantitative exposure analysis cannot be performed at this time due to a lack of information to assess. The sampling of on-site effluent could be recommended in this case to obtain the predited environmental concentration for use in risk characterization.

With respect to the sealers and adhesives applied in the paint shop or in general assembly, they are all applied after the rinse and wash stages that occur prior to painting and are therefore not rinsed after application. Consequently, no releases to on-site wastewater are expected.

8.3 Characterization of ecological risk

8.3.1 Consideration of lines of evidence

The substances in the medium-chain phthalate subgroup biodegrade relatively quickly in the environment and are therefore expected to have a relatively short residence time in water, soil and sediment. However, at very low concentrations, biodegradation processes have been observed to slow down, resulting in background levels. With low to moderate water solubilities and high log K_{oc} values, these substances are expected to be found in water, soils and sediments. Levels of medium-chain phthalates have been measured globally in these media, including Canadian locations. The analogues BBP and DBP have been measured in biosolids in Vancouver. There is limited evidence for long-range transport, based on a study of the smallest of the medium-chain phthalates, DIBP, which can potentially be attributed to fine particle transport. Medium-chain phthalates have low to moderate bioaccumulation potential. They are moderately toxic to organisms, acting through polar narcosis. Data related to endocrine effects of the medium-chain phthalates are limited. While *in vitro* studies suggest that the analogue phthalate BBP could be weakly estrogenic, the limited *in vivo* studies suggest lack of endocrine activity in fish. The analogue DEHP has been found to act as a weak estrogen agonist in fish in both *in vitro* and *in vivo* studies. DCHP was found to disrupt gene expression of the thyroid hormone, and cellular axes in amphibians.

Based on industry submissions for the medium-chain phthalates in response to a section 71 survey (Environment Canada 2014), the reported uses of these phthalates in Canada are in automotive sealants and coating applications, in high-temperature coating manufacturing and applications, in adhesive and sealant manufacturing and applications, and in printing ink manufacturing and applications. Also, the medium-chain phthalates are imported to Canada as solvents for manufacture of thermoplastic and

thermosetting resins or as a part of plastic resins and PVC cables for electronic equipment. However, only B84P and B79P were identified with high-use volumes in Canada. Five of the substances, CHIBP, BCHP, DMCHP, BIOP and DBzP, do not appear to be imported or used in Canada above the reporting thresholds, and three of the substances, DIBP, DCHP and DIHepP, are imported to Canada either in small quantities and distributed among different customers or imported to Canada as part of the final articles (e.g., PVC cables, computer parts and farm, lawn and garden machinery) (Environment Canada 2014). Therefore, for these eight phthalates, releases to the aquatic environment from industrial activities are expected to be dispersed and low.

CHIBP, BCHP, DMCHP, BIOP and DBzP

Given that CHIBP, BCHP, DMCHP, BIOP and DBzP are either not used or used in very limited quantities in Canada (Environment Canada 2014), exposure and risk characterization will not be further defined.

DIBP and DCHP

Releases to the aquatic environment from industrial activities and consumer uses of DIBP and DCHP are expected to be dispersed and low. Due to the limited information on the potential industrial process and releases from products of DIBP and DCHP, the predicted environmental concentrations (PECs) were not calculated using estimates or calculations for parameters such as substance loss to environmental media and removal rates. Instead, measured environmental concentrations in Canadian locations were used to define the PECs and to characterize risk. In selecting the PECs based on measured concentrations, consideration was given to the analytical precision of the reported values (i.e., proximity to detection limits) and the number of samples included in the estimate. For the medium-chain phthalates, the available measured concentrations that were selected as PECs are listed in Table 8-6. As monitoring data were not available for DCHP, the measured value for DIBP has been used to calculate the PEC for DCHP. This is expected to be a conservative assumption, given that DIBP quantities reported in Canada are higher than DCHP (Table 4-2), and the reported uses are similar (Table 5-1). This is further supported by a comparison of the DCHP concentrations reported in wastewater effluent in other countries (in the range of 5.43 to 15 ng/L), which are lower than those reported for DIBP in Canada (17.65 ng/L). A sediment PEC could only be calculated for DIBP (reported in Table 8-9), as other medium-chain phthalates have not been measured in sediment in Canada.

PEC values based on the measured substance concentration in the environment are presented in Table 8-9.

Table 8-9. Predicted environmental concentrations (PECs) based on measured environmental concentrations considered in ecological risk characterization

Common name	Location	Sampling period	Predicted environmental concentration	Reference
DCHP	Alberta, Canada Downstream of MWWTP	2002–2003	2.85×10^{-6} mg/L (2.85 ng/L)[1]	Sosiak and Hebben 2005
DIBP	Alberta, Canada Downstream of MWWTP	2002–2003	2.85×10^{-6} mg/L (2.85 ng/L)	Sosiak and Hebben 2005
DIBP	British Columbia, Canada False Creek Harbour sediment	1999	5.6 ng/g dw	McConnell 2007

[1] Based on the concentration of DIBP measured.

A risk quotient analysis for DIBP and DCHP, based on a qualitative analysis of exposure, predicted environmental concentrations (PEC) (based on measured quantities in the environment) and toxicity information, was performed. Table 8-10 provides a summary of this information.

Table 8-10. Summary of risk quotients obtained for different environmental media and exposure scenarios for DIBP and DCHP

Common name	Media	PNEC	PEC	RQ
DCHP	Water	6.0×10^{-2} mg/L	2.85×10^{-6} mg/L	4.75×10^{-5}
DIBP	Water	0.19 mg/L	2.85×10^{-6} mg/L	1.5×10^{-5}
DIBP	Sediment	16.64 mg/kg dw	5.6 mg/kg dw	0.34

Based on the information available, DIBP and DCHP are unlikely to cause harm in the Canadian environment. It is noted that the use of PECs derived from measured environmental concentrations may contribute to the underestimation of environmental risk. Sampling locations away from the actual sources of release, delayed timing of sampling allowing for environmental degradation, errors in detection, or degradation of samples may be some of the reasons that could influence the measurement of chemicals in the environment. For DIBP and DCHP, there is a five-order-of-magnitude margin of safety in the calculated aquatic RQs that reduces the significance of this uncertainty.

DIHepP

Releases to the aquatic environment from industrial activities and consumer uses of DIHepP are expected to be dispersed and low.

Results from an analysis of critical body residues (CBRs) derived using the water solubility limit of DIHepP indicated that maximum tissue concentrations of DIHepP based on solubility limits will be much lower than levels associated with adverse acute or chronic effects in organisms due to neutral narcosis. Similar analyses conducted for DIHepP in sediment organisms indicated that maximum tissue concentrations calculated from the saturation limit of DIHepP in a 4% OC sediment do not exceed minimum concentrations estimated to cause narcotic effects. Therefore, while DIHepP has been measured in Canadian surface waters and sediment (no soil monitoring data are available), it is unlikely that internal body concentrations in exposed organisms will reach levels that are sufficiently high to cause adverse effects. For example, a maximum freshwater concentration of 68.7 ng/L was reported for DIHepP upstream of a municipal wastewater treatment plant (Sosiak and Hebben 2005). This corresponds to a CBR in aquatic organisms of 0.085 mmol/kg (see CBR calculation in the ecological effects assessment section). As this value falls below the ranges of 2 to 8 mmol/kg and 0.2 to 0.8 mmol/kg for acute and chronic effects, respectively, aquatic organisms exposed to this concentration in the environment are unlikely to exhibit adverse effects resulting from baseline narcosis. Similarly, Mackintosh et al. (2006) reported a highest sediment concentration of 60.8 ng/g dw for DIHepP in an estuarine sediment collected in Vancouver, British Columbia. The CBR in sediment organisms is 8.8×10^{-5} mmol/kg (see CBR calculation in the ecological effects assessment section), indicating that adverse effects due to neutral narcosis are unlikely to occur.

Several studies report the presence of DIHepP in a number of Canadian aquatic species. A mean concentration in fish of 44 ng/g ww was measured in juvenile Shiner Perch (McConnell 2007). This was converted to CBR units in order to investigate whether tissue levels in the fish were high enough to potentially result in adverse effects attributable to baseline narcosis. The CBR for this tissue concentration is 1.2×10^{-4} mmol/kg (0.044 mg/kg / MW 362.51 g/mol). This value is below the ranges of 2 to 8 mmol/kg and 0.2 to 0.8 mmol/kg attributed to acute and chronic narcotic effects, respectively, suggesting that the Pacific staghorn sculpin in the study are not likely to be experiencing adverse narcotic effects due to the presence of DIHepP in their tissues.

B84P and B79P

Due to the limited information on the potential industrial process and releases from products of B84P and B79P and the lack of measured environmental concentrations, no Predicted Environmental Concentrations (PECs) for B84P and B79P are proposed at this time. When available, monitoring data may be considered for estimating potential exposure and in risk characterization.

8.3.2 Uncertainties in Evaluation of Ecological Risk

There is limited knowledge of industrial processes for the medium-chain phthalates, which has a direct impact on an accurate evaluation of their potential releases and risk characterization. For most substances, a derivation of a PEC based on modelled scenarios was not possible. PECs were therefore derived from measured environmental

concentrations. Lack of monitoring data and limitations in the availability of information on the potential industrial processes and releases from products of B84 and B79P do not allow for the calculation of a PEC.

Although monitoring data were available at numerous locations, they may not be ideal for characterizing the risk of the medium-chain phthalates, as the locations may not correspond to areas of environmental releases. A monitoring campaign of the ten medium-chain phthalates will be undertaken by Environment Canada from 2014 to 2015. It will include wastewater treatment plants situated across Canada.

Limited monitoring data for DIBP in the Arctic that show the presence of this substance in biota were presented by Morin (2003). It is thought that these findings require further investigation, as they point to an unexpected presence of these substances in locations distant from sources of exposure. Long-range transport predictions suggested that medium-chain phthalates do not have the potential to travel long distances. Fine particle transport is considered as a plausible explanation.

The monitoring data provide clear evidence that the medium-chain phthalates are found in the aquatic environment. Studies suggest that certain phthalates (such as BBP) have the potential to cause effects on the endocrine system; however, such studies have not been conducted for any of the substances in the medium-chain phthalates subgroup. The use of the analogue BBP for the evaluation of the potential for endocrine effects of the subgroup in aquatic organisms is uncertain. Such effects are substance-specific and structure-dependent and can affect organisms at different life stages through different mechanisms of action. Therefore, medium-chain phthalates should be evaluated independently for their potential to cause effects on the endocrine system.

For numerous medium-chain phthalates, there were no experimental data on physical-chemical properties, degradation, bioaccumulation and ecological effects. Consequently, the analogue and read-across approaches were heavily used throughout the assessment of these substances. These approaches were considered appropriate; analogues and (Q)SAR models were thoughtfully considered. However, because the data were not specific to the medium-chain phthalates, there is a level of uncertainty associated with the application of read-across and modelled data that, in effect, may translate into over- or underestimation of overall risk associated with the environmental presence of these substances.

There was uncertainty in the analysis of biodegradation of medium-chain phthalates. Although biodegradation studies are available for numerous substances, they follow different protocols of varied duration and degree of inoculum acclimation. This leads to difficulty in assessing biodegradation rates and comparing results across the studies.

To be more certain in the evaluation of risk, the data outlined in Table 8-11 are needed for the substances in the medium-chain phthalate subgroup.

Table 8-11. Summary of data needs to reduce uncertainties in the ecological assessment of medium-chain phthalates

Data gaps	Details
Sediment and soil effects	Toxicity studies in soil and sediment species conducted according to OECD or other internationally recognized protocols.
Effects studies addressing endocrine activity and effects on reproduction in aquatic and terrestrial organisms	Studies or assays addressing endocrine activity and effects on reproduction (including testicular dystrophy) in aquatic species, such as fish, and in terrestrial organisms, such as earthworms, according to OECD or other internationally recognized protocols.
Monitoring in urban areas and in the Arctic	Work to be undertaken by Environment Canada in 2014–2015 in urban areas. Additional studies in the Arctic are needed.
Industrial processes and applications	Information specific to industrial application in the automotive sector for B79P and B84P. General knowledge of processes and applications allowing evaluation of industrial releases of medium-chain phthalates.

9. Potential to Cause Harm to Human Health

9.1 Exposure

9.1.1 DIBP

Environment media and food

The predominant sources of exposure are indoor air, dust and food (see Appendix F-1). The subpopulation with the highest exposure from environmental media and food consisted of breastfed infants with total daily intakes of 1.6 and 5.9 µg/kg/day, based on central tendency and upper-bounding concentrations, respectively.

Ambient air, drinking water and soil

No Canadian data were identified for DIBP in ambient air. DIBP has been detected in ambient air internationally (see section 8.2.1; Rudel et al. 2010; Xie et al. 2007). Rudel et al. (2010) was identified as the relevant study for exposure characterization (sampling from North America), and median and maximum (3.6 ng/m^3, 18 ng/m^3) concentrations were used to estimate potential exposures to DIBP via ambient air.

Limited data was identified indicating the presence of DIBP in surface water. Available Canadian data was limited to wastewater concentrations downstream of industrial sites and are not relevant for estimating potential drinking water exposure. Additionally, DIBP was detected in tap water and surface water in China (Shao et al. 2013).

No Canadian data as to DIBP presence in soil was identified; however, it has been detected in agricultural, top soil and urban area soil in China at concentrations less than 4 µg/g (Liu et al. 2010; Zeng et al. 2009; Zeng et al. 2008b).

Due to limited data pertaining to the presence of DIBP in soil, potential exposures were not estimated.

Bottled water

As phthalates are plasticizers with applications in packaging, they may be present in bottled water. In Canada, Cao (2008) surveyed phthalates in bottled carbonated and non-carbonated water and detected and quantified DIBP in all 11 samples (range: 0.133–0.481 µg/L). DIBP was also detected and quantified in bottled water samples internationally (Fierens et al. 2012a; Montuori et al. 2008; Guo et al. 2012; Cao 2008; Keresztes et al. 2013; Santana et al. 2014; Shao et al. 2013; Sun et al. 2013).

In the absence of data on levels of DIBP in tap water, mean (0.225 µg/L) and maximum (0.353 µg/L) concentrations of DIBP in bottled non-carbonated water were used to estimate the general population daily intake from drinking water (Cao 2008). The highest exposed subpopulation is 0 to 0.5 year-old (formula-fed) infants, and estimates of exposure are 0.024 and 0.038 µg/kg/day based on mean and maximum concentrations, respectively. The assumption that 100% of water consumption is from bottled water is considered conservative.

Indoor air and dust

Phthalates are semi-volatile compounds and are generally present in the indoor environment, likely due to their presence in plastic products (Weschler and Nazaroff 2010; Fromme et al. 2004; Bergh et al. 2011ab; Rudel et al. 2010; Bornehag et al. 2005). While long-chain phthalates tend to partition more to settled dust and surfaces, short-chain and low-molecular-weight medium-chain phthalates may partition in greater proportions to gaseous or particle phases of indoor air (Weschler and Nazaroff 2010; Fromme et al. 2004; Bergh et al. 2011ab). DIBP is considered to be a low-molecular-weight medium-chain phthalate and has been shown to exhibit these properties in paired dust and indoor air samples taken from residences in Germany and Sweden (Fromme et al. 2004; Bergh et al. 2011a). DIBP was detected in 100% of samples in these studies (Fromme et al. 2004; Bergh et al. 2011a). Additional key studies pertaining to dust and indoor air concentrations are listed below in Tables 9-1 and 9-2.

DIBP may be used in automotive repair adhesives and as a plasticizer in the manufacturing of various vehicle components (ECHA c2007–2014b). Phthalates have been monitored in air and particulate matter in car cabins, and DBP, DEHP and DEP have been detected; DIBP, however, was not detected (Geiss et al. 2009). No submissions indicating DIBP use in the manufacturing of automotive parts or automobiles in Canada were identified (Environment Canada 2014).

Table 9-1. DIBP concentrations in indoor air

Location	Detection frequency	Concentration (µg/m^3)	Reference
United States	100% of 50 homes	Median: 0.130 95th percentile: 0.370 Range: 0.017–1.7	Rudel et al. 2010
Germany	100% of 59 apartments	Median: 0.459 Mean: 0.697 95th percentile: 1.466 Max: 5.887	Fromme et al. 2004
Germany	100% of 74 kindergartens	Median: 0.505 Mean: 0.610 95th percentile: 1.522 Max: 2.659	Fromme et al. 2004
Sweden	100% of 10 homes	Median: 0.270 Mean: 0.296 Range: 0.140–0.560	Bergh et al. 2011a
Sweden	100% of 10 daycare centers	Median: 0.190 Mean: 0.239 Range: 0.046–0.810	Bergh et al. 2011a
Sweden	100% of 10 workplaces	Median: 0.230 Mean: 0.310 Range: 0.110–0.950	Bergh et al. 2011a
Sweden	Not provided (169 apartments)	Median: 0.230 Mean: 0.430 Not Detected (ND)[a]–11.0	Bergh et al. 2011b

[a] Not detected below the method limit of detection (0.058 µg/m^3).

Table 9-2. DIBP concentrations in dust

Location	Detection frequency	Concentration (µg/g)	Reference
Canada	98% of 126 homes	Median: 5.17 Range: ND–69 95th percentile: 16.2	Kubwabo et al. 2013
Canada	100% of 56 homes	Median: 4.2 Mean: 5.8 Range: 0.8–17	Zhu et al. 2007
United States	100% of 33 homes	Median: 3.80 Range: 0.7–34.3	Guo and Kannan 2011
Germany	100% of 30 apartments	Median: 37.5 Mean: 54.6 95th percentile: 144.4 Max: 161.3	Fromme et al. 2004
China	100% of 75 homes	Median: 17.20 Range: 2.6–299	Guo and Kannan 2011

Denmark	85% of 497 homes	Median: 16.6 Mean: 27.0	Langer et al. 2010
Denmark	95% of 497 homes	Median: 18.1 Mean: 23.0	Langer et al. 2010
Sweden	100% of 10 homes	Median: 4 Mean: 6 Range: Limit of Quantification (LOQ)[a] – 18	Bergh et al. 2011a
Sweden	100% of 10 homes	Median: 3 Mean: 9.1 Range: LOQ[a]–32	Bergh et al. 2011a
Sweden	100% of 10 homes	Median: 37 Mean: 43 Range: LOQ[a]–106	Bergh et al. 2011a

[a] Detected but below limit of quantification.

As no Canadian indoor air survey was identified, median (0.130 µg/m^3) and maximum (1.7 µg/m^3) concentrations from a United States study (Rudel et al. 2010) were used to estimate the general population daily intake of DIBP from indoor air. While these concentrations are approximately five times lower than the levels measured in Germany (Fromme et al. 2004), Swedish studies conducted more recently show comparable levels (Bergh et al. 2011ab).

The Canadian survey (Kubwabo et al. 2013) was identified as the key study for exposure characterization and median (5.17 µg/g), and 95th percentile concentrations (16.2 µg/g) were used to estimate the Canadian general population daily intake of DIBP from dust.

Estimated intakes from indoor air and dust exposure to DIBP were 1.6 and 5.9 µg/kg/day for 0- to 6-month-old infants (highest exposed group) for central tendency and upper-bound concentrations, respectively (see Appendix F-1, Table F-1a).

Food, beverages and infant formula

Some phthalates may be present in food and beverages through their potential use in PVC tubing and gloves, food packaging films, PVC gaskets for glass jars, printing inks in food packaging and the like (Fasano et al. 2012). Consequently, they have been detected in various food packaging and processing articles and have been known to migrate into food and beverages (Alin and Hakkarainen 2011; Barros et al. 2010; Bradley et al. 2007; Gartner et al. 2009; Page and Lacroix 1992; Fierens et al. 2012; Petersen et al. 2010; Xu et al. 2010; Xue et al. 2010).

In Canada, phthalates were monitored in a targeted survey of butter and margarine, including their packaging as part of Health Canada's Total Diet Study (Page and Lacroix 1992; Page and Lacroix 1995). DIBP was not detected in any of the samples measured

(Page and Lacroix 1992: limit of detection (LOD) = 1000 ppb; Page and Lacroix 1995: LOD = 50–500 ppb). Recently, a survey of phthalates was also conducted on meat, fish and cheese and their packaging films, with DIBP not being detected in any samples (Cao et al. 2014: LOD = 110 ppb).[4]

Phthalates have been monitored in total diet surveys and duplicate diet surveys in the United Kingdom, Belgium, United States, Germany, China and Taiwan, with DIBP being detected in all surveys. Specifically, DIBP was detected in 75% of 400 food samples in Belgium (Limit of quantification (LOQ): 0.03–15 ppb), 55% of 65 food samples in the United States (LOD: 0.2 ppb), 45% of 20 total diet survey food groups in the United Kingdom (LOD: 11.1–37.0 ppb), 61% of 350 duplicate diet samples (LOD: 10 ppb) and 100% of 171 duplicate diet samples in Germany (LOD: 0.2 ppb), > 60% of 70 food samples in China (LOQ: 2 ppb), and a significant proportion (detection frequency not stated) of 1200 food samples in Taiwan (LOD: 25–50 ppb) (Bradley et al. 2013ab; Fierens et al. 2012a; Schecter et al. 2013; Fromme et al. 2007; Fromme et al. 2013; Guo et al. 2012; Chang et al. 2014).

Data collected for the US total diet survey (Schecter et al. 2013) was considered representative of Canadian food levels (based on vicinity and food types evaluated) and was consequently used to estimate daily intake of DIBP for the general population. Additionally, the UK total diet survey (Bradley et al. 2013b) was also used to inform data gaps.[5]

Probabilistic dietary intakes were derived for DIBP; the methodology used and results are outlined in Appendix F-2 and Table F-1a, respectively.

The highest intake estimates, among infants and children, based on median food concentrations are for 1–3 year-olds with a dietary intake of 0.024 µg/kg/day. For adults, the highest intakes are for females 19 to 30 years of age with a dietary intake of 0.0042 µg/kg/day. For infants less than 6 months, the 90th percentile[6] dietary intake was estimated to be 0.12 µg/kg/day (highest 90th percentile intake for all populations).[7] For 1–3 year-olds, food types that drive intake estimates of DIBP are cream, crackers and

[4] Paige and Lacroix (1995) as well as Cao et al. (2014) had relatively lower sample sizes than other evaluated international studies. Furthermore, Paige and Lacroix (1995) was based on samples from the 1989 total diet survey and, consequently, is not considered representative of the current state of knowledge with respect to phthalate presence in food. Finally, Cao et al. (2014) targeted specific foods most likely to contain certain plasticizers, and total diet survey data for these same phthalates would be considered a more representative and unbiased source of phthalate occurrence data to use in dietary exposure assessments. Therefore, the Paige and Lacroix (1995) and Cao et al. (2014) studies were not used to generate exposure estimates.

[5] DIBP concentrations in food types monitored in Bradley et al. (2013b) but not in Schecter et al. (2013) were used in the exposure analysis.

[6] The 90th percentile is presented because the 95th percentile was not generated.

[7] The coefficient of variation associated with the median intake estimates was not sufficiently low to allow for reporting the intake value.

ready-to-eat cereals. For adults, food types that drive intake estimates for DIBP are cream, pork and ready-to-eat cereals.

Breast milk

DIBP metabolizes to the monoester MIBP in the gut, prior to uptake, although the parent substance may also be absorbed (Koch et al. 2012). Therefore, both DIBP and MIBP may be found in breast milk. Recently, Health Canada analyzed breast milk samples in the Maternal-Infant Research on Environmental Chemicals (MIREC) survey. DIBP was observed to be detected in 27 of 305 samples (Detection frequency (DF): 9%, mean: 33 ng/g, range: < method detection limit (MDL)–85.4 ng/g) (personal communication from Food Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, November 2014). However, these data were not used to quantify intakes, as it is thought that a majority of DIBP will metabolize to MIBP quickly; thus, MIBP is expected to be found at greater quantities and higher detection frequency than DIBP in breast milk (Koch et al. 2012).

Calafat et al. (2004) did not detect MIBP in any samples (n = 3 pooled samples) collected in the United States, while Hogberg et al. (2008) detected MIBP in 2 out of 42 samples (0.5 and 2.1 µg/L) in Sweden. In Italy, MIBP was detected in all 62 samples at a range of 8.4 to 57.2 µg/L (Latini et al. 2009). In the most recent breast milk survey, MIBP was detected in 100% of 74 samples collected in Germany (mean: 13.8 µg/L, median: 11.8 µg/L, range: 4.4–43.8 µg/L, 95th percentile: 27.9 µg/L) (Fromme et al. 2011).

The parent compound DIBP was not detected in 10 samples in Sweden (Hogberg et al. 2008) but was detected in 82% of 78 samples (mean: 1.5 ng/g, median: 1.2 ng/g, range: ND–5.3 ng/g) in Germany (Fromme et al. 2011).

Results from the most recent published German survey were used to estimate exposure from breast milk (Fromme et al. 2011). Since concentrations of MIBP were detected at higher concentrations than DIBP (consistent with current knowledge), MIBP concentrations were used for exposure characterization (after a molecular weight adjustment: parent MW/metabolite MW = 1.252). Mean and maximum concentrations were used to derive general population intakes which were estimated to be 1.5 and 5.4 µg/kg/day (see Appendix F, Table F-1a) for breastfed infants.

Products Used by Consumers

Manufactured items/children's articles/children's toys/textiles

DIBP may also be present in a wide variety of manufactured items including plastic sandals, balance balls, furniture, and decorative articles (Danish EPA 2011; Danish EPA 2010ab). Canadian use of DIBP was identified in toys and exercise equipment (e.g., yoga mats, balance balls) (Environment Canada 2014).

DIBP has also been reported to be present in leather articles, textiles, and apparel (ECHA c2007–2014b) and has been detected in 6 out of 10 t-shirt samples at concentrations of less than < 0.002% (Danish EPA 2010a). Globally, other phthalates (DCHP, B79P, B84P) have been reported to be present as coatings in textiles and fabric (see Table 5-2); however no reports of this use of DIBP in Canada were identified. However, DIBP was found to be present at a low frequency rate (see Table 9-5) in children's articles, such as bibs, handbags, slippers and balls (Health Canada 2007b, 2014). Concentrations in these articles ranged from 0.003 to 61.7%.

It is expected that the general population may be exposed to DIBP from dermal contact with these articlesand, in the case of small children, potentially from mouthing articles, such as toys.

Dermal exposure

Dermal exposure to phthalates from products such as toys, balance balls and sandals has been assessed by other jurisdictions (Danish EPA 2011; Danish EPA 2010ab; NICNAS 2011). For DIBP specifically, the internal dose from dermal contact with these articles[8] was estimated to be 0.58 to 4.92 µg/kg/day and 1.0 to 3.6 µg/kg/day for adults and children, respectively (Danish EPA 2011; Danish EPA 2010ab). The Danish EPA also estimated dermal exposure to DIBP from dermal contact with school bags, toy bags, pencil cases and erasers (range between 0.01 and 32.54 µg/kg/day, Danish EPA 2007).[9]

A conservative exposure assessment was conducted to estimate exposure to DIBP from dermal contact with the various manufactured items mentioned above. Two representitative scenarios were developed to model exposure of infants in contact with various plastic articles (PVC, polyurethane, polyester, etc.) for 1 hour/day with 25% of their body surface area (representative of multiple diaper changes per day on a change pad) and for 4 hours/day with 50% of their body surface area (representative of holding a plastic article and being changed on a plastic change pad multiple times a day and playing on a plastic mat).

Two representitative scenarios to model exposure of adults in contact with various plastic articles were also assessed: the first for 3 hours/day with 16% of their body surface area (analogous to sitting on a couch or wearing plastic gloves), and the second for 3 hours/day with 50% of their body surface area (representative of various daily contacts with plastic articles including wearing gloves or holding a plastic steering wheel, sitting on a couch and wearing plastic clothing).

[8] Sandals and balance balls.
[9] This assessment was based on the assumption of 100% dermal absorption; however, this assumption was refined to 10% in a later assessment of various childcare articles (Danish EPA 2010ab; Danish EPA 2011).

Rates of DIBP migration from plastics into a solution simulating sweat have been studied and are summarized in Table 9-3.

Table 9-3. Rates of DIBP migration into simulated sweat from various articles

Method	Type of article	% content	Migration ($\mu g/cm^2$)	Reference
In vitro, static[a]	Sandals	ND–21	ND–7.9	Danish EPA 2010a
In vitro, static[b]	Balance ball	35	5.8	Danish EPA 2010b
In vitro, static[c]	Erasers, pencil cases	NS	0.0010–0.11	Danish EPA 2007
In vitro, static[c]	School bags, toy bags	NS	0.00028–3.0	Danish EPA 2007

Abbreviations: ND = not detected; NS = not specified
[a] 16-hour duration
[b] 1-hour duration
[c] 4-hour duration

An average migration rate of 2.5 $\mu g/cm^2/h$ was derived from these studies. Note that migration rates were derived without correcting for experiment duration (assuming all plasticizer comes out in the first hour; for example, 7.9 $\mu g/cm^2/h$ was averaged, not 7.9 $\mu g/cm^2$/16 h), as an evaluation of migration rate data shows that a majority of phthalates migrate out in the first 1 to 3 hours. Therefore, dividing the migration rate by 16 hours would lead to underestimation of exposure. This scenario assumes zero dermal lag times and does not account for plasticizer depletion, both of which are conservatisms in the scenario.

Estimates of exposure for adults and children from dermal contact with plastic articles are provided in Table 9-4.

Table 9-4. Estimated daily exposure to DIBP from dermal contact with plastic articles in two scenarios for infants (0-18 months) and adults.

Migration rate ($\mu g/cm^2/h$)	Infant exposure ($\mu g/kg/day$)[a]	Adult exposure ($\mu g/kg/day$)[a]
2.5	30.7 (SA[b]=922 cm^2; T[c]=1h) 245.3 (SA=1840 cm^2; T=4h)	30.8 (SA=2912 cm^2; T=3h) 96.3 (SA=9100 cm^2; T=3h)

[a] Based on the following algorithm: Daily exposure = (MR x SA x T x DA)/BW
Where:
[b] SA = surface area
[c] T = contact time
DA = dermal absorption of 10%. See Appendix H for approach to characterizing dermal absorption to medium-chain phthalates.
BW = body weight (7.5 kg for infants and 70.9 kg for adults); the same parameters (contact time, surface area) are assumed for infants 6 to18 months, but body weights are > 7.5 kg.

These exposure estimates are higher than estimates of systemic exposure following dermal contact reported by Danish EPA 2011 and others and much higher than estimates of exposure from biomonitoring studies (Tables 9-12–15). Additionally, these estimates have significant uncertainty associated with them, as there is high uncertainty with respect to factors such as surface area and contact time.

Oral exposure

DIBP has also been detected in childcare articles and toys; the results are summarized in Table 9-5.

Table 9-5. % Content of DIBP in childcare articles and toys

Location	Detection frequency	% Content	Reference
Canada	6 of 117 samples	0.003 to 61.7	Health Canada 2014
Canada	8 of 101 samples	Mean: 4.5 Range: 0.05–13.9	Health Canada 2007b
Canada	0 of 6 samples	ND	Stringer et al. 2000
Various countries (including Canada)	1.6% of 72 toys	range: ND–0.45	Stringer et al. 2000
Europe	9 of 252 samples	Mean: 22 Range: 0.4–35	Biedermann-Brem et al. 2008
Lebanon	1 of 21 samples	Range: 0–0.9	Korfali et al. 2013

The various types of toys and articles tested included items such as dolls, figurines, building blocks and cars to modelling clays, bath toys and bibs (Health Canada 2007b; Stringer et al. 2000; Biedermann-Brem et al. 2008; and Korfali et al. 2013).

Several jurisdictions have evaluated the migration of phthalates (DINP, DEHP, DBP, etc.) from toys and childcare articles into simulated saliva (Danish EPA 2010a; RIVM 1998; RIVM 2001; NICNAS 2010; Danish EPA 2011). DIBP migration into saliva has been evaluated in one study (balance ball), while DBP[10] has been evaluated in numerous studies[11] (Danish EPA 2010a; RIVM 2001; Niino et al. 2001, 2003).

Migration rates for DIBP and DBP have been organized according to % content and magnitude of migration, and are outlined in Table 9-6. The data indicates that DBP migration rates follow a linear relationship with % concentration and *in vivo* migration rates are approximately ten-fold lower. However, DBP has been shown to metabolize in

[10] A phthalate similar to DIBP in terms of structure, molecular weight and solubility: DBP CAS RN 84-74-2, MW: 278.34 g/mol, log K_{ow}: 4.46, water solubility: 11.4 mg/L.
[11] Examples of PVC toys sampled: toy balls, dolls, aprons, teething rings.

saliva as concentrations of the monoester, MBP, reach 87% within 60 minutes (Niino et al. 2001, 2003). Therefore, DBP *in vivo* migration rates, if calculated solely on DBP appearance in saliva, may be underestimated.

Table 9-6: *In vivo* and *in vitro* migration rates into saliva from children's toys and articles

Method[a,b]	Migration rate (µg/cm^2/h)	% content	Reference
In vitro			
Static (DIBP)	3.7	35.40	Danish EPA 2010a
Dynamic (DBP)	1.38–5.04	1.56–3.46	RIVM 2001
Dynamic (DBP)	12.78	7.11	RIVM 2001
Dynamic (DBP)	33.9	10	Niino et al. 2001
Dynamic (DBP)	17.2–58	10–13.50	Niino et al. 2003
Dynamic (DBP)	79.2	22	Niino et al. 2003
Dynamic (DBP)	69.9–82.62	32.71–36.30	RIVM 2001
Dynamic (DBP)	144.8	47.10	Niino et al. 2003
In vivo			
Chewing/sucking (DBP)	1.2	10	Niino et al. 2001
Chewing/sucking (DBP)	11.7	10	Niino et al. 2003

[a] For *in vitro* methods, various PVC objects (e.g., toys, toy balls, dolls, aprons, teething rings) were immersed in a solution simulating saliva and were either kept static or dynamic (shaken to simulate sucking and chewing).
[b] All tests are 60 minutes, except for Niino et al. 2003, which evaluated *in vitro* migration over 15 minutes.

Mouthing time, surface area exposed and frequency of mouthing have been evaluated and summarized in numerous publications (Babich et al. 2004; USEPA 2011; Greene 2002; Juberg et al. 2001; Xue et al. 2010). ECHA evaluated these parameters for phthalates in a recent DINP and DIDP risk assessment, and used daily mouthing durations of children's toys and articles to be 0.5 to 2 hours/day for typical and worse case scenarios, respectively. A surface area mouthed of 10 cm^2 was used (ECHA 2013a).

Exposure to DIBP from mouthing of toys and childcare articles was estimated as a range based on *in vitro* migration rates of DIBP and DBP.[12] Exposure estimates for infants 0 to 18 months ranged from 2.47 to 251.0 µg/kg/day (see Table 9-7).

Table 9-7. Daily exposure estimates from mouthing toys and childcare articles

% content,	Migration	Exposure	Exposure

[12] *In vivo* migration studies were not used, as they may underestimate migration of DBP from the product (see above).

substance, and type of article used in migration rate study	rate (µg/cm^2/h)	µg/kg/day (mouthing time 0.5 h/day)[a,b,c]	µg/kg/day (mouthing time 2 h/day)[a,b,c]
35.4 (DIBP, balance ball)	3.70[d]	2.47	9.87
1–10 (DBP, toy balls, yellow hand, red feet)	5.31[e]	3.54	14.2
10–15 (DBP, toy balls)	36.0[f]	24.0	95.9
> 20 (DBP, toy balls, formulated toy)	94.1[f]	62.8	251.0

[a] A surface area of 10 cm^2 mouthed was used to estimate exposure.
[b] Algorithm: Exposure (per day) = (MR x SA x T)/BW
[c] A body weight of 7.5 kg was used for infants 0 to 6 months; for infants > 6 months to 18 months, the same migration rates and mouthing time were used, but due to higher body weight (> 7.5 kg), intakes will be lower than above and not presented (< 251.0 µg/kg/day).
[d] Danish EPA 2010a
[e] RIVM 2001; Niino et al. 2001, 2003
[f] Niino et al. 2003

Cosmetics and personal care products

Based on notifications submitted under the Cosmetic Regulations Health Canada DIBP is not expected to be present in cosmetics in Canada (September 2014 email from the Consumer Product Safety Directorate (CPSD), Health Canada to Existing substances Risk Assessment Bureau (ESRAB), Health Canada). DIBP has been detected in various types of cosmetics and personal care products[13] (Koniecki et al. 2011; Guo and Kannan 2013ab; Liang et al. 2013). This presence may be due to potential migration from packaging. A summary of recent studies measuring concentrations of DIBP in cosmetics and personal care products is outlined in Table 9-8.

Table 9-8. Concentrations of DIBP in cosmetics and personal care products

Detection frequency and product types[a]	Concentration (µg/g)	Reference (country)
5% of 85 fragrance, haircare and deodorant products	ND–4.5	Koniecki et al. 2011 (Canada)
7% of 69 nail polish, lotion and skin cleanser products	ND–4.1	Koniecki et al. 2011 (Canada)
0% of 98 baby products	ND	Koniecki et al. 2011 (Canada)

[13] For the purpose of this document, a personal care product is defined as a substance or mixture of substances, in a product, that is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada, cosmetics, drugs or natural health products.

27% of 41 rinse-off products	ND–0.39	Guo and Kannan 2013a (USA)
23% of 109 leave-on products	ND–58.9	Guo and Kannan 2013a (USA)
10% of 20 baby products	ND–0.09	Guo and Kannan 2013a (USA)
17% of face cream, body or hand lotion products	ND–3.4	Guo and Kannan 2013b (China)
15% of face cleanser, shampoo and body wash products	ND–1.3	Guo and Kannan 2013b (China)

[a] The detection limits are as follows: Guo et al. 2013 and Guo and Kannan 2013 report detection limits of 0.1 µg/g and 0.01 µg/g, respectively, while Koniecki et al. 2011 report a detection limit of 0.1 µg/g.

Since the two North American studies report that detection frequencies are low (5 to 7% in Canada, 10 to 27% in USA), and a majority of the concentrations in all three studies are in the sub-ppm range, exposure from personal care products and cosmetics may not be significant.

Estimates of dermal exposure from cosmetic products associated with the highest potential exposure are presented in Table 9-9. The products presented were chosen because they are associated with leave-on application, highest frequency of use and highest DIBP concentration.

Table 9-9. Estimates of dermal exposure from cosmetics use

Product type	Concentration (µg/g)	Intake (µg/kg/day)
Dermal[a]		
Body lotion (adult)	Median: ND; Max: 4.1[b]	Median: N/A; Max: 0.028
Face cream (adult)	Mean: 0.3; Max: 3.4[c]	Mean: < 0.001; Max: 0.010
Deodorant	Mean: ND; Max: 4.5[a]	Mean: N/A; Max: 0.0050
Nail polish	Mean: 11; Max: 58.9[d]	Mean: < 0.001; Max: 0.0018

[a] Applied a 10% dermal absorption factor. See Appendix H for approach to characterizing dermal absorption to medium chain phthalates.
[b] Koniecki et al. 2011
[c] Guo et al. 2013
[d] Guo and Kannan 2013

The highest estimate of dermal exposure to DIBP from cosmetics is from use of body lotion, with an estimated systemic exposure of 0.028 µg/kg/day generated using maximal concentrations from Koniecki et al. (2011). For the oral route, exposure to DIBP from presence in lipstick was estimated to be < 1 ng/kg/day.

For baby products, Guo and Kannan et al. (2013) surveyed shampoo, lotions and oils, baby powder, sunscreen and diaper cream, with DIBP being present in only two baby

shampoo samples out of four (mean: 0.03 µg/g, max: 0.09 µg/g). Additionally, Koniecki et al. (2011) showed non-detection in 98 baby products (lotions, oil, diaper creams and shampoo). Using mean and maximum concentrations in Guo et al. (2013), exposure estimates were generated for infants 0 to 6 months (baby shampoo use) and were estimated to be < 0.001 µg/kg/day.

Koniecki et al. (2011) did not generate estimates for DIBP, stating that concentrations were less than 10 µg/g, while Guo et al. 2013 generated aggregate leave-on exposure estimates of 0.0005 and 0.004 µg/kg/day using mean and max concentrations, respectively. These aggregate exposure estimates are generally consistent with the estimates presented above.

Biomonitoring

DIBP is expected to be metabolized in the body primarily to the unique monoester MIBP (Koch et al. 2012). The fractional urinary excretion (FUE) of a substance is defined as the mole ratio of the amount of metabolites excreted in urine (at 24 hours) to that of total parent compound ingested. FUEs of MIBP and the secondary metabolite 2OH-MIBP are presented below in Table 9-10.

Table 9-10. Major Fractional Urinary Excretion (FUE) for DIBP primary and secondary metabolites

Metabolite	Molecular weight	FUE	Reference
Mono-iso-butyl phthalate (MiBP)	222	0.71	Koch and Calafat 2009; Koch et al. 2012
2OH-MiBP	239	0.20	Koch et al. 2012

MIBP has been monitored in the Canadian Health Measures Survey (CHMS) Cycle 2 (2009–2011) with 100% detection in all samples (Health Canada 2011, 2013). MIBP and 2OH-MIBP were also monitored by Health Canada in two cohort surveys: Plastics and Personal Care Product Use in Pregnancy survey (P4, n = 31 women, 542 individual urine spot samples; women provided multiple urine samples over two visits), and Maternal-Infant Research on Environmental Chemicals – Child Development Plus study (MIREC-CD Plus, 194 children, 2–3 years old, 1 spot sample per individual). Both these surveys reported a 100% detection of both metabolites (personal communication from Environmental Health Science and Radiation Directorate [EHSRD] to Existing Substances Risk Assessment Bureau [ESRAB], October 2013, 2014).

Finally, in the United States, the National Health and Nutrition Examination Survey (NHANES) also monitored MIBP in urine during survey years 1999–2012 and show high detection frequencies (CDC 2014).

Using the CHMS, P4 and MIREC-CD Plus datasets, reverse dosimetry intake estimates were generated. Metabolite concentrations were adjusted for urine dilution using the creatinine correction method, a commonly used method for phthalate biomonitoring assessment (Fromme 2007; Christensen et al. 2014a; US CPSC CHAP 2014; Frederiksen et al. 2014). Daily creatinine excretion rates for participants were estimated using the Mage equation. Biomonitoring intakes are presented in Tables 9-12 through to 9-15 below (see Appendix G for further information on the methodology).

Table 9-11. Metabolites used for intake calculations in CHMS and P4 analyses

Survey used for intake analysis	Metabolite	Total FUE
CHMS[a]	MIBP	0.71
P4[a], MIREC-CD+[b]	MIBP + 2OH-MIBP	0.92

[a] In the event of non-detects, ½ LOD was imputed in intake calculation.
[b] Machine readings were used for values below the detection limit.

Table 9-12. CHMS biomonitoring intakes (µg/kg/day) for 3–5 year-olds (males and females)

Ages	n	Arithmetic mean	50th	75th	95th
3–5	514	1.5	1	1.7	3.7

Table 9-13. CHMS biomonitoring intakes for males (µg/kg/day)

Ages	n	Arithmetic mean	50th	75th	95th
6–11	260	1.5[a]	0.76 [a]	1.5 [a]	5.3 [a]
12–19	255	0.67	0.53	0.84	1.4
20–49	289	0.56	0.42	0.6	1.6
50–79	211	0.44	0.3	0.45 [a]	1.1 [a]

[a] Cumulative variation between 16.6 and 33.3%.

Table 9-14. CHMS biomonitoring intakes for females (µg/kg/day)

Ages	n	Arithmetic mean	50th	75th	95th
6–11	253	1.1	0.75	1.2	2.6
12–19	251	0.90 [a]	0.44	0.72	b
20–49	286	0.56	0.46	0.66	1.4 [a]

50–79	215	0.39	0.33	0.50	0.85

[a] Cumulative variation between 16.6 and 33.3%.
[b] Cumulative variation > 33.3%; data too unreliable to be reported.

Table 9-15. P4 pregnant women and MIREC-CD Plus (preliminary data) children daily intakes (µg/kg/day)

Age group (years)	n	Arithmetic mean	50th	75th	95th
2–3	198	1.1	0.85	1.4	2.9
19+	31[a]	0.55	0.36	0.54	1.2

[a] n = 31 women, 542 individual spot samples; women provided multiple urine samples over two visits.

The highest exposed group (all sources, CHMS) is 6–11 year-old male children with median and 95th percentile intakes of 0.76 and 5.3 µg/kg/day, respectively. For older populations, the highest exposed group (all sources, CHMS) is 12–19 year-old males with median and 95th percentile intakes of 0.53 and 1.4 µg/kg/day, respectively.

9.1.2 DCHP

Environment media and food

Ambient air, drinking water and soil

No Canadian data were identified for DCHP in ambient air, water or soil. Limited international monitoring data on DCHP presence in ambient air and surface water were identified. In ambient air, DCHP was not detected at industrial and rural sites in California (MDL: 1 ng/m^3). In surface water, DCHP has been detected in the Netherlands, Germany and China (see Section 8.2 for concentrations), while in groundwater, DCHP was not detected on Belgian farmland (Fierens et al. 2012b). Monitoring data on DCHP presence in drinking water were not identified.

DCHP was detected in topsoil, urban soil and agricultural soils in China and Belgium; however, concentrations (ND–0.30 µg/g) were generally lower than concentrations found in house dust (see Table 9-16) (Zeng et al. 2009; Liu et al. 2010; Fierens et al. 2012b).

Due to the absence of Canadian data on DCHP presence in ambient air, soil and water intake estimates were not generated for these sources.

Indoor air and dust

No Canadian data were identified for DCHP in indoor air. Elsewhere, DCHP has been detected in indoor air (both volatile and particulate matter) in one survey of homes conducted in Cape Cod, USA (21% of 102 homes; arithmetic mean: 3.4; median: ND; 90th percentile[14]: 210; range: ND–280 ng/m^3) (Rudel et al. 2003).[15] Additionally, a survey in Norway measured DCHP in $PM_{2.5}$ and PM_{10} particulates and reported no significant differences in the presence of DCHP in both particle phases ($PM_{2.5}$: ND–20 ng/m^3, mean: 4 ng/m^3, PM_{10}: ND–19 ng/m^3, mean: 5 ng/m^3) (Rakkestad et al. 2007).

DCHP has applications as a plasticizer in the manufacturing of automobiles and automobile parts (Environment Canada 2014). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the assessment.

Table 9-16. Dust concentrations of DCHP

Study location	Detection frequency and sample size	Concentration (µg/g)	Reference
Canada	59% of 126 homes	ND–3.4 median: 0.21 95th percentile: 1.0	Kubwabo et al. 2013
USA	18% of 33 homes	ND–0.3 median: ND	Guo and Kannan 2011
USA	77% of 101 homes	ND–62.1 median: 1.88	Rudel et al. 2004
China	15% of 75 homes	ND–0.3 median: ND	Guo and Kannan 2011
China	Detection frequency not reported: 23 homes	Homes: < LOQ–12.4 median: 0.71 µg/g	Kang et al. 2012
Kuwait	24% of 21 homes	median: 2.90, mean: 0.30	Gevao et al. 2013

The Canadian survey, Kubwabo et al. 2013 (median: 0.21 µg/kg, 95th percentile: 1.0 µg/kg) and Rudel et al. 2004 (arithmetic mean: 3.4, maximum: 280 ng/m^3) were identified as relevant studies for exposure characterization of the general population. Estimated intakes from indoor air and dust exposure to DCHP were 0.0018 and 0.15 µg/kg/day for infants 0.5 to 4 years (highest exposed group), for central tendency and upper-bound concentrations, respectively (see Appendix F-1, Table F-2).

[14] The 90th percentile is presented because this study did not report a 95th percentile
[15] Study authors also analyzed paired settled dust samples, while other surveys monitored DCHP presence in settled house dust exclusively, as described in Table 9-16.

Food, beverages and infant formula

DCHP has been identified as a component of food packaging material (US FDA 2014). In Canada, phthalates were monitored in a targeted survey of butter and margarine, including their packaging, and as part of Health Canada's Total Diet Study (Page and Lacroix 1992; Page and Lacroix 1995). DCHP was not detected in any of the samples.[16]

Internationally, DCHP has been monitored in three total dietary surveys conducted in the United States, United Kingdom and Belgium (Schecter et al. 2013; Fierens et al. 2012a; Bradley et al. 2013b). Schecter et al. (2013) detected DCHP in 4 out of 65 total diet survey samples,[17] while Bradley et al. 2013b did not detect DCHP in a majority of total diet survey samples. Fierens et al. (2012a) detected DCHP in 97 out of 400 total diet survey samples, with DCHP being detected in all food groups tested. Levels detected in food in the US total diet survey (Schecter et al. 2013) were used as the most relevant data to estimate dietary exposure of the general population. Additionally, the UK total diet survey (Bradley et al. 2013b) was also used to inform data gaps.

Probabilistic dietary intake estimates were derived for DCHP, with median and 90th percentile[18] intakes were <0.001 µg/kg/day.

Breast milk

Recently, an analysis of breast milk samples obtained from 56 Canadian women in the P4 cohort survey showed no detection of MCHP, the monoester of DCHP (LOD: 0.009 µg/L) (personal communication from EHSRD to ESRAB, October 2013).

Products used by consumers

DCHP was not detected in any samples from an emission chamber study measuring and modelling the emission of phthalates from 101 manufactured items (e.g. shower curtains, cable/wire) sampled from the Ottawa area (NRC 2012).

With respect to DCHP reported international use in the production of plastisols used in fabrics, textiles and apparel (ECHA . c2007–2014c), due to a lack of data on the migration of DCHP or a similar phthalate, exposure estimates from this source were not generated and are currently an uncertainty in this assessment.

[16] Paige and Lacroix (1995) included relatively lower sample sizes than other evaluated international studies. Furthermore, Paige and Lacroix (1995) was based on samples from the 1989 total diet study and, consequently, is not considered representative of the current state of knowledge with respect to phthalate presence in food. Therefore, Paige and Lacroix (1995) was not used to generate exposure estimates.

[17] DCHP was detected in the other dairy (cheese, yogurt, etc.), vegetable oil, condiments and infant food groups.

[18] The 90th percentile is presented because the 95th percentile was not generated.

Finally, DCHP was detected in 1 out of 36 perfume samples at a concentration of 3 mg/kg (SCCP 2007). Dermal exposure was estimated to be < 10 ng/kg/day.

Biomonitoring

DCHP is expected to be metabolized in the body primarily to the unique monoester MCHP (See section 9.2.1), and has been monitored in several surveys in North America. Specifically, MCHP has been monitored in CHMS Cycle 1 and 2, with 87 and 72% of samples being measured below the limit of detection (Health Canada 2011, 2013).[19] MCHP was also monitored by Health Canada in the MIREC, MIREC-CD Plus and P4 cohort surveys (Arbuckle et al. 2014; personal communication to ESRAB from EHSRD, October 2013, 2014).

In the United States, the National Health and Nutrition Examination Survey (NHANES) monitored MCHP in urine during survey years 1999–2010. From 1999 to 2004, MCHP was detected at the 90th percentile and above. In subsequent survey years, however, MCHP was not detected at the 95th percentile (CDC 2013).

Urinary concentrations and detection frequencies of MCHP are presented in Table 9-17.

Table 9-17. Uncorrected urinary concentrations of MCHP in various North American surveys

Study location	Detection frequency (DF) and sample size	Concentration	Reference
Canada[a]	7.8% of 1788 women	Geometric mean (GM): ND[f] 95th percentile: 0.38 µg/L	Arbuckle et al. 2014
Canada[b]	11.5% of 1056 samples	GM: not available (N/A) Maximum: 21 µg/L	Oct 2013 Personal Comm. EHSRD
Canada[c] (Cycle 1)	12.5% of 3227 individuals	GM: N/A 95th percentile: 0.89 µg/L	Health Canada 2013
Canada[c] (Cycle 2)	28% of 1594 individuals	GM: N/A 95th percentile: 0.45 µg/L	Health Canada 2013
Canada[d]	5% of 200 individuals	GM: N/A Maximum: 2.7 µg/L	Oct 2014 Personal Comm. EHSRD
USA[e] (1999–2004)	2541–2782 individuals;	Range of 95th percentiles: 0.603–2.21 µg/L	CDC 2013

[19] Cycle 2 has a lower detection limit than Cycle 1 (0.09 vs. 0.2 µg/L), which may explain the increased detection frequency between the two survey cycles.

	DF not stated		
USA[e] (2005–2010)	2548–2749 individuals; DF not stated	95th percentile: ND	CDC 2013

[a] 1st trimester pregnant women aged > 18 years: MIREC cohort
[b] 1st trimester pregnant women aged > 18 years: P4 cohort
[c] CHMS Cycle 1 and 2: 6–49 years of age, males and females
[d] 2–3 year-old children, MIREC-CD Plus cohort
[e] NHANES (1999–2010): 6 to 20+ years of age, males and females
[f] Not detected

Currently, information regarding DCHP toxicokinetics in humans is limited (e.g. FUEs cannot be determined), and reverse dosimetry intake estimates could not be derived from urine concentrations measured in humans.

9.1.3 DMCHP

Environment media and food

Monitoring data were not identified for DMCHP in ambient air, indoor air, surface water or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for DMCHP in food or food packaging materials (US FDA 2014).

Although DMCHP was not reported to be in commerce above the reporting threshold in Canada (see Uses section), it was detected in dust samples collected as part of the Canadian House Dust Study (CHDS), which analysed dust from 126 homes in ten cities across Canada (Kubwabo et al. 2013). Two isomers of DMCHP were identified in selected standards (DMCHP1 and DMCHP2) and the two isomers were detected in 37 and 89% of homes, respectively (DMCHP1 levels ranged from ND to 4.1µg/g, median: ND, while DMCHP2 levels ranged from ND to 24.3 µg/g, median: 0.53 µg/g, 95th percentile: 10.7 µg/g) (Kubwabo et al. 2013).

Levels of DMCHP2 were used to characterize exposure from dust, as this substance was present in more homes and was detected at higher levels. Estimates of exposure from DMCHP presence in dust were 0.0027 µg/kg/day (median) and 0.054 µg/kg/day (95th percentile) for the 0-to-6-month age group (highest exposed age group) (see Appendix Table F-3).

Products used by consumers

Based on information collected in the section 71 survey, no import, manufacture or export was identified for DMCHP (Environment Canada 2014). DMCHP was also identified to be not in commerce as per the DSL IU initiative (Canada 2009).

Generic uses have been reported for DMCHP in other jurisdictions (see Uses), and analysis of these uses indicated potential use of DMCHP in manufactured items. However, an emission chamber study measuring and modelling the emission of

phthalates in 101 manufactured items (cable/wire, shower curtains, caulking/sealant, etc.) did not detect emitted DMCHP in any of the samples (NRC 2012).

Therefore, based on the above considerations, direct exposure to DMCHP from use of products used by consumers or contact with manufactured items is not expected.

9.1.4 CHIBP

Monitoring data were not identified for CHIBP in ambient air, indoor air, surface water or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for CHIBP in food or food packaging materials (US FDA 2014).

CHIBP was an analyte in the CHDS and was not detected in any of the samples (MDL: 0.008 µg/g) (email from the EHSRD, Health Canada, to ESRAB, Health Canada, October 2013). An emission chamber study measuring and modelling the emission of phthalates from 101 manufactured items (cable/wire, shower curtains, caulking/sealant, etc.) detected CHIBP emission in six samples (NRC 2012). Specifically, CHIBP was detected in three shower curtain and three cable/wire samples, and a modelled average indoor air concentration of 2 ng/m^3 was derived by NRC (NRC 2012).

Based on information collected in the section 71 survey, no import, manufacture or export was identified for CHIBP (Environment Canada 2014). Therefore, given the absence of reporting to the section 71 industry survey, non-detection in dust, negligible modelled indoor air concentrations, and the absence of information as to CHIBP presence in product databases, general population exposure to CHIBP from environmental media and products used by consumers is expected to be negligible.

9.1.5 BCHP

Monitoring data were not identified for BCHP in ambient air, indoor air, surface water or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for BCHP in food or food packaging materials (US FDA 2014).

BCHP was an analyte in the CHDS and was not detected in any of the samples (MDL: 0.008 µg/g) (email from the EHSRD, Health Canada, to ESRAB, Health Canada, October 2013). Additionally, an emission chamber study measuring and modelling the emission of phthalates from 101 manufactured items (cable/wire, shower curtains, caulking/sealant, etc.) did not detect BCHP in any of the samples (NRC 2012).

Based on information collected in the section 71 survey, no import, manufacture or export was identified for BCHP (Environment Canada 2014).

Therefore, given the absence of reporting to the section 71 industry survey, non-detection in dust and products (emission chamber study), and the absence of information as to BCHP presence in product databases, general population exposure to

BCHP from environmental media and products used by consumers is expected to be negligible.

9.1.6 DBzP

Environment media and food

Monitoring data were not identified for DBzP in ambient air, indoor air, surface water or drinking water in Canada or elsewhere. DBzP may be used as an indirect additive in food packaging materials (US FDA 2014). However, monitoring data as to its presence in food were not identified. DBzP was monitored in two brands of bottled water in France and was not detected in any of the samples (Devier et al. 2013). DBzP has been identified as a candidate for monitoring as part of Health Canada's Total Diet Study (January 2014, email from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada).

DBzP was surveyed in the CHDS; however, chromatography analysis showed that DBzP co-eluted with another phthalate (BIOP, CAS RN 27215-22-1) under experimental conditions (Kubwabo et al. 2013). These methodological issues precluded separate quantification of the compounds, and DBzP and BIOP concentrations were reported together (DF: 83%; range: < DL–61.2 µg/g, median: 3.09 µg/g, 95th percentile: 19.1 µg/g) (Kubwabo et al. 2013). Since no BIOP manufacture, import or export was reported under the section 71 industry survey (Environment Canada 2014) and a search of databases revealed no evidence of BIOP use in products globally, chromatogram peaks in the CHDS are attributed to DBzP.

Therefore, estimates of exposure from DBzP presence in dust were derived, with the highest intakes (for infants 0 to 6 months) being 0.016 and 0.097 µg/kg/day for median (3.09 µg/g) and 95th percentile (19.1 µg/g) concentrations, respectively (see Appendix Table F-4).

Products used by consumers

DBzP was imported at quantities of less than 100 000 kg during 2008 (Canada 2009); however, it was not reported to be imported, exported or manufactured during 2012 (Environment Canada 2014).

DBzP uses, identified in the 2009 survey, were adhesives, sealants, paints and coatings, and these uses were corroborated by global uses (see Uses section). However, searches for concentrations did not identify any concentration information (HPD 2014). Finally, DBzP was measured in a study monitoring emission of phthalates in 101 manufactured items (vinyl flooring, wall coverings, caulking/sealant, shower curtains, cable/wire) and was not detected in any of the samples surveyed (NRC 2012).

Based on the above considerations, exposure to DBzP from use of products by consumers or contact with manufactured items is not expected.

9.1.7 B84P

Environment media and food

Monitoring data were not identified for B84P in ambient air, indoor air, surface water or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for B84P in food or food packaging materials (US FDA 2014).However, it is important to note that B84P has no laboratory standard, meaning that monitoring of this substance in different media is currently not feasible and unavailability of data does not indicate an absence of exposure. Additionally, a similar plasticizer with similar uses (B79P) was found to be present in 100% of dust samples in the CHDS (Kubwabo et al. 2013). It is therefore plausible that the general population may also be exposed to B84P.

In the absence of an appropriate analytical method for measuring B84P in dust, and because similar quantities and uses were reported in Canada (Environment Canada 2014), B79P dust intakes were used as a surrogate for B84P dust exposure. The highest estimate exposure (for infants 0 to 6 months) being 0.0063 and 0.047 µg/kg/day for median (1.2 µg/g) and maximum (52.3 µg/g) concentrations, respectively (see Appendix Table F-5).

B84P has applications in the production of automotive sealants and compounds used in the manufacturing of automobiles and vehicle parts (Environment Canada 2014). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the assessment.

Products used by consumers

B84P may also be used as a plasticizer in the coating of textiles and fabrics in multiple applications (e.g., personal apparel, vehicle upholstery) (ECHA c2007–2014d). Given high import volumes (see Section 4) and its global use pattern, potential exposure to the general population to B84P, from its use as a plasticizer in manufactured items (e.g. PVC, polyurethane, polyester), was characterized.

A conservative exposure assessment was conducted to estimate exposure to B84P from dermal contact with the various manufactured items (see Table 9-19). Two scenarios were developed to model exposure of infants in contact with various plastic articles (PVC, polyurethane, polyester, etc.) for 1 hour/day with 25% of their body surface area (representative of multiple diaper changes per day on a change pad) and for 4 hours/day with 50% of their body surface area (representative of holding a plastic article and being changed on a plastic change pad multiple times a day and playing on a plastic mat).

Two scenarios to model exposure of adults in contact with various plastic articles were also assessed: the first for 3 hours/day with 16% of their body surface area (analogous to sitting on a couch or wearing plastic gloves), and the second for 3 hours/day with

50% of their body surface area (representative of various daily contacts with plastic articles including wearing gloves or holding a plastic steering wheel, sitting on a couch and wearing plastic clothing).

Migration studies have shown that various phthalates can migrate from articles (sandals, children's articles, toys, etc.) into saliva and sweat (Danish EPA 2010ab; RIVM 2001; Babich et al. 2004). Given that B84P is similar in molecular weight, log K_{ow} and solubility to DEHP,[20] rates of DEHP migration into simulated sweat were used as an analogue to quantify exposure to B84P from dermal contact with plastic articles. An outline of the migration rates used for B84P is provided below (Table 9-18).

Table 9-18. Rates of DEHP migration into simulated sweat from various articles

Method	Type of product	Migration (µg/cm^2)	% content	Reference
In vitro, static[a]	Sandals	ND–1.7	ND–46	Danish EPA 2010a
In vitro, static[b]	Balance balls, articles	ND–0.38	ND–47	Danish EPA 2010b
In vitro, static[c]	Pencil cases	0.039	NS	Danish EPA 2007
In vitro, static[c]	School bags, toy bags	0.0098–0.011	NS	Danish EPA 2007

Abbreviations: ND = not detected; NS = not specified
[a] 16-hour experiment duration
[b] 1-hour experiment duration
[c] 4-hour experiment duration

An average migration rate of 0.22 µg/cm^2/h was derived from these studies. Migration rates were derived without correcting for experiment duration (assuming all plasticizer comes out in the first hour; for example, 1.7 µg/cm^2/h was averaged, not 1.7 µg/cm^2/16 h), as an evaluation of migration rate data shows that a majority of phthalates leach out in the first 1 to 3 hours. Dividing the migration rate by 16 hours would therefore lead to an underestimation of exposure. Note that this scenario assumes zero dermal lag times and does not account for plasticizer depletion, both of which are conservatisms.

Estimates of exposure for adults and children from dermal contact with plastic articles are provided in Table 9-19.

[20] DEHP: molecular weight: 391 g/mol; log K_{ow}: 7.14; water solubility: 0.003–0.03 mg/L

Table 9-19. Daily exposure estimates for B84P from dermal contact with plastic articles for infants (0–18 months) and adults

Migration rate (µg/cm^2/h)	Infant exposure µg/kg/day[a]	Adult exposure µg/kg/day[a]
0.22	2.7(SA[b]=922 cm^2; T[c]=1h) 21.6(SA=1840 cm^2; T=4h)	2.7 (SA=2912 cm^2; T=3h) 8.5 (SA=9100 cm^2; T=3h)

[a] Based on the following algorithm: daily exposure = (MR x SA x T x DA)/BW
Where:
[b] SA = surface area
[c] T = contact time
DA = dermal absorption of 10%. See Appendix H for approach to characterizing dermal absorption to medium-chain phthalates.
BW = body weight (7.5 kg for infants and 70.9 kg for adults); the same parameters (contact time, surface area) are assumed for infants 6 to18 months, but body weights are > 7.5 kg.

Conservative estimates of dermal exposure from contact with plastic articles, depending on the scenario, were 2.7 and 21.6 µg/kg/day for infants. For adults, conservative estimates of dermal exposure, depending on the scenario, were 2.7 and 8.5 µg/kg/day.

Finally, B84P was reported to be used mainly in industrial coatings applied to exterior and interior systems (Environment Canada 2014), but a do-it-yourself use is also feasible. Given that phthalates are metabolized quickly, do not bioaccumulate in the body and are known to have low acute toxicity, acute dermal exposure from incidental use of these types of products is not anticipated to contribute significantly to the overall exposure of the general population in Canada. Therefore, estimates were not generated, and the focus will be on subchronic and chronic exposure assessments (see risk characterization in Section 9.3.5 for additional information).

9.1.8 DIHepP

Environment media and food

Limited monitoring data on the presence of DIHepP in surface water were identified. Specifically, DIHepP was detected in surface water in False Creek Harbour, British Columbia, at a range of 2.91 to 153 ng/L. However, monitoring data were not identified for DIHeP in ambient air, indoor air, or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for DIHeP in food or food packaging materials (US FDA 2014).

DIHepP was surveyed in the CHDS and was detected in 96% of homes (range: ND–1223 µg/g, median: 18.90 µg/g, 95th percentile: 222.5 µg/g) (Kubwabo et al. 2013). The highest estimates of exposure (for infants 0 to 6 months) were 0.096 and 1.1 µg/kg/day for median (18.9 µg/g) and 95th percentile (222.5 µg/g) concentrations, respectively (see Appendix Table F-6).

Products used by consumers

DIHepP was imported in quantities of < 10 000 kg in 2012 and at higher quantities (100 000 to 1 000 000 kg) in 2008 (Canada 2009; Environment Canada 2014).

DIHepP was identified to be used in flooring products (Canada 2009). Exposure from this source is predominantly expected through indirect sources (e.g., dust) and is already addressed in the environmental media and food section.

Finally, DIHepP was also reported to be used in the production of caulking and sealants (Environment Canada 2014). Caulking and sealant use was confirmed by industry MSDSs (HPD 2014); a do-it-yourself use is therefore expected. Given that phthalates are metabolized quickly, do not bioaccumulate in the body and are known to have low acute toxicity, acute dermal exposure from incidental use of these types of products is not anticipated to contribute significantly to the overall exposure of the general population in Canada. Therefore, estimates were not generated, and the focus will be on subchronic and chronic exposure assessments (see risk characterization in Section 9.3.6 for additional information).

9.1.9 BIOP

Monitoring data were not identified for BIOP in ambient air, indoor air, or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for BIOP in food or food packaging materials (US FDA 2014).
BIOP was surveyed in the CHDS, but it co-eluted with DBzP under experimental conditions (Kubwabo et al. 2013). These methodological issues precluded identification of both compounds separately, and DBzP and BIOP concentrations were reported together (DF: 83%; range: < DL–61.2 µg/g, median: 3.09 µg/g) (Kubwabo et al. 2013).

However, DBzP was imported into Canada in quantities of < 100 000 kg for 2008 (Canada 2009) and may also be present as an impurity in BBP, a high volume phthalate. Given that there is no reported production of BIOP in the US and Europe and no reported manufacturing or import in Canada (US EPA 2014ab; ECHA c2007–2014a; Environment Canada 2014), BIOP is not expected to be present in significant levels in Canadian home dust. Therefore, presence in dust samples will be attributed to the more likely presence of DBzP in Canadian homes.

Based on information collected in the section 71 survey, no import, manufacture or export was identified for BIOP (Environment Canada 2014). Therefore, exposure of the general population to BIOP from environmental media or products used by consumers is expected to be negligible.

9.1.10 B79P

Environment media and food

Monitoring data were not identified for B79P in ambient air, indoor air, or drinking water in Canada or elsewhere. Similarly, monitoring data were not identified for B79P in food or food packaging materials (US FDA 2014).

B79P has applications in the production of compounds used in the manufacturing of automobiles and automobile parts (Environment Canada 2014). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the assessment.

B79P was surveyed in the CHDS and was detected in 95% of homes (range: ND–52.3 µg/g, median: 1.24 µg/g, 95th percentile: 9.2 µg/g) (Kubwabo et al. 2013). Estimates of exposure from B79P presence in dust for the highest exposed group (infants 0 to 6 months) were 0.0063 and 0.047 µg/kg/day based on median (1.2 µg/g) and 95th percentile (9.2 µg/g) concentrations, respectively (see Appendix Table F-7).

Products used by consumers

B79P may also be used as a plasticizer in the coating of textiles and fabrics in multiple applications (e.g., personal apparel, vehicle upholstery) (ECHA c2007–2014d). Given high import volumes (see Section 4) and its global use pattern, potential exposure to the general population to B79P, from its use as a plasticizer in manufactured items (e.g. PVC, polyurethane, polyester), was characterized.

A conservative exposure assessment was conducted to estimate exposure to B79P from dermal contact with the various manufactured items (see Table 9-19). Two scenarios were developed to model exposure of infants in contact with various plastic articles (PVC, polyurethane, polyester, etc.) for 1 hour/day with 25% of their body surface area (representative of multiple diaper changes per day on a change pad) and for 4 hours/day with 50% of their body surface area (representative of holding a plastic article and being changed on a plastic change pad multiple times a day and playing on a plastic mat).

Two scenarios to model exposure of adults in contact with various plastic articles were also assessed: the first for 3 hours/day with 16% of their body surface area (analogous to sitting on a couch or wearing plastic gloves), and the second for 3 hours/day with 50% of their body surface area (representative of various daily contacts with plastic articles including wearing gloves or holding a plastic steering wheel, sitting on a couch and wearing plastic clothing).

Given that B79P is similar in molecular weight, log K_{ow} and solubility to DEHP[21], DEHP migration rates into simulated sweat were used to quantify exposure from dermal contact with selected articles. The migration rates used, approach for characterizing dermal exposure are outlined in section 9.1.7, (Tables 9-18 and 9-19). Conservative estimates of dermal exposure from contact with plastic articles, depending on the scenario, were 2.7 and 21.6 µg/kg/day for infants 0–18 months. For adults, conservative estimates of dermal exposure, depending on the scenario, were 2.7 and 8.5 µg/kg/day.

B79P was also reported to be used in the production of sealants and coatings, for which consumer use may occur (Environment Canada 2014; ECHA c2007–2014d; SPIN 2006; 3M 2012ab). A search of industry MSDSs revealed that a majority of these products are for industrial or commercial use and are used to apply coatings to various types of surfaces (mechanical, glass, fibreglass, etc.) (3M 2013; Flexbar 2011; 3M 2012ab); however, a do-it-yourself scenario is feasible. Given that phthalates are metabolized quickly, do not bioaccumulate in the body and are known to have low acute toxicity, acute dermal exposure from incidental use of these types of products is not anticipated to contribute significantly to the overall exposure of the general population in Canada. Therefore, estimates were not generated, and the focus will be on subchronic and chronic exposure assessments (see risk characterization in Section 9.3.7 for additional information).

9.2 Health Effects

A critical effect of medium-chain phthalates consists of adverse effects on the development of the male reproductive system following exposure. Exposure to these phthalates during the critical development window of gestation have been shown to result in disturbances in the androgen-mediated development of the reproductive system in male rats, with the biological pathways leading to common effects or adverse outcomes in reproduction. The effects detected in early postnatal life include altered feminization parameters, such as decreased anogenital distance (AGD) and areolar/nipple retention (NR) in juveniles (Gray et al., 2000)[22]. Other effects observed include reproductive tract malformations (cryptorchidism [CRY], hypospadias [HYP] and testicular pathological changes) and effects on sperm counts, motility and quality at adulthood (Gray et al. 2006). This spectrum of effects on male reproductive development has been described as the “rat phthalate syndrome” (RPS) and although primarily studied in rats, it has also been demonstrated in other species (reviewed in NAS 2008).

[21] DEHP = molecular weight: 391 g/mol; log K_{ow}: 7.14; water solubility: 0.003–0.03 mg/L

[22] AGD in newborn male rats is a biomarker of androgen exposure during development. Alterations in AGD result from the disruption of testosterone signalling during fetal development. Nipple regression in male rats is also androgen-dependent (Kratochwil 1977; Imperato-McGinley et al. 1986) and retention of these nipples/areolae in males further demonstrates disruption in androgen-mediated development.

Conceptually, the effects associated with RPS can be divided into three subsets with different mode of action considerations. The first subset of effects is related to androgen insufficiency (decreased testicular testosterone production) in the fetal rat and is caused by altered functioning of Leydig cells. The second subset of phthalate syndrome effects has also been attributed to altered functioning of Leydig cells; however, the effects are separate from the role that testosterone plays in development. INSL3 gene expression is reduced and is attributed to a second proposed mechanism of action for cryptorchidism (McKinnell et al. 2005; Wilson et al. 2004). Finally, the third subset of phthalate syndrome effects is related to altered functioning of Sertoli cells in the fetal testes. Certain phthalates can also affect Sertoli cells *in utero* and may result in altered Sertoli-germ cell interactions, leading to multi-nucleated gonocytes (MNG) (Kleymenova 2005). The long-term biological significance of fetal MNGs is not clearly understood (Clewell et al. 2013). For a more detailed consideration of the current knowledge of the mode of action of phthalate-induced toxicity, please see the Category Approach Document (Health Canada 2015a).

Based on the above mentioned understanding of phthalate toxicity, the hazard assessment of each phthalate in this grouping is structured to present the evaluation of studies at three different life stages (gestational exposure [GD0–21], (pre)pubertal-pubertal [PND1–55], and adult [PND55+]), with particular focus on the male gender.[23] The purpose of the hazard assessments is to identify the most sensitive life stage of phthalate toxicity for risk characterization if adequate information is available. As the focus of the SOS report is on presenting lines of evidence pertinent to developing a screening assessment moving forward, descriptions of effects for each life stage are structured to present a summary of effects starting from the lowest doses at which these effects were observed, from an overall database perspective in lieu of a study by study narrative. Adverse effects observed subsequent to *in utero* exposure to phthalates (Sections 9.2.X.1) in this grouping are presented as follows: 1) changes in hormone levels (serum or testicular); 2) feminization effects; 3) reproductive tract malformations and/or effects on fertility; and 4) other developmental effects. Each section also tabulates critical information for each of the identified studies reporting effects.

The potential reproductive developmental effects of each phthalate in female animals were also assessed in a similar manner in considering life stage and species sensitivity.

Exposure to phthalates is also associated with other systemic effects in laboratory animals. Repeated-dose studies indicated that the liver may be a target of phthalate adverse effects. Effects on other organs, such as kidneys, have also been observed. A review of studies examining these effects (i.e., repeated-dose studies,

[23] The evaluation of all toxicological information currently available was not limited to RPS endpoints in males alone, but also included review of all potential effects of phthalate exposure in both sexes at all life stages.

chronic/carcinogenicity studies, genotoxicity studies) is presented in the appropriate sections.

When no studies were available for a particular phthalate at a specific life-stage or exposure period, an analysis of health effects of the closest analogue as identified in the Category Approach Document (Health Canada 2015a) was conducted.

Additionally, available information on the potential effects of phthalates on humans was evaluated. The published literature was searched and human studies with an epidemiological focus were identified for further consideration. The evaluation included cross-sectional, case-control and cohort studies that encompassed 14 phthalate parent compounds and their metabolites. Given the large number of studies available in humans and the diverse outcomes identified for this substance grouping, all studies collected were scored for quality using a consistent evaluation metric[24] (Downs and Black 1988).This allowed for a reliable, objective assessment tool that captured the dimensions of study quality across various study designs. Statistically significant exposure-response associations were evaluated for each health outcome. A conclusion as to the level of evidence of association of a phthalate and each health outcome was based on the strength and consistency of the relationship as well as the quality of the epidemiology studies, as determined by the Downs and Black scores. Based on the overall score obtained from the evaluation approach, the level of evidence for an association was designated as sufficient, limited, inadequate, or evidence suggesting no association. Studies that were rated in the lowest quartile (Quartile 1) based on the evaluation were not included in this report. This evaluation did not consider the biological plausibility of the relationship, meaning that no causal inference was established. More detail is provided in Health Canada (2015b) available upon request.

9.2.1 Toxicokinetics of medium-chain phthalates

A summary of the toxicokinetics of medium-chain phthalate estersis provided in Appendix H.

9.2.2 DIBP

9.2.2.1 Reproductive and developmental effects in males

9.2.2.1.1 Early development: *in utero* exposure

The European Commission classified DIBP as Category 2 (causes developmental toxicity in humans) Risk phrase R61 (may cause harm to unborn child) for developmental toxicity and as Category 3 (causes concern for human fertility) Risk phrase R62 (possible risk of impaired fertility) for reproductive toxicity (ECHA 2009).

[24] A more detailed description of the Downs and Black scoring system appears in Appendix J.

Subsequent changes to the classification schemes for the hazard class within the European Union Classifying, Labelling, and Packaging (CLP) regulations (EC No 1272/2008) resulted in a change in the status of DIBP to Category 1B – reproductive toxicant (presumed human reproductive toxicant).

A literature search identified six studies examining the potential toxicity of DIBP during gestation in rats focusing on exposure during the masculinization programming window (gestational days [GD] 15–17) where any potential anti-androgenic effects would be observed. Summaries of the studies are described in Table 9-20 below. A limited study in mice using only one high dose exposure to DIBP was also identified. It should be noted, however, that most of the reproductive parameters directly pertaining to the male reproductive system as it relates to the general rat phthalate syndrome (RPS) were not measured in this species, meaning that no conclusions can be made regarding the particular potential of DIBP to induce this syndrome in mice.

In utero oral exposure to DIBP in rats causes effects in the male foetus related to RPS, which increased in severity with increasing dose. In a critical study by Saillenfait et al. (2008), pregnant Sprague-Dawley rats were administered 125, 250, 500 or 625 mg/kg bw/day of DIBP by gavage on gestation days (GD) 12–21. They observed that the more sensitive effects included decreased AGD at postnatal day 1 (PND1), nipple retention (NR) at PND12–14, and effects in sperm (oligospermia and total azoospermia) and tubular degeneration in seminiferous tubules at maturity (postnatal weeks 11 and 16) at doses starting at 250 mg/kg bw/day in the absence of maternal effects.

A more recent study presenting the potential for DIBP and other phthalates to affect foetal testosterone production (*ex vivo*) in pregnant SD rats showed that DIBP administration altered testicular testosterone production during gestation at doses of 200 mg/kg bw/day and higher with a calculated ED_{50} value of 288 mg/kg bw/day (Furr et al. 2014).

At higher doses, the onset of puberty (preputial separation, PPS) was delayed along with reproductive tract malformations, such as undescended testes (cryptorchidism [CRY]), hypospadias (HYP), exposed *os* penis, cleft prepuce, and reduced testis, epididymis, seminal vesicles and prostate weights. Histopathological lesions were also present in testes of these males at maturity that mainly consisted of seminiferous tubule degeneration. Similar findings were also observed in earlier studies at higher doses (Table 9-20; Saillenfait et al. 2005; Borch et al. 2006; Saillenfait et al. 2006; Boberg et al. 2008).

Other effects at higher doses included embryotoxicity, reduced foetal viability and foetal visceral and skeletal malformations (Saillenfait et al. 2005, 2006; Howdeshell et al. 2008). Slight maternal toxicity became evident at dose levels starting at 500 mg/kg bw/day, with transient body weight changes becoming significant at 900 mg/kg bw/day in some studies (Saillenfait et al. 2005, 2006; Howdeshell et al. 2008), while in others, no maternal toxicity was observed at similar dose levels (Saillenfait et al. 2008; Hannas et al. 2011).

Two separate studies examined the potential of DIBP to affect steroidogenesis in the developing male foetus by measuring testicular testosterone levels. Howdeshell et al. (2008) and Hannas et al. (2011) both determined that *in utero* exposure to DIBP during the critical masculinization programming window caused a decrease in testicular testosterone levels at similar dose levels where effects on masculinization parameters and reproductive tract malformations were observed in other studies (300 mg/kg bw/day. See Table 8-20 and the Category Approach Document for more details on these studies (Health Canada 2015a).

In order to further investigate DIBP-induced steroidogenesis, Boberg et al. (2008) performed *in vivo* gene expression analysis for some of the genes known to be involved in steroidogenesis. Results showed that DIBP reduced testicular mRNA levels of SR-B1, StAR, P450c17, P450scc and INSL3 in male offspring exposed to DIBP during gestation (GD19 and GD21). Additionally, DIBP reduced testicular SF-1 mRNA levels. Hannas et al. (2011) also confirmed some gene expression changes at dose levels lower than those where testosterone levels were reduced (300 mg/kg bw/day). DIBP reduced foetal testis RNA expression levels for StAR and Cyp11a at ED_{50} values of 191 and 171 mg/kg/day, respectively. Further analysis published in 2012 showed that DIBP reduced expression of additional relevant genes in the steroid biosynthesis pathway, such as SR-B1, 3βHSD and CYP17A1 (Hannas et al. 2012). See the Category Approach Document for more details on these studies (Health Canada 2015a).

Table 9-20: Effects from gestational exposure to DIBP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration **(reference)**	**Testosterone levels[a]** **(T, S)**	**Feminization parameters[a]**	**Reproductive tract malformations and/or fertility[c]**	**Other developmental parameters[d]**	**Maternal effects**
SD rats; 0, 125, 250, 500, 625; gavage; GD12–21 (Saillenfait et al. 2008)	NM	**250** (AGD) **250** (NR) 500 (PPS @ PND40)	500 (CRY) 500 (HYP) **250** (TP) **250-500** (FER)	250 (prostate): 500 (ROW) 625 (BW) NE (FV) NE (EMB) NM (ESV)	NE
Harlan SD rats; 0, 100, 200, 300, 500, 600, 750, 900; GD14–18 (Furr et al. 2014)	**200** (T) [ED_{50} = 288, *ex vivo*] NM (S)	NM	NM	NM (BW) NM (ROW) NE[e] (FV) NM (EMB) NM (ESV)	NE
SD rats; 0, 100, 300, 600, 900;	**300 (↓T)** NM (S)	NM	NM	NM (ROW) NM (BW) 900 (FV)	LOAEL = 900 (↓BW)

gavage; GD8–18 (Howdeshell et al. 2008)				900 (EMB) NM (ESV)	
SD rats; 0, 250, 500, 750, 1000; gavage, daily; GD6–20 (Saillenfait et al. 2006)	NM	NM	750 (CRY, TTM= 500) NM (HYP) 750 (TP-Ectopic) NM (FER)	NM (ROW) 500 (BW) NE (FV) 750 (EMB) 750 (ESV)	LOEL = 500 (transient BW)
SD rats; 0, 100, 300, 600, 900; gavage; GD14–18 (Hannas et al. 2011)	**300 (↓T) (*ex vivo*)** NM (S)	NM	NM	NM	NE
Wistar rats; 0, 600; gavage; GD7–21 (Borch et al. 2006; Boberg et al. 2008)	600 (↓T) NM (S)	600 (AGD) NM (NR) NM (PPS)	NM (CRY) NM (HYP) 600 (TP) NM (FER)	NM (ROW) 600 (BW) NM (FV) NM (EMB) NM (ESV)	NP
SD rats; 0, 250, 500, 750, 1000; gavage; GD6–20 (Saillenfait et al. 2005 in Saillenfait et al. 2006)	NM	NM	750 (CRY) NM (HYP) NM (TP) NM (FER)	NM (ROW) 750 (BW) 750 (FV) NE (ESV) 500 (EMB)	LOEL = 750 (transient BW, ROW[NS] corrected for uterine weight)
CD-1 mice; 0, 4000; gavage; GD6–13 (Hardin et al. 1987)	NM	NM	NM	NM (ROW) NM (BW) 4000[e] (FV-all pups dead) 4000 (EMB) NM (ESV)	LOAEL = 4000[f] (54% maternal death)

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone

[b] Feminization parameters can include anogenital distance (AGD), nipple retention (NR) and preputial separation (PPS).

[c] Malformations include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration
[d] Other developmental effects include decreases in overall foetal body weight at PND1 (BW), decreases in reproductive organ weight (ROW), foetal viability (FV) and embryotoxicity (EMB), or effects on the incidence of external, skeletal or visceral malformations (ESV).
[e] Limited information on effects of DIBP on foetal viability was presented in this paper (Furr et al. 2014).
[f] Lowest dose tested in the study.
NP = results not reported (but measurement was stated in the methods and materials)
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns of effects, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest oral no-observed-adverse-effect level (NOAEL) for developmental toxicity of DIBP at the *in utero* life stage was 125 mg/kg bw/day based on effects on the developing male reproductive system as seen by decreased testicular testosterone production, decreased AGD, nipple retention and effects in sperm, seminiferous tubules and decreased prostate weights (above 10%) in males at maturity at the next doses tested (lowest observed-adverse-effect level [LOAEL] of 250 mg/kg bw/day) (Saillenfait et al. 2008; Furr et al. 2014). This effect level from this study was identified as a critical effect level by other jurisdictions in recent assessments (Danish EPA 2012; US CPSC CHAP 2014; Germany 2014). No marked maternal effects were reported, with decreases in body weight gain during pregnancy occurring at 900 mg/kg bw/day (LOAEL; Howdeshell et al. 2008). As mentioned previously, the one study in mice was of limited value for examining the potential of DIBP to affect male reproductive development. No developmental studies were identified examining gestational exposure to DIBP using other species.

9.2.2.1.2 Exposure at prepubertal/pubertal life stages

Results from repeated-dose oral exposure studies in sexually immature rats (PND1–55) have shown that administration of DIBP can causereproductive effects in male rats. Summaries of the studies are described in Table 9-21 below.

In the prepubertal rat (PND~21–39), exposure to DIBP at this life stage causes effects in sperm and in the testes. Zhu et al. (2010) exposed young Sprague–Dawley male rats to 100, 300, 500, 800 and 1000 mg/kg bw/day once on PND21 and daily for seven days (PND21–28), and observed that DIBP caused an increase in apoptotic spermatogenic cells at 500 mg/kg bw/day and above for both exposure durations. The repeated oral administration of DIBP also induced a decrease in testes weight and alterations in the distribution of vimentin filaments in Sertoli cells, which, according to the authors, correlates with sloughing of spermatogenic cells from the seminiferous epithelium. These effects were not observed in prepubertal C56BL/6N mice when tested under the same conditions, with the exception of decreased testes weight at the highest dose (1000 mg/kg bw/day) after the repeated exposure (Zhu et al. 2010).

Oishi and Hiraga (1980a) observed effects in spermatogenesis and decreased relative testes weight in Wistar rats after administration of a high dose of DIBP during PND35-42 (Table 9-21). The authors also noted a significant increase in testicular testosterone

concentrations in rats administered 1212 mg/kg bw/day ($P < 0.05$), but not in mice administered 2083 mg/kg bw/day (Oishi and Hiraga 1980a,b). Further, mice, but not rats, exhibited increased relative testes weight at high doses (Oishi and Hiraga 1980b), which is not consistent with the other, more recent study in mice which observed decreased testes weight (Zhu et al. 2010).

In an older study (Hodge 1954) in weanling Albino rats (species and age not provided) administered 0, 0.1, 1.0 and 5% DIBP in their diet for 16 weeks, significant decreases in body weights, and both absolute and relative testes weights were observed in the high-dose group. Slight systemic effects included increased relative liver weights at the highest dose with no histopathological effects (Hodge 1954).

Table 9-21. Effects from oral exposure to DIBP in prepubertal/pubertal males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration **(reference)**	**Life stage at the start of dosing (age)**	**Hormone levels[a]** **(T, S, LH)**	**Fertility[b]**	**Reproductive tract pathology[c]**	**Other effects[d]**
SD rats; 0,100, 300, 500, 800, 1000; gavage; PND21–28 (Zhu et al. 2010)	Prepubertal	NM	**500** (↑apoptotic spermatogenic cells**)**	**500** (vimentin filament disorganization in Sertoli cells)	NP (BW) **500 (ROW)** NM (ST)
SD rats;0,100, 300, 500, 800, 1000; gavage, once; PND21 (Zhu et al. 2010)	Prepubertal	NM	**500** (↑apoptotic spermatogenic cells**)**	NM	NP (BW) NE (ROW) NM (ST)
Wistar rats; 0, 2%, est. 0, 1212 according to US CPSC 2010a; diet; PND35–42 (Oishi and Hiraga 1980a)	Prepubertal/pubertal	1212[e] (↑T) 1212 [e, NS] (↑S)	1212[e] (↓ spermato-genesis)	NM	1212[e, NS] (BW) 1212[e] (ROW) LOEL= 1212[e] (↑ liver wt)
Strain? Rat; 0, 0.1, 1.0, 5% (est. as 0, 67, 738, 5960 (males) according to US CPSC 2010a;	Weanling /age not specified	NM	NM	NM	4861-5960 (BW) 4861-5960 (ROW) 4861-5960 (↑

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
diet; 16 weeks (Hodge 1954 as cited by NICNAS 2008; US CPSC 2010a)					rel & abs liver weight)
C56BL/6N mice; 0, 100, 300, 500, 800, 1000; gavage, once; PND21 (Zhu et al. 2010)	Prepubertal	NM	800[NDR] (apoptotic spermatogenic cells)	NM	NR (BW) NE (ROW) NM (ST)
C56BL/6N mice; 0, 100, 300, 500, 800, 1000; gavage; PND21–28 (Zhu et al. 2010)	Prepubertal	NM	NE	NM	NR (BW) 1000 (ROW) NM (ST)
JCL:ICR mice; 0, 2%, est. 0, 2083 according to US CPSC 2010a; diet; 5–7d (Oishi and Hiraga 1980b)	"Young"/ age not specified	NE (T) NM (S) NM (LH)	NM	NM	2083[e] (BW) 2083[e] (↑ROW) 2083[e] (↑ liver, ↓ kidney weight)

[a] Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S) or luteinizing hormone (LH).
[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis or reproductive success at adult stage after *in utero* exposure.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] Lowest dose tested in the study.
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
NS = not statistically significant
NDR = no dose relationship

Overall, the highest oral NOAEL for the reproductive toxicity of DIBP at the prepubertal/pubertal life stage was 300 mg/kg bw/day based on effects on the male reproductive system, as seen by decreased testes weight, increased number of apoptotic spermatogenic cells and alterations in the distribution of vimentin filaments in Sertoli cells at the next dose tested (500 mg/kg bw/day) (Zhu et al. 2010). The dose of 300 mg/kg bw/day from the Zhu et al. (2010) study was also identified as the NOAEL for reproductive effects by the US CPSC CHAP (2014). Studies in mice indicates that this species may not be as sensitive to reproductive effects of DIBP during this life stage (Oishi and Hiraga 1980b; Zhu et al. 2010). Mild systemic effects included increased liver weight in rats as well as increased liver and decreased kidney weights in mice at dose levels of 1212 mg/kg bw/day and above (Oishi & Hiraga 1980a,b; Hodge 1954). No studies were identified on any other species by any route of exposure at this life stage.

9.2.2.1.1 Oral exposure at the mature male adult stage

No studies examining the potential health effects of DIBP were identified in sexually mature adult male rats (PND55+) by any route of exposure. Dibutyl phthalate (DBP) (1,2-Benzenedicarboxylic acid, dibutyl ester: CAS RN 84-74-2) was identified as the "closest analogue" to DIBP based on similarity in the length and nature of the ester chains (Section 2.3.2; Health Canada 2015a). Summaries of the relevant studies conducted with DBP are described below and summarized in Table 9-22.

An examination of the effects of DBP on the reproductive system of the adult male rat showed effects on sperm count and motility starting at 500 mg/kg bw/day, with testicular pathology at similar doses. Srivistava et al. (1990) administered 250, 500 and 1000 mg/kg bw/day of DBP to adult Wistar rats by gavage for 15 days. They reported a 30% decrease in sperm count as well as evidence of disorganized seminiferous tubules, disturbed spermatogenesis, and irregular spaces devoid of sperm in rats exposed to 500 mg/kg bw/day DBP, along with alterations in the activity of enzymes related to specific events of spermatogenesis. These effects became more severe at the highest dose with a decrease of approximately 70% in sperm count and severely damaged seminiferous tubules.

A more recent 14-day study in adult male Sprague–Dawley rats reported decreased epididymal weights with evidence of epididymal tubule atrophy, hyperemia of the interstitial vasculature, and oligospermic lumina at the highest dose tested (500 mg/kg bw/day) (Zhou et al. 2011). The study authors also found significant effects in the activities of antioxidant enzymes in the epididymis.

A similar study reported decreases in serum testosterone at 500 mg/kg bw/day DBP as well as testicular pathology at higher dose ranges (750-1000 mg/kg bw/day) in Sprague–Dawley rats after the same exposure period (O'Conner et al. 2002). Mild systemic effects included increased liver weight with no corresponding histopathological indications at 500 mg/kg bw/day (O'Conner et al. 2002).

There are a significant number of studies examining the potential toxicity of DBP in adult male mice, which indicate that mice could potentially be less sensitive to the effects of DBP at this life stage compared to rats. DBP did not cause any adverse effects on fertility or in the testes at up to significantly high doses (900-3689 mg/kg bw/day and above) (Lamb et al. 1987; Morrissey et al. 1988; Marsman et al. 1995; Dobryznska et al. 2011; Hao et al. 2012). Marsman et al. (1995) compared the changes in serum testosterone in both rats and mice and reported that DBP caused a decrease in testosterone concentrations in rats at 1540 mg/kg bw/day and above after a 90-day DBP administration, but did not affect levels in mice exposed for the same duration at similar dose.

In a study by Higuchi et al. (2003), adult males rabbits (6–8 months) where administered 0 and 400 mg/kg bw/day of DBP via gavage for 12 weeks. Evidence of testicular pathology (germinal epithelial loss) and abnormalities in sperm morphology were reported in exposed animals. There were no effects on serum testosterone levels or on mating behaviour at this life stage and no effects on body weight gain. An increase in thyroid weight was reported (Higuchi et al. 2003).

Two inadequately reported studies examining the effects of DIBP in other species were described in secondary sources (cat, BASF 1961 in EC 2004; dog, Hodge 1954 in NICNAS 2008). These studies were determined to be of limited value due to the small sample size and nature of parameters measured. There was, however, some indication of decreased sperm in one male dog administered 0.1 mL/kg/day of DIBP in the diet for two months (Hodge 1954 in NICNAS 2008).

Table 9-22. Effects from oral exposure to DBP in adult males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration **(reference)**	**Age at the start of dosing**	**Hormone levels[a]** **(T, S, LH)**	**Fertility[b]**	**Reproductive tract pathology[c]**	**Other effects[d]**
SD rats; 0, 100, 250, 500; Gavage; 14 days (Zhou et al. 2011) 1 ml/100g bw in corn oil	Not specified	NM	NM	**500** (atrophy of epididymal tubules, hyperemia of interesititial vascular)	NM (BW) 500 (ROW-epididymis) NM (ST)
Wistar Albino rats; 0, 250, 500, 1000; gavage; 15 days (Srivastava et al. 1990b)	Not specified “adult” (225 g)	NM	**500** (↓ 30% sperm count)	**500** (disorganized seminiferous tubules, spermatog	NE (BW) NE (ROW) NM (ST)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Age at the start of dosing	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
0.4 ml doses in groundnut oil, no mention of per kg/bw				enesis)	
SD rats; 0, 250, 500, 750, 1000; gavage; 15 days (O'Connor et al. 2002)	PND70	NM (T) 500 (S) NM (LH)	NM	750[e] (minimal bilateral testicular degeneration, increase in germ cells in epi.)	NE (BW) NE (ROW) 500 (ST- ↑ liver wt)
SD rats; 0, 1.0%, est. 0, 509; diet [Task 3] "Crossover mating"; 14 weeks (Wine et al. 1997)	PND70	NM	NE	NE	NE (BW) NP (ROW) 509[f] (ST-↑ liver and kidney wt)
F344 rats; 0, 2500, 5000, 10000, 20000, 40000 ppm est. 0, 176, 359, 720, 1540, 2964 (HC 1994); Diet; 90 days (Marsman et al. 1995)	PND56	NE (T) 1540 (↓S) NM (LH)	1540 (hypospermia, spermatid count, epididymal spermatozoal motility)	720 (testicular lesion-germinal epithelium atrophy)	720 (BW) 1540 (ROW) 720 (ST- liver and kidney wt, liver pathology)
SD rats; 0, 10000 ppm DBP, est. 0, 1400 (HC 1994); diet; 26 wks (Marsman et al. 1995)	PND70–84	NM	NP	NM	NE (BW) 1400[f] (ROW cauda epididymis) NP (ST)
B6C3F1 mice; 0, 1250, 2500, 5000, 10000, 20000 ppm, est. 0, 163, 353, 812, 1601, 3689;	PND56	NM (T) 163[f,NDR] (↑ S) NM (LH)	NE	NE	812 (BW) 812 (ROW) 812 (ST- ↑ liver wt), 1601 (ST- liver

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Age at the start of dosing	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
Diet; 90 days (Marsman et al. 1995)					pathology)
Swiss CD-1 mice; 0, 300, 3000, 10000 ppm, est. 0, 60, 600, 2000 (HC 1994); Diet; 26 wks, 2-gen (Marsman et al. 1995)	PND70–84	NM	NE (mating in cross-over and sperm)	NE	2000 (BW-only dose tested) NE (ROW) NE (ST)
COBS Crl: CD-1, (IRC) BR Outbred Albino mice; 0, 0.03%, 0.3, 1.0%, est. 0, 39, 390, 1300; diet; 7 days prior to mate-PND98, 18 wks (Lamb et al. 1987; Morrissey et al. 1988)	PND42	NM	NE (mating in cross-over and sperm)	NE	1300^{NS} (BW) NE (ROW) NE (ST)
Pzh: Sfis Outbred mice; 0, 500, 2000; gavage; 8 wks, 3 times/wk (Dobryznska et al. 2011)	PND56	NM	2000^{NS}	NM	NM (BW) NM (ROW) 3) 2000 (ST- effects on F1 repro.)
Kuming mice; 0, 900; Gavage; 35 days, every other day (Hao et al. 2012)	Not specified	NM	NE (sperm quantity, survival, malform.)	NE	NM
Dutch-Belted rabbits; 0, 400; gavage; 12 weeks (Higuchi et al. 2003)	6–8 months	NM (T) NE (S) NM (LH)	400[f] (sperm defects, NE for mating behaviour)	400[f] (germinal epithelial loss)	NE (BW) NE (ROW) 3) 400[f] (ST- ↑ thyroid wt)

[a] Hormone levels can includes quantity/production of testicular testosterone (T), serum testosterone (S) or luteinizing hormone (LH).

[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis or reproductive success after mating.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] Statistical analysis was not reported by O'Connor et al. 2002 for the reproductive pathology parameter. The study did note that at the 1000 mg/kg dose, 6/15 samples displayed bilateral testicular degeneration and an increased number of sloughed germ cells within the epididymal tubules. No testes or epididymis pathology was detected at doses ≤ 500.
[f] Lowest dose tested.
NP = results not reported (but measurement was stated in the methods and materials).
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.
NDR = no dose relationship
NS = not statistically significant

Overall, the highest NOAEL for reproductive toxicity identified for DBP was 250 mg/kg bw/day based on atrophy of epididymal tubules, hyperemia of the interstitial vascular, oligoszoospermic lumina and decreased reproductive organ weight (epididymis) as well as effects on sperm count, motility, disorganized seminiferous tubules, altered spermatogenesis and irregular spaces devoid of sperm at the next dose tested of 500 mg/kg bw/day in adult male rats in two studies (Srivastava et al. 1990; Zhou et al. 2011). The lowest LOAEL for systemic toxicity was 720 mg/kg bw/day based on increased kidney and liver weights, hepatocellular cytoplasmic alterations, and increased number of peroxisomes in male rats (Marsman et al. 1995). Limited oral studies with DIBP in cats and dogs did not provide any further information, and no studies were identified on any other species by any route of exposure at this life stage. Therefore, the NOAEL of 250 mg/kg bw/day will be used as the critical effect level for the reproductive toxicity of DIBP for this life stage.

9.2.2.2 Oral exposure in females

Eight published studies on the reproductive and developmental effects of DIBP in females were identified. Most of these studies were performed in rats, where animals were administered DIBP by the oral route during different gestational times.

The lowest oral LOAEL identified for developmental toxicity in females (500 mg/kg bw/day) is based on the same study described in the section above in rats (Saillenfait et al. 2006). Developmental toxicity occurred at doses that were not maternally toxic and included alteration of growth (statistically significant reduction of foetal body weights at 500 mg/kg bw/day and above with a NOAEL of 250 mg/kg bw/day).

The lowest LOAEL identified for reproductive toxicity in adult females (750 mg/kg bw/day) is also based on the Saillenfait et al. (2006) developmental toxicity study as well as on a similar preliminary study in which exposure occurred via gavage on GD6–20 to doses of 0, 250, 500, 750 and 1000 mg/kg bw/day (Saillenfait et al. 2005, as cited in Saillenfait et al. 2006 and ECHA 2009). The critical effects included alteration of

fertility and pregnancy outcomes (statistically significant increase in post-implantation losses per litter, resorptions per litter and number of live foetuses per litter) (Saillenfait et al. 2006) and an increased number of resorptions (Saillenfait et al. 2005), occurring at doses of 750 mg/kg bw/day and higher (NOAEL of 500 mg/kg bw/day).

Overall, developmental effects in females were identified at doses of 500 mg/kg bw/day and above after oral exposure with critical endpoints related to growth alterations, alterations of reproductive development, functional deficit, lethality and mild teratogenicity. When gender effects were examined separately, effects of DIBP-induced developmental effects in males and females were observed at the same dose levels, with some studies reporting male pups as more sensitive than female pups. Reproductive effects of DIBP in females and alterations of fertility and pregnancy outcomes (embryolethality) were observed at 750 mg/kg bw/day and above, higher doses than at which reproductive effects were observed in males.

9.2.2.3 Reproductive and developmental toxicity: evidence in humans

Available epidemiological studies examining the potential relationship between observed effects and exposure to DIBP in humans were reviewed (Appendix J; Health Canada 2015b). Overall, there were no associations established for DIBP and its metabolite, mono-isobutyl phthalate (MIBP), and effects on male reproductive hormones (Joensen et al. 2012), preterm birth and gestational age (Wolff et al. 2008; Meeker et al. 2009; Ferguson et al. 2014c), birth measures (Wolff et al. 2008; Philippat et al. 2012) or any other reproductive parameters (endometriosis, gynecomastia, time to pregnancy) examined (Mieritz et al. 2012; Upson et al. 2013; Buck Louis et al. 2014) . Inadequate evidence was identified for an association for MIBP and placental gene expression (Adibi et al. 2010). There was inadequate evidence for associations between MIBP exposure and mental and psychomotor neurodevelopment, or behavioural and cognitive function (Engel et al. 2010; Yolton et al. 2011; Whyatt et al. 2012; Téllez-Rojo et al. 2013).

More recent studies have found associations between DIBP and various endpoints, but these have not yet been assessed using the Downs and Black evaluation approach. There were inconsistent results on the association of MIBP and hormone levels (e.g. estradiol, testosterone, DHEA-S) in both genders (Ferguson et al. 2014a; Meeker and Ferguson 2014; Sathyanarayana et al. 2014; Watkins et al. 2014). There were no associations with MIBP and female puberty (Wolff et al. 2014; Watkins et al. 2014), male puberty (Ferguson et al. 2014a), gene expression in placenta (LaRocca et al. 2014), and preterm birth (Ferguson et al. 2014b). There were inconsistent associations between MIBP and neurobehavioral and cognitive functioning, and psychomotor development (Kobrosly et al. 2014; Polanska et al. 2014; Braun et al 2014).

9.2.2.4 Other systemic effects[25]

9.2.2.4.1 Repeated-dose studies

The database for repeated-dose toxicity of DIBP is limited to a few short-term and subchronic oral studies investigating the effects of DIBP on rats and mice. Based on the available data, DIBP is of very low systemic toxicity. Summaries of the studies are described below.

In a short-term study in rat in which females were treated with 0, 50, 100, 200, 2000 mg DIBP/kg-bw/din feed for 14 days, increased changes in liver dodecanoic acid 12-hydroxylase activity and a decrease in serum triglyceride levels were observed at 100 mg/kg bw/day and higher. Increased absolute and relative liver weights, increased serum albumin levels and decreased cholesterol levels were also observed at the highest dose tested. No histopathological changes in the liver were reported (BUA 1998).

When male rats were exposed for one month to 0, 0.01, 0.1, 1, 2 or 5% DIBP in feed (equivalent to 0, 15, 142, 1417, 2975 and 8911 mg/kg bw/day according to US CPSC 2010a), reduced growth was observed in animals exposed at the highest dose (terminal body weight was approximately 62% of controls and 75% of other dose groups). A significant increase in absolute and relative liver weight and a significant increase in relative kidney weight were also observed in animals treated with 1417 and 2975 mg/kg bw/day, respectively. Histological examination did not identify any significant treatment-related lesions in both the liver and the kidneys (Hodge 1953).

In another study, two dogs were fed diets containing DIBP for two months (a male treated with 0.1 mL/kg feed and a female treated with 2.0 mL/kg feed; equivalent to 1 and 16 mg/kg bw/day, respectively, according to US CPSC 2010a). In the female, relative liver weight was increased (in comparison with the relative liver weight of the male), without histopathological lesions. However, due to the limitations of the study (small number of animals tested and lack of concurrent controls or information on historical controls), an effect level could not be derived (Hodge 1954).

In a subchronic feeding study in which male and female albino rats were exposed for 16 weeks (see Section 9.2.2.1.2 and Hodge 1954 for more details on study protocol), a decrease in body weight gain (more than 10%) was observed in males and females treated at the highest dose (males: 5960 mg/kg bw/day; females: 4861 mg/kg bw/day). Terminal body weights were significantly lower than controls among rats treated at the highest dose (decreased 43% for males and 13% for females). Increases in absolute and relative liver weight were also observed in both sexes at the highest dose tested, and absolute and relative testes weights were significantly reduced at that dose level in

[25] This section presents studies examining effects other than reproductive effects.

males. No histopathological changes were noted in the liver and kidneys (histopathology of the other organs was not performed).

In another subchronic study in which four cats were administered 1486 mg DIBP/kg-bw/d by gavage for three months, decreased body weight and food intake, diarrhoea, and emesis were observed. Survival was unaffected, and blood parameters and liver function were unchanged (BASF 1961). However, the lack of details from this study limits the interpretation of these results.

9.2.2.4.2 Carcinogenicity

DIBP has not been classified for its potential carcinogenicity by other international agencies and no chronic toxicity/carcinogenicity studies were identified for this phthalate. There was also no study available in the literature for its closest analogue DBP. However, no pre-cancer effects were noted in animals exposed to a high dose of DIBP in short-term and subchronic studies. Also, in a multigenerational study in which Sprague–Dawley rats (20/sex/group; 40/sex for controls) were given DBP at 0, 0.1, 0.5 and 1.0% in the diet (0, 52, 256 and 509 mg/kg bw/day for males and 0, 80, 385 and 794 mg/kg bw/day for females), the only systemic effect reported in F1 adults (exposed for a significant period of their lifetime) was a decrease in body weight (NTP, 1995*; Wine et al. 1997).

9.2.2.4.3 Genotoxicity

DIBP was found to be non-mutagenic in several bacterial reverse mutation assays using *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, with and without metabolic activation (Simmon 1977; Zeiger 1982; Zeiger 1985; Huels AG 1988; Sato 1994). In an 8-azaguanine resistance assay, DIBP was also not mutagenic both in the presence and in the absence of metabolic activation (Seed 1982). However, DIBP induced DNA damage (single-strand breaks) *in vitro* in a comet assay using human cells (oropharayngeal and inferior nasal turbinate mucosal cells and lymphocytes) (Kleinsasser 2000; Kleinsasser 2001a,b).

9.2.2.4.4 Evidence of systemic toxicity in humans

Available epidemiological studies examining the potential relationship between observed effects and exposure to DIBP in humans were reviewed (Appendix J; Health Canada 2015b). Overall, there was limited evidence for an association between exposure to diisobutyl phthalate (DIBP) and its mono-isobutyl phthalate (MIBP) and diabetes (Lind et al. 2012b; James-Todd et al. 2012; Trasande et al. 2013a). There was inadequate evidence for associations between MIBP and oxidative stress (Ferguson et al. 2011; Ferguson et al. 2012), cardiovascular function (Lind and Lind 2011; Shiue 2013; Trasande et al. 2013b; Trasande et al. 2014), and obesity (Lind et al. 2012a; Teitelbaum et al. 2012; Trasande et al 2013c; Wang et al. 2013). Inadequate evidence was identified for an inverse association with MIBP and the breast cancer risk (Lopez-Carrillo et al. 2010; Martinez-Nava et al. 2013). No associations were observed between DIBP or MIBP and asthma/allergy related symptoms (Hoppin et al. 2013; Callesen et al. 2014a), or serum levels of thyroid hormones (Meeker and Ferguson 2011).

More recent studies have found associations between DIBP and various endpoints, but these have not yet been assessed using the Downs and Black evaluation approach. Significant associations were found between MIBP and biomarkers of diabetes (Huang et al. 2014) and obesity (Christensen et al. 2014b; Buser et al. 2014). Callesen et al. (2014b) reported no associations with MIBP and asthma, atopic dermatitis or rhinoconjunctivitis. However, Bamai et al. (2014) found associations between atopic dermatitis and DIBP in floor dust, but not in multi-surface dust. Significant association was reported between MIBP and blood pressure in women (Shiue and Hristova 2014), but no associations were reported considering both genders together (Shiue 2014a,b; Shiue and Hristova 2014), and considering men only (Shiue and Hristova 2014). MIBP was associated with oxidative stress, but not with inflammation (Ferguson et al. 2014d). No association was found between MIBP and osteoporosis (Min and Min 2014).

9.2.3 DCHP

9.2.3.1 Reproductive and developmental effects in males

9.2.3.1.1 Early development: *in utero* exposure

A literature search identified four studies examining the potential toxicity of DCHP during gestation in rats, all focusing on male reproductive effects during the masculinization programming window (GD15–17) where any potential anti-androgenic effects would be observed. The studies are described in Table 9-23 below. No other developmental studies were identified examining gestational exposure to DCHP in other species.

In a 2-generation toxicity study, DCHP was associated with effects in the parental (F0) and both filial generations (F1 and F2) in a dose-responsive manner. In this study, male and female rats of both F0 and F1 generations were administered 0, 240, 1200 and 6000 ppm DCHP in the diet for ≥ 10 weeks of pre-mating and mating periods (see Table 9-23). Estimated dose levels for the F0 generation males were 0, 16, 80 and 402 mg/kg bw/day and 0, 18, 90 and 457 mg/kg bw/day for the F1 generation males. Developmental effects were observed in F1 and F2 male pups. There was a statistically significant decrease in AGD measured in length as well as when adjusted by body weight and retained nipples/areolae (NR) in male F2 offspring treated at 1200 ppm or higher (107 mg/kg bw/day based on amount ingested by F1 dams). In male F1 offspring, these effects were observed at the highest dose only. Foetal body weight was reduced in F1 and F2 offspring at the highest dose (Hoshino et al. 2005). Slight maternal toxicity was observed at 1200 and 6000 ppm based on reduced body weight gain and reduced food consumption and diffuse hypertrophy of hepatocytes (identified as statistically significant at $P<0.05$, but less than 10% reduction in food consumption and body weight during gestation) in F0 females (LOAEL for maternal toxicity was estimated at 104 mg/kg bw/day). As other general physical development parameters, such as eye opening, pinna unfolding, and incisor eruption, were not affected, the reproductive/developmental effects of AGD and NR in F1 male pups at the high dose level were not considered to be a secondary effect of maternal toxicity.

In the F1 generation, reproductive effects observed when F1 animals reached reproductive age included a 15 and 24% decrease in spermatid head counts in the testes and testicular atrophy in F1 males treated at the two highest doses, 90 (2 of 20) and 457 (9 of 14) mg/kg bw/day, respectively. At the highest dose, 3 males had small and/or soft testes, with one male examined showing no sperm. Relative prostate weight was also decreased in high dose F1 males. Sex ratio, number of implantations, mating, fertility and birth indices did not differ from the control, and there were no changes in serum testosterone levels in this generation when examined at the adult stage (Hoshino et al. 2005). Reduced body weight gain and reduced food consumption were observed in F1 males at 90 mg/kg bw/day (Hoshino et al. 2005).

A developmental study conducted by Saillenfait et al. (2009) observed a dose-dependent decrease in AGD in male neonates of dams exposed to DCHP during gestation (GD6–20) at the lowest dose tested and above (250, 500 and 750 mg/kg bw/day; gavage). No effects on testicular descent (i.e., cryptorchidism) were identified. The body weights of males were decreased at the highest dose (750 mg/kg bw/day), but this dose was also associated with maternal toxicity and decreased food consumption. There was no evidence of teratogenicity or embryolethality at any of the maternal treatment doses. The LOAEL for maternal toxicity in this study was 750 mg/kg bw/day based on a significant reduction in body weight gain in dams. A LOEL for maternal toxicity of 500 mg/kg bw/day was identified based on an increase in absolute and relative maternal liver weight at the two highest doses tested with no histological findings.

In a study in which pregnant rats were exposed by gavage to 0, 20, 100 and 500 mg DCHP/kg-bw/d during GD6 to PND20, effects on the reproductive system, such as prolonged preputial separation, reduced AGD, increased areola/nipples retention, hypospadia, decreased relative weights of the ventral prostate and ani/bulbocavernosus muscles, and histological changes in the testis and kidney (decreased testicular germ cells and degenerated renal proximal tubules) were observed in animals treated at the highest dose tested. The authors attributed these findings to the anti-androgenic effects of DCHP. A decrease in body weights and a slight but significant reduction in the viability index were also observed in male pups at this dose level. A NOAEL of 100 mg/kg bw/day and a LOAEL of 500 mg/kg bw/day for developmental toxicity were determined from this study. A LOEL of 100 mg/kg bw/day was identified in this study for slight maternal toxicity based on increased absolute and relative liver weights in dams at 100 and 500 mg/kg bw/day (6 and 19% compared to controls, respectively) (Yamasaki et al. 2009). No histopathological observations of the liver in dams or general physical development parameters, such as eye opening, pinna unfolding, and incisor eruption in pups were reported, limiting the interpretation of maternal health on developmental outcomes.

In another developmental study, Ahbab and Barlas (2013) administered 0, 20, 100 or 500 mg/kg bw/day DCHP to pregnant Wistar Albino rats via gavage on GD6–19 (Table 9-23). The results from this study are limited based on the dosing method, but histopathological evidence of reproductive tract malformations (in the testis, epididymis

and prostate gland) and a significant increase in abnormal sperm were observed in male pups exposed to DCHP at all dose levels, although the sperm effects did not follow a dose-responsive trend. Typical dose response relationships were not observed for many metrics, and maternal health was not reported (Ahbab and Barlas 2013).

A more recent study presenting the potential for DCHP and other phthalates to alter foetal testosterone production (*ex vivo*) in pregnant SD rats showed that this phthalate altered testicular testosterone production during gestation at doses of 100 mg/kg bw/day and above with a calculated ED_{50} value of 61.6 mg/kg bw/day (Furr et al. 2014).

Table 9-23. Effects from gestational exposure to DCHP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration **(reference)**	**Testosterone levels[a]** **(T, S)**	**Feminization parameters[b]**	**Reproductive tract malformations and/or fertility[c]**	**Other developmental parameters[d]**	**Maternal effects**
SD rats; 0, 240, 1200, 6000 ppm: est. **F1 female intake**: 0, 21, 107, 534; diet; 2-gen 3 wks old-PND21 of F2 (16–18 wks) (exposed *in utero* GD1–21) (Hoshino et al. 2005)	NE (tested in adults only)	**107**(AGD) **107** (NR) NM (PPS)	NM (CRY) NM (HYP) NM (TP) NM (FER)	534 (BW @ PND21) NM (ROW @ birth) NE (EMB) NE (FV) NE (ESV) 534 (↑ rel. Brain, ↓rel. spleen weight)	LOAEL= 534 (BW) 534 (hypertrophy in liver & thyroid follicular cells, ↑ rel. liver wt)
SD rats; 0, 240, 1200, 6000 ppm; est. **F0 Female intake**: 0, 21, 104, 511; 2 gen diet; 5 wks old-PND21 of F1 (16–18 wks) (Hoshino et al. 2005)	NE (tested in adults only)	511(AGD) 511 (NR) 511^{NS}(PPS)	NM (CRY) NM (HYP) 104 (TP- F1 when adults, ~90 mg/kg) 104 (FER, sperm when adults, ~90 mg/kg)	511 (BW PND0–21) NM (ROW @ birth) NE (EMB) NE (FV) NE (ESV) 511 (↑ rel. Brain, ↓abs. thymus & spleen wt)	LOAEL= 104 (↓BW gain, liver hypertrophy) 511(BW, ↓food consumption, hypertrophy in liver & thyroid follicular

Strain and species; dose (mg/kg bw/day); route; duration **(reference)**	**Testosterone levels[a]** **(T, S)**	**Feminization parameters[b]**	**Reproductive tract malformations and/or fertility[c]**	**Other developmental parameters[d]**	**Maternal effects**
					cells,↑ rel. & abs. liver and rel. thyroid wt)
Wistar rats; 0, 20, 100, 500; gavage; GD6–19 (Ahbab and Barlas 2013)	NM (T) 100^{NDR} (↑S @ PND20) 500 (↓S @ PND32)	NM	NM (CRY) NM (HYP) 20^{e} (TP) 20^{e} (FER)	$20^{e, NDR}$(BW) 500 (ROW) NM (EMB) NM (FV) NM (ESV)	NM
Harlan SD rats; 0, 33, 100, 300, 600, 900; GD14–18; (Furr et al. 2014)	**100** (T) ED_{50} = 61.6 [*ex vivo*] NM (S)	NM	NM	NM (BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	NE
SD rats; 0, 250, 500, 750; gavage; GD6–20 (Saillenfait et al. 2009b)	NM	250^{e} (AGD) NM (NR) NM (PPS)	NE (CRY) NM (HYP) NM (TP) NM (FER)	750 (BW) NM (ROW) NE (EMB) NE (FV) NE (ESV)	LOAEL= 750 (BW)
SD rats; 0, 20, 100, 500; gavage; GD6–PND20 (Yamasaki et al. 2009)	NM	500(AGD) 500 (NR) 500 (PPS)	NM (CRY) 500 (HYP) 500 (TP) NM (FER)	500 (BW-embryo) 500 (ROW) 500 (FV-PND4) NE (EMB) NM (ESV)	LOEL= 100 (↑ liver wt)

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone

[b] Feminization parameters can include anogenital distance (AGD), nipple/areolae retention (NR) and preputial separation (PPS).

[c] Malformations include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration
[d] Other developmental effects include decreases in overall foetal body weight at PND1 (BW), decreases in reproductive organ weight (ROW), embryotoxicity (EMB) and foetal viability (FV), or effects on the incidence of external, skeletal or visceral malformations (ESV).
[e] Lowest dose measured in the study
NM = not measured.
NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.
NDR = no dose relationship.

Overall, the lowest NOAEL for developmental toxicity identified for DCHP was 21 mg/kg bw/day based on reduced AGD and increased areola mammae retention (NR) at the next highest dose of 107 mg/kg bw/day (1200 ppm) and above in a 2-generation study (Hoshino et al. 2005) conducted according to OECD guidelines. The dose level of 16–21 mg/kg bw/day from this study was also identified as the NOAEL for developmental effects by the Australian NICNAS (2008) and the US CPSC CHAP (2014). Foetal testicular testosterone production was also altered at similar dose levels (NOAEL of 33 mg/kg bw/day; Furr et al. 2014). The lowest LOAEL for maternal toxicity of DCHP was 104 mg/kg bw/day based on reduction in body weight gain in exposed F0 dams in the same study. Developmental effects of AGD and NR in male pups were not considered to be secondary to maternal toxicity.

9.2.3.1.2 Exposure at prepubertal/pubertal life stage

There was only one repeated-dose oral exposure study in sexually immature animals (PND1–55) with DCHP where most parameters related to RPS were not examined and males were only observed for reproductive tract malformations at high doses (Lake et al. 1982).

After a seven-day oral gavage exposure of DCHP to young PND30 male SD rats, testes sections from control and 1500 mg/kg/d DCHP animals had no abnormalities. However, examination of one of the five animals treated with 2500 mg/kg/d of DCHP exhibited a bilateral tubular atrophy of 30 to 40% of the germinal cells of the testes. There were no effects on testes weight in any of the high-treatment groups (1500 and 2500 mg/kg bw/day). In contrast to treatment with DCHP, administration of 1130 mg/kg bw/day with one of its metabolites, MCHP, resulted in a significant reduction in relative testes weight to 44% of control values. Morphological examination showed an almost complete bilateral atrophy of the germinal epithelium of the seminiferous tubules (Lake et al. 1982).

Overall, the lowest NOEL for the reproductive toxicity of DCHP at the prepubertal/pubertal life stage was based on a limited study where effects on the male reproductive system (bilateral tubular atrophy in 1 out of 5 animals) were observed at 2500 mg/kg bw/day. It will therefore not be used to characterize risk for this life stage based on this limitation (Lake et al. 1982). No studies were identified on any other species via any route of exposure at this life stage.

9.2.3.1.3 Oral exposure at the mature male adult stage

Using the 2-generation toxicity study described in the previous section (Hoshino et al. 2005), information was extracted to determine the effects of DCHP on the adult male (PND55+). Summaries of the studies are described in Table 9-24 below.

DCHP was predominantly associated with slight systemic toxicity in the parental (F0) animals. In parental animals treated at the highest dose, effects included reduced body weight gain, increased liver and thyroid weights, as well as increased hyaline droplets in the proximal tubules of males (Table 9-24). A LOAEL for systemic toxicity was identified based on diffuse hypertrophy of hepatocytes (identified as a "slight" effect) in F0 males (and females) and increased incidence of thyroid follicular cell hypertrophy (also identified as a "slight" effect) in F0 males at 1200 and 6000 ppm (80 and 402 mg/kg bw/day). Sex ratio, number of implantations, mating, fertility, and birth indices did not differ from the control, and there were no effects on testes or sperm parameters in F0 males.

Table 9-24. Effects from exposure to DCHP in adult males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	**Life stage at the start of study (age)**	**Hormone levels[a] (T, S, LH)**	**Fertility[b]**	**Reproductive tract pathology[c]**	**Other effects[d]**
SD rats; 0, 240, 1200, 6000 ppm, est. **F0 adult males**: 0, 16, 80, 402; 2 gen diet; 10–12 wks (Hoshino et al. 2005)	5 wks	NM (T) 80^{NDR}(↑ S) NE (LH) NE (FSH)	NE	402^{NS} (focal atrophy in 1 male)	402 (BW) NM (ROW) **80** (ST-hypertrophy in liver & thyroid follicular cells) **402** (↑ rel. & abs. liver and left thyroid weight, hyaline droplets in kidney)
SPF Albino rats; 0, 0.05, 0.15, 0.4, 1%, est. 0, 25, 75, 200, 500; diet; 90 days (De Ryke and Willems 1977)	NP "not specified"	NP	NP	NP	NM (BW) NP (ROW) 200 (ST↑ relative liver wt)
SPF Albino rats; 0, 0.075, 0.1, 0.15, 1%,est. 0, 37.5, 50, 75, 500; diet; 90 days (De Ryke and	NP "not specified"	NP	NP	NP	NM (BW) NP (ROW) 75[e] (ST - ↑ relative liver wt)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Life stage at the start of study (age)	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
Bosland 1978)					

[a] Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S) or luteinizing hormone (LH).
[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis or reproductive success after mating.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] NICNAS 2008 stated that it is unclear if only 500 mg/kg yielded a significantly increased relative liver weight.
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
NS = not statistically significant
NP = not reported
NDR = no dose relationship

The highest NOAEL for reproductive toxicity identified for DCHP was 402 mg/kg bw/day based on appearance of one F0 male with slight focal seminiferous tubule atrophy in a 2-generation OECD guideline study (Hoshino et al. 2005). There was evidence of systemic effects at this dose (decreased body weight gain). The lowest LOEL for systemic toxicity for males was 80 mg/kg bw/day based on slight hypertrophy of liver and thyroid in F0 males (Hoshino et al. 2005). The lowest LOAEL for systemic toxicity for F0 females was 104 mg/kg bw/day based on decreased body weight gain and increased relative liver weights with slight hypertrophy (Hoshino et al. 2005).

9.2.3.2 Oral exposure in females

Five published studies on the reproductive and developmental effects of DCHP in females were identified. These studies were performed in rats exposed to DCHP before mating only, during gestation (GD6–20, GD6–PND20) or continuous breeding via feed or gavage. One 2-generation study was identified.

The lowest LOAEL identified for developmental toxicity in females is 402 to 534 mg/kg bw/day (6000 ppm [0.6%] in the diet) derived from the 2-generation study described in Section 9.2.3.1.1 above (Hoshino et al. 2005). Developmental toxicity occurred at doses inducing maternal toxicity in the F1 generation. The critical endpoints included altered growth (statistically significant decrease in body weight and altered organ weights at 402–534 mg/kg bw/day in F1 and F2 pups with a NOAEL of 80–107 mg/kg bw/day,

1200 ppm). Maternal effects (F0) included a statistically significant decrease in body weights and food consumption. A statistically significant increase in diffuse hypertrophy of hepatocytes and in relative liver weight occurred at 104 mg/kg bw/day and above (1200 ppm; NOAEL of 21 mg/kg bw/day, 240 ppm).

The lowest LOAEL identified for reproductive toxicity in adult females is 511 mg/kg bw/day (6000 ppm [0.6%] in the diet) in F0 parents in the same study (Hoshino et al., 2005). The critical endpoint was based on altered fertility and pregnancy (statistically significant decrease in F1 body weight at 511 mg/kg bw/day, 6000 ppm with a NOAEL of 104 mg/kg bw/day, 1200 ppm). A prolongation of the estrous cycle was also reported at this dose. However, it was not considered as a direct effect of DCHP on the endocrine system, but rather on the suppression of body weight gain (observed at 104 mg/kg bw/day and above). In F1 parents, no reproductive adverse effect was identified.

Overall, the few studies on the reproductive and developmental effects of DCHP in females have indicated no evidence of teratogenicity or embryolethality. Developmental toxicity (growth alterations [organs and body weights] and lethality) and reproductive toxicity (pregnancy outcome alterations) were reported at high doses (500 mg/kg bw/day and above). When gender effects were examined separately, DCHP-induced developmental effects in males and females were observed at the same dose levels, with some studies reporting males as more sensitive than females.

9.2.3.3 Endocrine studies

In vitro studies have been conducted to examine the potential effects of DCHP on the endocrine system including steroidogenesis in mammalian systems and are related to measurements of reproductive hormones and glucocorticoid effects.

With respect to the potential mechanisms for reproductive effects, studies on estrogen receptor (ER) and androgen receptor (AR) binding by DCHP have been identified. DCHP appeared to be an inducer of MCF-7 cell proliferation in a breast cancer cell line assay for ER activation (Okubo et al. 2003), but this result was not reproducible *in vivo* (Hong et al. 2005). In a β-Galactosidase Activity Assay (which can measure estrogenic, anti-estrogenic, androgenic and anti-androgenic activity in Chinese Hamster Ovarian [CHO] cells), DCHP was shown to have estrogenic activity with one form of ER (ERα), but no estrogenic and possibly anti-estrogenic effects with ERβ (Takeuchi et al. 2005). DCHP was shown to be estrogenic in the Yeast Two-Hybrid Assay (Nishihara et al. 2000). Furthermore, DCHP appeared to show anti-androgenic effects on the AR. In a competitive binding assay for ER and AR, DCHP had low binding affinity for AR and ERα, but had partial inhibitory effects on binding to AR (45% inhibition at 10^{-4} M DCHP) and ERα (IC_{50} at 5.8 x 10^{-8} M) (Satoh et al. 2001). DCHP was also shown to have inhibitory effects on two enzymes that are involved in testosterone production. These are 3β-hydroxysteroid dehydrogenase (HSD) and 17β-HSD3 (Yuan et al. 2012).

Other studies investigated the potential effect of DCHP on corticosteroid production. DCHP was shown in microsomal assays to inhibit 11β-HSD2 (Oshima et al. 2005; Zhao et al. 2010), which is involved in the inactivation of cortisol. This inactivation could result in mineralocorticoid excess, with systemic symptoms similar to pseudoaldosteronism. Zhao et al. (2010) speculated that the inhibition of 11β-HSD2 could also have implications on Leydig cell cortisol levels, resulting in higher tissue levels of cortisol, which could subsequently result in a decrease in testosterone production. Conversely, DCHP was shown to inhibit dibutyryl cAMP-induced cortisol secretion from H295R, an adrenal cell line that serves an *in vitro* model for human steroidogenic cells (Nakajin et al. 2001). DCHP has also been shown to bind to the glucocorticoid receptor (GR), but results were mixed with respect to whether this binding was associated with changes in adipocyte differentiation (Sargis et al. 2010). Liu et al. (2002) and Lu et al. (2004) evaluated the effect of DCHP on neuroendrocrine processes. DCHP suppressed Ca^{+2} release through the nicotinamide acetyl choline receptor (nAChR) of bovine adrenal chromaffin cells (Liu et al. 2002). This result was confirmed in a human cell line (SH-SH5Y), and the effect of DCHP on this process in SH-SH5Y was ten times greater than for estradiol (Lu et al. 2004).

There have been *in vitro* studies on the potential immunological effects of DCHP. One study (Ohnishi et al. 2008) investigated whether phthalate exposure could increase susceptibility to infection, but showed no adverse effect on microphages incubated with 100 µM DCHP. Estrogen-receptor mediated effects on acquired immunity were investigated by Yano et al. (2003). DCHP inhibited mouse spleen cell production of Type 1 helper T-cells (Th1) and Type 2 helper T-cells (Th2); however, this effect did not appear to be mediated by an estrogen receptor.

9.2.3.4 Reproductive and developmental toxicity: evidence in humans

Available information on the potential effects of DCHP on humans was reviewed, rated and assessed for human health risk (Appendix J; Health Canada 2015b). No associations were established for reproductive paramaters such as time to pregnancy (Buck Louis et al. 2014).

9.2.3.5 Other systemic effects[26]

9.2.3.5.1 Repeated-dose studies

The database for repeated-dose toxicity of DCHP is limited to a few short-term and subchronic oral rat studies identified in the literature. The available health effects information for DCHP is summarized below. In a gavage study in rats, no effects were reported when animals were exposed to 200 mg DCHP/kg-bw/d, twice a week for six weeks (Bornmann 1956). In another gavage study in male rats, a LOAEL of 500 mg/kg

[26] This section presents studies examining effects other than reproductive effects.

bw/day (the lowest dose level) was identified. In this study, the animals were administered 0, 500, 1000, 1500, 2000 and 2500 mg DCHP/kg-bw/d for a shorter time period (7 days). The LOAEL was based on a dose-related increase in liver weight and induction of hepatic enzymes in treated animals. Histopathological examination (limited to the liver, kidney and testes of animals treated with 1500 and 2500 mg/kg bw/day) revealed slight hepatic centrilobular hypertrophy at those dose levels, as well as marked proliferation of the smooth endoplasmic reticulum. There was no evidence of peroxisome proliferation. The authors characterize the induction of xenobiotic metabolism observed in this study as weak, drug-type induction, different from the peroxisomal proliferation seen with DEHP (Lake et al. 1982). In a single dose, 21-day feeding study, a LOAEL of 4170 mg/kg bw/day was determined based on a number of toxic effects in treated animals, including testicular atrophy, liver enlargement, alopecia and stomach squamous cell hyperplasia. However, this study is limited since little information is available on the number of animals treated, the species or study design (Grasso et al. 1978).

A subchronic feeding study in which rats were exposed to 0, 0.05, 0.15, 0.4 or 1% (corresponding to doses of 0, 25, 75, 200 and 500 mg/kg bw/day) DCHP for 90 days yielded a LOAEL of 75 mg/kg bw/day based on increased relative liver weight in female rats. An increase in relative liver weight was observed in males only from 200 mg/kg bw/day. Those increases in liver weight were accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses tested. An increase in serum alkaline phosphatase levels was observed in male rats exposed to doses of 25 mg/kg and above and in females at the highest dose. Decreased body weight gain and food consumption in males was noted at the highest dose. No mortality or clinical signs of toxicity were observed (de Ryke and Willems 1977).

In these studies, the lowest LOAEL for repeated-dose oral exposure was 75 mg/kg bw/day based on increased relative liver weight in female rats, accompanied by histological changes in the liver at exposure to a dose of 200 mg DCHP/kg-bw/day and higher.

9.2.3.5.2 Carcinogenicity

DCHP has not been classified for its potential carcinogenicity by other international agencies.

No effects were reported in rats fed DCHP at 27 mg/kg bw/day for two years or in dogs treated with 14 mg/kg bw/day for a year in their diet. No further details were available (Shibko and Blumenthal 1973). No effects were reported among rats exposed by gavage to 0.5 or 1 ml/kg of a preparation containing 25% DCHP in olive oil (approximately 100 or 200 mg DCHP/kg-bw per day) twice weekly for up to 52 weeks (Bornmann 1956). In an 18-month study in the Wistar rat, no carcinogenicity or changes in body weight were noted at low, medium or high exposure doses when compared with the control. The highest dose tested was estimated at 5 mg/kg bw/day (Lefaux 1968).

Based on available information, there is no indication that DCHP is a potential carcinogen. Lake et al. (1982) concluded that DCHP does not appear to be a peroxisome proliferative agent, as the authors did not identify an increase in the number of peroxisomes or any changes in mitochondrial structure or function.

9.2.3.5.3 Genotoxicity

As part of the National Toxicology Program's Environmental Mutagenesis Test Development Program, DCHP was tested for mutagenicity in the Ames test with and without metabolic activation (NTP 1983; Zeigler 1985). *Salmonella typhimurium* (*S. typhimurium*) strains TA1535, TA1537, TA98 and TA100 were tested either as-is or with the inclusion of the S-9 fraction of liver homogenate from Aroclor 1254 exposed Sprague-Dawley rats. The Ames test results were all negative for DCHP. The Ames test (in *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100), the *E. coli* DNA repair assay and the mesenchymal fibroblast-like cell transformation assay for the plasticizer Nuoplax 6938, which is composed of 61.2% BCHP, 21.9% DBP, 15.2% DCHP and 1.7% DMP, were also all negative (with and without metabolic activation) (Nuodex 1982a,b). No *in vivo* studies have been identified in the literature.

9.2.3.5.4 Evidence of systemic toxicity in humans

Available information on the potential effects of DCHP on humans was reviewed, rated and assessed for human health risk (Appendix J; Health Canada 2015b). There was inadequate evidence of an association with MCHP (metabolite of DCHP) and obesity in children and adolescents (Wang et al. 2013). No associations were established for cardiovascular function (Shiue 2013; Trasande et al. 2014).

9.2.4 DMCHP

9.2.4.1 Reproductive and developmental effects of DMCHP in males

No studies examining the potential health effects of DMCHP were identified for any species or gender. DCHP (1,2-Benzenedicarboxylic acid, dicyclohexyl ester: CAS RN 84-61-7) was identified as the "closest analogue" to DMCHP based on similarity in the nature of the ester chains (Section 2.3.2; Health Canada 2015a). Ester groups of DMCHP and DCHP both consist of cyclohexyl chains, with DMCHP having an additional methyl group on the cyclohexyl ring. Due to structural similarities, the physical-chemical

properties for DMCHP and DCHP are also similar. Refer to Section 9.2.3 for summaries of the studies using DCHP for all life stages.

9.2.5 CHIBP

No studies examining the potential reproductive/developmental health effects of CHIBP were identified for any species or gender. DIBP (1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester: CAS RN 84-69-5) and DCHP (1,2-Benzenedicarboxylic acid, dicyclohexyl ester: CAS RN 84-61-7) were identified as the “closest analogue” phthalates to CHIBP within the subcategory based on consideration of similarities in monoester metabolism as well as the length and nature of the ester chains (Section 2.3.2; Health Canada 2015a). CHIBP is expected to yield monoester metabolites identical to the monoester metabolites of DIBP and DCHP.

Based on health effects information on the analogues DIBP and DCHP, a potential health effect of concern may be associated with CHIBP. A review of the potential developmental and reproductive toxicity of the analogue(s) showed that this medium-chain phthalate could have adverse effects on the reproductive system of the developing male, in addition to systemic effects (liver, kidney).

Given the absence of reporting to the section 71 industry survey, non-detection in dust, negligible modelled indoor air concentrations, and the absence of information as to CHIBP presence in product databases, general population exposure to CHIBP from environmental media and prodcuts used by consumers is expected to be negligible. Therefore, risk to human health for this substance is not expected.

9.2.6 BCHP

No studies examining the potential reproductive/developmental health effects of BCHP were identified for any species or gender. DBP (1,2-Benzenedicarboxylic acid, dibutyl ester: CAS RN 84-74-2) and DCHP (1,2-Benzenedicarboxylic acid, dicyclohexyl ester: CAS RN 84-61-7) were identified as the “closest analogue” phthalates to BCHP within the subcategory based on consideration of similarities in monoester metabolism as well as the length and nature of the ester chains (Section 2.3.2; Health Canada 2015a).

Based on health effects information on the analogues DBP and DCHP, a potential health effect of concern may be associated with CHIBP. A review of the potential developmental and reproductive toxicity of the analogue(s) showed that this medium-chain phthalate could have adverse effects on the reproductive system of the developing male, in addition to systemic effects (liver, kidney).

given the absence of reporting to the section 71 industry survey, non-detection in dust and products (emission chamber study), and the absence of information as to BCHP presence in product databases, general population exposure to BCHP from environmental media and products used by consumers is expected to be negligible. Therefore, risk to human health for this substance is not expected.

9.2.7 DBzP

9.2.7.1 Reproductive and developmental effects in males

9.2.7.1.1 Early development: *in utero* exposure

No studies examining the potential reproductive/developmental health effects of DBzP were identified for any species or gender. MBzP (1,2-Benzenedicarboxylic acid, mono[phenylmethyl] ester: CAS RN 2528-16-7) is the monoester hydrolysis product of DBzP. Ortho phthalates are generally known to be rapidly absorbed following oral exposure, and the diester is cleaved into one or more monoesters in the digestive tract. Monoesters are generally considered to be responsible for the health effects of the parent compound (Health Canada 2015a). MBzP is the monoester hydrolysis product of DBzP and is therefore suitable for inferring toxicity in oral developmental studies. Toxicological studies conducted with MBzP were examined to characterize the health effects of DBzP. Summaries of the studies are described in Table 9-25 below.

Several studies examined the potential for MBzP to induce developmental effects in rodents; however, only one study was performed during gestation in rats focusing on the male programming window (GD15–17) where any potential anti-androgenic effects would be observed (see Table 9-25 below). Pregnant Wistar rats were given MBzP via gavage at doses of 167, 250 or 375 mg/kg bw/day on GD15–17 of pregnancy, and offspring were examined on GD21 (Ema et al. 2003). Developmental effects included significant increases in the incidence of CRY, decreases in AGD and the ratio of AGD to the cubic root of body weight in male foetuses at 250 mg/kg bw/day and higher as well as significantly decreased foetal weight at 375 mg/kg bw/day (also described in Table 9-25). However, a significant and dose-dependent decrease in maternal body weight gain (22%) and food consumption (8–15%) was also noted at the lowest dose (167 mg/kg bw/day) and higher.

Saillenfait et al. (2003) evaluated the embryotoxic effects of MBzP in OF1 mice and Sprague–Dawley rats on GD8 and GD10, respectively. In mice, maternal deaths occurred, and maternal body weight gain (statistically significant at the highest dose, 1380 mg/kg bw/day) was reduced along with the corresponding developmental effects in offspring (embryolethality and teratogenicity). In rats, MBzP did not cause significant developmental effects up to doses that produced maternal mortality and/or weight loss (1380 mg/kg bw/day). Previously, Ema et al. treated rats during GD7–15 with MBzP via gavage at dose levels of 250, 313, 375, 438 and 500 mg/kg and reported skeletal malformations at doses equal to or higher than 313 mg/kg as well as increased incidences of post-implantation loss at the two highest doses (1996a). In stage-sensitivity studies by the same authors, teratogenic effects were observed in rats given MBzP (250–625 mg/kg) on GD7–9 and GD13–15. MBzP also caused a dose-related increase in the incidence of resorptions regardless of the periods of administration (Ema et al. 1996b). Maternal effects (reductions in maternal body weight with corresponding reduced food consumption) were observed at lower or equal doses compared to those at which foetal effects occurred, in both studies (see Table 9-25 for a summary).

Table 9-25. Effects from gestational exposure to MBzP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[b]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
Wistar rats; 0, 167, 250, 375; gavage; GD15–17 (Ema et al. 2003)	NM	**250(AGD)** NM (NR) NM (PPS)	**250 (CRY)** NM (HYP) NM (TP) NM (FER)	NM (ROW) 375 (BW) NE (FV) NE (EMB) NM (ESV)	167 (↓food consumption, ↓BW, no embryolethality)
SD rats; 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (est. 0, 230, 460, 920, 1380); gavage; once at GD10 (Saillenfait et al. 2003)	NM	NM	NM	NM (ROW) NE (BW) NE (FV) NE (EMB) NE (ESV)	1380 (↓BW on GD10,11))
rats; 0, 250, 313, 375, 438, 500; gavage; GD7–15 (Ema et al. 1996a)	NM	NM	NE (CRY) NM (HYP) NM (TP) NM (FER)	NM (ROW) 438 (BW) 500 (FV) 438 (EMB) 313 (ESV)	250 (↓food consumption, 313 ↓BW)
Wistar rats; 0, 250, 375, 500, 625; gavage; 1) GD7–9 2) GD10–12 3) GD13–15 (Ema et al. 1996b)	NM	NM	NM	NM (ROW) 625 (BW) 500 (FV) 500 (EMB) 500 (ESV)	375 (↓food consumption, ↓BW)
OF1 mice; 0, 0.9, 1.8, 3.6, 5.4 mmol/kg; (est. 0, 230, 460, 920, 1380);	NM	NM	NM	NM (ROW) NE (BW) 1380 (FV) 1380 (EMB) 920 (ESV)	1380 (↓BW on GD8–9; death)

oral; once at GD8 (Saillenfait et al. 2003)					

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone
[b] Feminization parameters can include anogenital distance (AGD), nipple retention (NR) and preputial separation (PPS).
[c] Malformations can include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration
[d] Other developmental effects include decreases in overall foetal body weight at PND1 (BW), decreases in reproductive organ weight (ROW), embryotoxicity (EMB) and , foetal viability (FV), or effects on the incidence of external, skeletal or visceral malformations (ESV).
NM = not measured
NE = no effect observed at the dose range tested

Overall, the highest oral NOAEL for developmental toxicity of MBzP at the *in utero* life stage was 167 mg/kg bw/day based on increased incidence of CRY and decreased AGD in male foetuses at 250 mg/kg bw/day and higher as well as significantly decreased foetal weight at 375 mg/kg bw/day (Ema et al. 2003). The lowest dose, and above, in this study also caused slight maternal toxicity, as seen by decreased food consumption and body weight gain, with no evidence of embryolethality such as number of corpora lutea, implantations, resorptions, and dead fetuses, the incidence of post-implantation loss per litter, or the sex ratio of live fetuses (LOAEL of 167 mg/kg bw/day). Therefore, the NOAEL of 167 mg/kg bw/day is considered the critical effect level for the developmental toxicity of DBzP for this life stage.

9.2.7.1.2 Exposure at prepubertal/pubertal life stage

There were no repeated-dose oral exposure studies in sexually immature animals (PND1–55) with DBzP via any route of exposure identified in the literature. As with the previous section, studies conducted with MBzP were reviewed to characterize the health effects of DBzP (Health Canada 2015a).

To determine the potential reproductive toxicity of phthalate diesters and monoesters on sperm parameters in young male rats, Kwack and colleagues (2009) orally exposed six 5-week-old Sprague–Dawley rats to 250 mg/kg bw/day of MBzP for four weeks. No adverse effects were found on reproductive organ weights. The authors reported that MBzP significantly lowered the sperm counts (20% decrease compared to controls) and increased sperm motility (VCL) at 250 mg/kg bw/day (Kwack et al. 2009).

Overall, the LOEL for the reproductive toxicity of MBzP at the prepubertal/pubertal life stage was 250 mg/kg bw/day based on decreased sperm counts after four weeks of exposure (Kwack et al. 2009). No studies were identified on any other species via any route of exposure for this life stage. Therefore, the LOEL of 250 mg/kg bw/day will be used as the critical effect level for the reproductive toxicity of DBzP for this life stage.

9.2.7.1.3 Oral exposure at the mature male adult stage

No studies examining the potential reproductive toxicity of DBzP at the adult male life stage were identified. There were no studies available where MBzP was administered to adult males starting after PND55. Therefore, the effects observed in the MBzP study examining pubertal animals will be used to characterize the reproductive toxicity of DBzP for the adult life stage as administration of MBzP continued into adulthood (PND63) in these animals (Kwack et al. 2009).

9.2.7.2 Oral exposure in females

Five published studies on the reproductive and developmental effects of MBzP in females were identified. Four studies were performed in rats and one in mice, in which pregnant animals were exposed via gavage to MBzP during gestation.

A group of researchers (Ema et al.) conducted studies at different gestation times (GD7–15, GD7–9, GD13–15) in order to determine the most sensitive period. A study was also conducted in female mice and rats exposed during their period of neurulation (GD8 and GD10, respectively) in order to determine the most sensitive species.

The lowest LOAEL for developmental toxicity in females (313 mg/kg bw/day) was identified in a study in which pregnant Wistar rats were exposed by gavage to MBzP (0, 250, 313, 375, 438 and 500 mg/kg bw/day) during the whole period of organogenesis (GD7–15) (Ema et al., 1996a). The effects occurred at a dose at which maternal effects were also observed and included a statistically significant increase in skeletal malformations (primarily cleft palate, dilated renal pelvis and fusion of ribs, cervical and/or thoracic vertebral arches) at 313 mg/kg bw/day and above. A NOAEL of 250 mg/kg bw/day was identified. Maternal effects were reported as a statistically significant and dose-dependent decrease in food consumption at 250 mg/kg bw/day and above, the lowest dose tested.

The lowest LOAEL identified for the reproductive toxicity in adult females (438 mg/kg bw/day) is based on the rat study where there were observations of increased post-implantation loss along with decreased food consumption after gavage treatment of MBzP at GD7–15 (NOAEL of 375 mg/kg bw/day) (Ema et al., 1996a). One study by Zhang et al. (2011) examined the potential estrogenic effects of DBzP using an *in vitro* yeast estrogen screen (YES) and *in vivo* immature mouse uterotrophic assay (three-day exposure via oral gavage). In the uterotrophic assay, DBzP significantly inhibited the effects of E2 at the high dose (400 µg/kg-bw/d) and low dose (40 µg/kg-bw/d) ($P < 0.05$), which demonstrated its strong estrogenic antagonistic ability. The authors compared these results to those using BBP. In an *in vivo* uterotrophic assay with BBP (2240 mg/kg bw/day and above), uterine growth was not promoted in immature females (ECJRC 2007), whereas the results obtained by Zhang et al. (2011) showed that DBzP did effect uterine growth and suggested that the (*in vivo*) estrogenic potency of DBzP is higher than that of BBP. In the YES assay, DBzP inhibited the agonist activity of 10^{-9}M E2 at 1.95×10^{-6}M and above. Similar results were shown for BBP in this study (the EC_{50}

value of DBzP was 8.06×10^{-6} M, slightly lower than BBP at 1.17×10^{-5} M) (Zhang et al. 2011).

Overall, the studies related to the reproductive and/or developmental effects of MBzP in females indicate that MBzP is teratogenic and embryolethal (313 mg/kg bw/day only at doses which also cause maternal toxicity. The gestational age at the time of exposure is critical to the teratogenic effects of MBzP. Some gender-related differences were reported (male pups more sensitive than female pups).

9.2.7.3 Reproductive and developmental toxicity: evidence in humans

No information is currently available on the potential reproductive/developmental effects of DBzP in humans.

9.2.7.4 Other systemic effects[27]

9.2.7.4.1 Repeated-dose studies

No repeated-dose studies have been identified in the literature for DBzP. There was one repeated-dose study available for the closest analogue MBzP.

In a short-term study in which six 5-week-old Sprague–Dawley rats were orally exposed to MBzP at 250 mg/kg bw/day for four weeks, no adverse effects were found on body weight gain, food consumption or relative organ weights, or hematology measurements. Some serum parameters (glucose by ~25%, glutamate oxaloacetate transaminase by ~40%) were found to be significantly higher from controls. Leukocyte counts were also changed (data not shown) (Kwack et al. 2009).

Systemic toxicity has been reported in developmental toxicity studies in which rodents were exposed orally to this substance (Ema et al. 1996ab, 2003; Saillenfait et al. 2003). The common systemic effect reported was reduction in maternal body weight gain and, in one study, maternal death was reported at the highest dose tested (1380 mg/kg bw/day) (Saillenfait et al. 2003). The lowest LOAEL for short-term exposure was 167 mg/kg bw/day based on a dose-dependent decrease in body weight gain (22% decrease for adjusted weight gain) associated with a decrease in food consumption (8–15%) in dams in a developmental toxicity study in rats (Ema et al. 2003, as described in Section 9.2.7.1).

9.2.7.4.2 Carcinogenicity

[27] This section presents studies examining effects other than reproductive effects.

DBzP has not been classified for its potential carcinogenicity by other international agencies, and no chronic toxicity/carcinogenicity studies were available for this phthalate. There was also no study available for the closest analogue MBzP.

9.2.7.4.3 Genotoxicity

No genotoxicity studies were identified for DBzP or its closest analogue MBzP.

9.2.7.4.4 Evidence of systemic toxicity in humans

No information has been identified on the potential effects of DBzP in humans.

9.2.8 B84P

9.2.8.1 Reproductive and developmental effects in males

9.2.8.1.1 Early development: *in utero* exposure

No studies examining the potential reproductive/developmental health effects of B84P were identified for any species or gender. DIBP (1,2-Benzenedicarboxylic acid, bis[2-methylpropyl] ester: CAS RN 84-69-5), BBP (1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester: CAS RN 85-68-7) and MBzP (1,2-Benzenedicarboxylic acid, mono[phenylmethyl] ester: CAS RN 2528-16-7) were identified as the "closest analogue" phthalates to B84P within the subcategory based on consideration of similarities in monoester metabolism (Section 2.3.2; Health Canada 2015a). The health effects of DIBP and MBzP have been characterized in sections 9.2.2.1 and 9.2.7.1 above.

The European Commission classified BBP as Category 2 (causes developmental toxicity in humans) Risk phrase R61 (may cause harm to unborn child) for developmental toxicity and as Category 3 (causes concern for human fertility) Risk phrase R62 (possible risk of impaired fertility) for reproductive toxicity (ECHA 2008). Subsequent changes to the classification schemes for the hazard class within the European Union Classifying, Labelling, and Packaging (CLP) regulations (EC No 1272/2008) resulted in a change in the status of BBP to Category 1B – reproductive toxicant (presumed human reproductive toxicant).

A literature search identified many studies examining the effects of BBP during gestation in rodents. For the purpose of characterizing effects during early male development, only studies in rats in which effects of BBP were observed at doses at and below 500 mg/kg bw/day following *in utero* exposure during the masculinization programming window are reported here. Summaries of the studies are described below and in Table 9-26.

Overall, adverse effects in the parameters used to measure RPS in male rat offspring after *in utero* exposure to BBP include decreased testicular testosterone levels, delayed preputial separation (PPS), AGD, NR, CRY, gross and testicular malformations, and effects on fertility.

The dose level at which developmental effects were first observed after gestational exposure to BBP appeared to be somewhat consistent across studies. A decrease in male rat offspring body weights, but no significant change in body weight gain, was observed at 100 mg/kg bw/day and above at birth in F1 and/or F2 pups in two separate 2-generation studies (Aso et al. 2005; Nagao et al. 2000). Decreased pup weight was also observed at higher doses in other studies (see Table 9-26) (Ema et al. 1990; Piersma et al. 1999; Tyl et al. 2004).

Effects related to feminization parameters associated with RPS have been reported starting as low as 100 mg/kg bw/day, where BBP-induced effects on AGD at birth (PND1–4) were observed in F2 offspring in rats after oral exposure in a 2-generation study (Aso et al. 2005). Other studies have also shown reduced AGD in newborn male pups at 250 mg/kg bw/day and above (Nagao et al. 2000; Hotchkiss et al. 2004; Tyl et al. 2004; Liu et al. 2005). Nipple retention (NR) in young males, when measured at one to two weeks after birth, was observed at doses as low as 500 mg/kg after short gestational exposure (GD14–18), although it was not statistically significant (Hotchkiss et al. 2004). This effect became statistically significant in a 2-generation study at higher doses when measured on PND11–13 (750 mg/kg bw/day) (Tyl et al. 2004).

Delays in PPS have been reported at doses as low as 400 mg/kg bw/day and above in F1 males in three separate 2-generation studies using BBP. It is interesting to note that a short gestational exposure (GD14–18) did not elicit delays in this endpoint at similar doses (500 mg/kg bw/day) (Hotchkiss et al. 2004).

Reproductive tract malformations, such as CRY and HYP, were reported after BBP gestational exposure at higher dose ranges. The lowest dose at which significant incidences of CRY were reported was 580 mg/kg bw/day and above after short (GD5–20) exposure to BBP (Piersma et al. 1999 in NICNAS 2008). It is of interest to note that a number of studies examining CRY in short and longer (2-generation) exposures to 500 mg/kg bw/day of BBP during gestation did not observe significantly increased occurrences of this malformation (Nagao et al. 2000; Hotchkiss et al. 2004). A separate 2-generation study by Tyl et al. (2004) noted male pups with undescended testes at 750 mg/kg bw/day in both F1 and F2 generations in the presence of maternal toxicity. Gray et al. (2000) also observed CRY at this dose level after gestational exposure (GD14–PND3). See Table 9-26.

Gross malformations of the penis (HYP) appeared to follow a somewhat similar pattern as CRY, where there were no significant incidences of HYP at 500 mg/kg and below. They did become evident at 750 mg/kg bw/day but only in F1, not F2 pups in the presence of maternal toxicity (see Table 9-26) (Nagao et al. 2000; Tyl et al. 2004). Gray et al. (2000) also observed HYP at this dose level after gestational exposure (GD14–PND3).

A decrease in postnatal relative testis weights was reported at doses of BBP as low as 270 mg/kg bw/day, the lowest dose tested, and above after gestational exposure to BBP from GD5–20 (Piersma et al. 1999 in NICNAS 2008). No histopathological effects were reported and/or measured. No changes in testes weight were observed in a separate short (GD14–18) exposure to 500 mg/kg bw/day BBP, but a decrease in

relative levator ani+bulbocavernosus muscle (LABC) weight (10%) was reported (Hotchkiss et al. 2004). In multigenerational studies, relative and absolute testes weights were decreased in F1 male pups at PND22 at the highest dose tested (Nagao et al. 2000). This effect was consistent at higher doses in both F1 and F2 offspring in another study (750 mg/kg bw/day) (Tyl et al. 2004).

Histopathological effects in the testes after exposure to BBP included seminiferous tubule atrophy, Leydig cell hyperplasia, absence of gubernaculi and flaccid fluid-filled testes; these effects were observed regardless of the length of exposure. Multiple effects in the testes included aplasia/dysplasia of the epididymis, diffuse atrophy of the seminiferous tubules and Leydig cell hyperplasia at 400 mg/kg bw/day in F1 males when examined in adulthood (Aso et al. 2005). Severe seminiferous tubule degeneration and atrophy were also observed in F1 males in adulthood along with Leydig cell hyperplasia at 500 mg/kg bw/day and above in other studies (Nagao et al. 2000; Tyl et al. 2004).

The effect of gestational exposure to BBP on fertility, whether measured by sperm parameters at a young age or by reproductive success as adult males, was evident at doses higher than testicular histopathology. Aso et al. (2005) did not find any adverse effects in sperm parameters (sperm count, motility, morphology) in F1 adult males, nor were there any adverse effects related to BBP on male fertility or mating indices at doses up to and including 400 mg/kg bw/day. Similarly, Nagao et al. (2000) reported no effects on sperm parameters or the reproductive performance of F1 adult males at doses up to 500 mg/kg bw/day[28] BBP via gavage. At higher doses, Tyl et al. (2004) reported decreases in sperm concentration and sperm motility as well as decreased mating and fertility indices at 750 mg/kg bw/day as adults. Pregnancy indices were also reduced by 15% at this dose as well. It should be noted that these males also exhibited decreased body weights and decreased relative adrenal, brain and pancreas weights at this dose level.

Alterations of steroidogenesis have been reported with exposure to BBP as decreases in serum and testicular testosterone levels when measured post birth. Only two studies examined serum testosterone levels; one found a statistically significant (44%) decrease in levels in F1 adult males at 500 mg/kg bw/day (highest dose tested) (Nagao et al. 2000), while another reported a similar, non-statistically significant decrease at lower doses of 400 mg/kg bw/day in F0 adult males (Aso et al. 2005). Testicular testosterone levels were measured in three short-term gestational studies (GD18) immediately after cessation of *in utero* exposure. Howdeshell et al. (2008) reported a dose-dependent decrease in testosterone levels (from 27 up to 91% at 900 mg/kg bw/day) in foetal pup testes at 300 mg/kg bw/day and above. It should be noted that maternal toxicity was evident through decreased body weight gain during gestation at this dose and above as well. Both testicular testosterone production and testosterone

[28] It should be noted that nine males exhibited decreased spermatocytes at 500 mg/kg bw per day.

concentrations were statistically significantly reduced in GD18 male foetuses at 500 mg/kg bw/day with no apparent maternal toxicity (Hotchkiss et al. 2004). A more recent study presenting the potential for BBP and other phthalates to alter foetal testosterone production (*ex vivo*) in pregnant SD rats showed that this phthalate disturbed testicular testosterone production during gestation at doses as low as 100 mg/kg bw/day and above with a calculated ED_{50} value of 172.4 mg/kg bw/day (Furr et al. 2014).

Maternal toxicity was examined in relation to the effects in offspring at similar or lower doses. Overall, maternal toxicity after exposure to BBP became evident in the form of decreases in body weight gain, increased kidney and liver weights, and changes in reproductive organ weights (ovaries and uterus), although not consistently. In multi-generational studies, decreased body weight gain was observed at 500 mg/kg bw/day in F1 (data not shown) (Nagao et al. 2000) and 750 mg/kg bw/day (Tyl et al. 2004) in both F0 and F1 females. No changes in body weight gain were observed at lower doses (Aso et al. 2005; Nagao et al. 2000). In shorter term studies (GD5–20), maternal body weight gain was significantly reduced at 300 mg/kg bw/day (18%) and above (Ema et al. 1990; Piersma et al. 1999; Howdeshell et al. 2008).

Liver weight changes (relative and absolute) occurred at doses as low as 200 mg/kg bw/day BBP, without an increase in magnitude or histopathological lesions in F0 but not F1 females (Aso et al. 2005). Tyl et al. (2004) observed significant (16%) increases in relative and absolute liver weights in F0 females at necropsy, but not in F1 females at the highest dose tested (750 mg/kg bw/day), with histopathological lesions in both generations at this dose.

Kidney weight changes (relative and absolute) occurred at doses as low as 400 mg/kg bw/day BBP, without an increase in magnitude or histopathological lesions in F0 but not F1 females (Aso et al. 2005). Similar results were reported by Tyl et al. (2004), where a small increase (less than 10%) in kidney weights was reported in both F0 and F1 females up to as high as 750 mg/kg bw/day, without histopathological outcome.

Nagao et al. (2000) observed a significant decrease (12%) in ovary weight in P0 dams at necropsy at 500 mg/kg bw/day. This was not observed in F1 females at the same dose levels of BBP. In another multi-generational study, relative uterine weights were decreased at 200 mg/kg bw/day. However, according to the authors, this is most likely not due to BBP treatment, as it is not dose-dependent and did not occur in F1 females (Aso et al. 2005). This effect appeared more consistent across generations and increased in severity at higher doses (Tyl et al. 2004). See Table 9-26.

A search of the available literature revealed only two studies examining the effects of gestational exposure of BBP in mice, tested prior to the masculinization programming window. Neither examined the parameters used to measure those related to RPS (see Table 9-26).

Table 9-26. Effects from gestational exposure to BBP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	**Testosterone levels[a] (T, S)**	**Feminization parameters[a]**	**Reproductive tract malformations and/or fertility[c]**	**Other developmental parameters[d]**	**Maternal effects**
Crj:CD (SD) IGS rats; F_1: 0, 100, 200, 400; gavage; 3 weeks of age (10 weeks before mating) - lactation (Aso et al. 2005) [F2 up to PND21]	NM	**100**[e] (AGD-PND4) NM (NR NM (PPS)	NM	**100**[e] (BW-PND0, data not clear) NM (ROW) NE (FV) NE (EMB) NE (ESV)	LOEL= 400 (↑ rel. + abs. liver & kidney wt)
Crj:CD (SD) IGS rats; F_0: 0, 100, 200, 400; gavage; 5 weeks of age (10 weeks before mating) - lactation (Aso et al. 2005)	1)NM (T) 2) NE[t] (S-measured @ 400 only)	NE (AGD-PND4) NM (NR) 400[t] (PPS-PND43)	NM (CRY) NM (HYP) 400[t] (TP-small testes, aplasia/dysplasia of epidid., diffuse atrophy of seminiferous tubules, Leydig cell hyperplasia) NE[t] (FER-number of sperm in testes and in caudal epididymes, epididymal sperm motility, abnormality)	100[e] (BW-PND0, data not clear) NE(ROW) NE (FV) 4) NE (EMB) NE (ESV)	LOEL= 400 (↓ relative uterine wt[NDR])
Harlan SD rats; 0, 11, 33, 100, 300, 600, 900;	**100** (T) ED_{50} = 172.4 [*ex*	NM	NM	NM (BW) NM (ROW) NE (FV)	NE

Strain and species; dose (mg/kg bw/day); route; duration (reference)	**Testosterone levels[a] (T, S)**	**Feminization parameters[a]**	**Reproductive tract malformations and/or fertility[c]**	**Other developmental parameters[d]**	**Maternal effects**
GD14–18; (Furr et al. 2014)	*vivo*] NM (S)			NM (EMB) NM (ESV)	
CD rats; F_0: 0, 750, 3750, 11250 ppm (est. 0, 50, 250, 750); diet; 10 weeks prebreeding (Tyl et al. 2004)	NM	**250** (AGD-PND0) 750 (NR-PND11–13) 750 (PPS)	750 (CRY) $750^{g,s}$ (HYP) $750^{g,s}$ (TP-., semini. tubule degeneration and atrophy, dilatation of rete testis) 750^{s} (FER-aspermia in epidid, epidid. sperm conc, sperm motility)	750 (BW-PND0) 750 (ROW) NE (FV) NE (EMB) NM (ESV)	LOAEL=750 (↓ body wt, ↑rel. + abs liver with histopath[g] ↓rel. & abs. ovary and uterus wts)
CD rats; F_1: 0, 750, 3750, 11250 (est. 0, 50, 250, 750); diet; 10 weeks prebreeding (Tyl et al. 2004)	NM	**250** (AGD-PND0) 750 (NR-PND11–13) 3) NM (PPS)	750 (CRY, data not shown) 750^{g} (HYP-one pup) NM (TP) NM (FER)	NE (BW-PND0); 750 (BW- at weaning) 750 (ROW) 750 (FV) 750 (EMB) NM (ESV)	LOAEL= 750 (rel. uterus and ovary wts, liver histopathology[g], ↓ body wt)
Crj:CD (SD) IGS rats; F_0: 0, 20, 100, 500; gavage; 2 weeks prior to cohabitation - necropsy (Nagao et al. 2000)	NM (T) NE (S); 500^{o} (↓ S)	500 (AGD-PND0) NM (NR) 500^{o} (PPS)	NE (CRY) NE (HYP) 500 (TP-bilateral severe atrophy of the semini. tubules in one male[NS], bilateral Leydig cell hyperplasia in one male[NS]) NE^{o} (FER-	100 (BW, ↓ 6%) 500 (ROW) 500 (FV) NE (EMB) 20^{e} (ESV-data not shown)	LOAEL= 500 ↓ relative ovary wt, 12%)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[a]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
			sperm conc. and motility, ↓ spermatocytes in 9 males, ↓ in 3 males[NS])		
Crj:CD (SD) IGS rats; F_1: 0, 20, 100, 500; gavage; PND22-necropsy (Nagao et al. 2000)	NM (T) NP (S)	NM	NM (CRY) NM (HYP) NE (TP) NP (FER)	500[NS] (BW) NM (ROW) NE (FV) NE (EMB) 500[g] (ESV)	LOEL= 500 (↓ body wt, data not shown)
Cpb:WU rats; 0, 270, 350, 450, 580, 750, 970, 1250, 1600, 2100; gavage; GD5–15 (short exposure) or GD5–20 (long exposure) (Piersma et al. 1999 in NICNAS 2008)	NM	NM	580 (CRY-higher incidence after long exposure) NM (HYP) NM (TP) NM (FER)	350 (BW-long exposure); 450 (BW-short exposure) 270[e] (ROW-long exposure) NM (FV) 750 (EMB-long and short exposure) 750 (ESV)	LOAEL= 750 (↑ rel. liver wt with peroxisome prol, ↓ body wt gain)
SD rats; 0, 100, 300, 600, 900; gavage; GD8–18 (Howdeshell et al. 2008)	300[k] (↓ T-GD18) NM (S)	NM	NM	NM (BW) NM (ROW) 600 (FV) 600 (EMB) NM (ESV)	LOAEL= 300 (↓ body wt gain)[l]
Wistar rats; 0, 0.25, 0.5, 1.0, 2.0% (est. 0, 185, 375, 654,	NM	NM	NM	375 (↑ BW); 654 (↓ BW) NM (ROW) 375 (FV)	LOAEL= 654 (↓ body wt

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[a]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
974); diet; GD0–20 (Ema et al. 1990)				974 (EMB- no live foetuses from any dams) 375^{NDR} (ESV)	gain, food consumption)
SD rats; 0, 500; gavage; GD14–18 (Hotchkiss et al. 2004)	500^{e} (T) NM (S)	500^{e} (AGD) 500^{NS,e}(NR) NE (PPS)	NE (CRY) NE (HYP) NE (TP) NM (FER)	NE (BW- data not shown) 500^{e} (ROW- ↓ LABC wt) NE (FV) NE (EMB) NM (ESV)	NE
SD rats; 0, 500; gavage; GD12–19 (Liu et al. 2005)	NM	500^{e} (AGD) NM (NR) NM (PPS)	NM	NM	NR
SD rats; 0, 750; gavage; GD14–PND3 (Gray et al. 2000)	NM (T) NE (S)	750^{e} (AGD-PND2) 750^{e} (NR-PND13) 750^{e} (PPS-PND28 and onward)	750^{e} (CRY) 750^{e} (HYP) 750^{e} (TP- small, atrophic testes, flaccid fluid-filled testes, absence of gubernaculum) 750^{e} (FER- sperm prod, caudal sperm numbers (data not shown))	750^{e} (BW- PND2); NE (BW- PND28) 750^{e} (ROW) 750^{NS,e} (FV- one litter did not survive to two days of age, another litter had no male pups at weaning) NM (EMB) NM (ESV)	NE
OF1 **mice**; 0, 0.9, 1.8, 3.6, 5.4 mmol/kg (0, 280, 560, 1120, 1690);	NM	NM	NM	1690 (BW- GD8) NM (ROW) 31120 (FV) 560 (EMB) 560^{g} (ESV)	LOEL= 1120 (↓ body wt gain on GD9–18^{h},

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[a]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
gavage; single dose on GD8 (Saillenfait et al. 2003)					1–3 deaths[NS])
Swiss DC-1 **mice**; 0, 0.1, 0.5, 1.25, 2.0[f]% (est. 0, 182, 910, 2330, 4121); diet; GD6–15 (NTP (1990) cited in NICNAS (2008))	NM	NM	NM	NM (BW) NM (ROW) NM (FV) 910 (EMB) 910 (ESV)	LOAEL= 910 (↓ body wt gain)

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone
[b] Feminization parameters can include anogenital distance (AGD), nipple retention (NR) and preputial separation (PPS).
[c] Malformations include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration
[d] Other developmental effects include decreases in overall foetal body weight (BW), decreases in reproductive organ weight (ROW), foetal viability (FV) and embryotoxicity (EMB), or effects on the incidence of external, skeletal or visceral malformations (ESV).
[e] Lowest dose tested in the study.
NDR = no dose response relationship
NS = not statistically significant
NP = results not reported (but measurement was stated in the methods and materials)
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns of effects, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
[f] This dose was removed from the study because all conceptuses in this group were resorbed.
[g] No statistical significance was presented for this parameter. The LOAEL presented for this parameter is the lowest dose that was discussed by the authors in the text section of the results (if the authors did not present any details in the text concerning the parameter, the LOAEL presented here reflects the lowest dose at which any number of pups were affected according to tables and/or figures).
[h] There were no significant changes in the weight gain of dams at any dose when the values were corrected for gravid uterine weight (i.e., body weight - gravid uterine weight). The authors attributed the significant decreases in body weight gain at the two highest doses on GD9–18 to the reduction in the number of live foetuses.
[I] AGD was significantly increased in the treatment group at PND2, but the authors state that this effect was related to the increased weight of pups.
[j] The authors attribute the increase in pup weight to the low average litter size of the BBP-exposed dams (compared to the average litter size of control dams). Moreover, at PND7, 14, 20, 56 and 90, the average body weights of pups in the treatment group were not significantly different from those of the pups in the control group.
[k] Foetal testicular hormone production was evaluated *ex vivo* as per Wilson et al. (2004). The majority of the individual phthalate dose-response studies used a three-hour testes incubation period, with the exception of the BBP and DEP study. The BBP and DEP studies incubated the testes for two hours, thus resulting in lower total levels of

testosterone production. Testosterone was extracted directly from the testes on GD18 from the rats exposed to DBP (Howdeshell et al. 2008).
[l] Two dams in the 600 mg/kg/day group and two dams in the 900 mg/kg/day group died or were excluded from the study because of dosing errors.
[m] The low dose for parental females in mg/kg/day was not indicated in the summary presented in the EU RAR.
[n] There appeared to be no significant effect on this parameter based on the presented data. However, whether or not the data were actually significant was unclear from the text.
[o] These doses were reported for post-weaning F_1 animals. F_1 animals were treated by oral gavage after weaning (PND22), in addition to having been exposed to BBP while *in utero.*
[p] Ema et al. included a pair-fed group in their study in order to determine whether the effects observed were due to reduced food consumption during pregnancy or due to dietary BBP. The effects observed for this parameter were significantly different at this dose when compared both to the control group and to the pair-fed group.
[q] Body weight gain was adjusted by excluding gravid uterus weight.
[r] Ema et al. included a pair-fed group in their study in order to determine whether the effects observed were due to reduced food consumption during pregnancy or due to dietary BBP. The effects observed for this parameter were significantly different at this dose only when compared to the pair-fed group (i.e., they were not significantly different from the control group).
[s] This parameter was reported for F1 parental males. F_1 parental males were dosed directly through diet for ten weeks prebreeding, in addition to having been exposed to BBP while *in utero*.
[t] These doses were reported for F1 parental males. F_1 parental males were treated by gavage starting at three weeks of age, in addition to having been exposed to BBP while *in utero.*

Overall, the highest NOAEL for developmental toxicity identified for BBP was 50 mg/kg bw/day based on pup body weights (both male and female) at 100 mg/kg bw/day and decreased AGD at birth in males at 100–250 mg/kg bw/day and above (Aso et al. 2005; Nagao et al. 2000; Tyl et al. 2004). Foetal testicular testosterone was also reduced at this dose level and above (Furr et al. 2014). The lowest LOAEL for maternal toxicity of BBP was 300 mg/kg bw/day based on significantly reduced maternal body weight gain (Howdeshell et al. 2008). The available information indicates that BBP causes developmental effects in male pups at lower doses than the other two analogues, DIBP and MBzP. Refer to sections 9.2.2.1 and 9.2.7.1 above for summaries of the studies conducted with DIBP and DBzP (MBzP), respectively.

Therefore, the critical effect level for developmental toxicity of B84P for this life stage, based on effects observed after exposure to DBP and DIBP, is 100–250 mg/kg bw/day.

9.2.8.1.2 Exposure to B84P at prepubertal/pubertal life stage

There were no repeated-dose oral exposure studies in sexually immature animals (PND1-55) with B84P via any route of exposure. As with the previous section, DIBP and MBzP were identified as the most appropriate candidates for read-across. Refer to sections 9.2.2.1 and 9.2.7.1 above for summaries of the studies using DIBP and DBzP (MBzP), respectively. Summaries of the studies are described in Table 9-27 below.

To determine the potential reproductive toxicity of phthalate diesters on sperm parameters in young male rats, Kwack and colleagues (2009) orally exposed six 5-week-old Sprague–Dawley rats to 500 mg/kg bw/day of BBP for four weeks. Adverse effects included decreased body weight gain as well as increased relative liver weights. The authors reported that BBP significantly lowered the sperm counts (31% decrease compared to controls) and decreased sperm motility at 500 mg/kg bw/day (Kwack et al. 2009). Effects on sperm parameters could potentially be secondary to systemic toxicity.

No changes in reproductive organ weights were observed after ten-day oral BBP exposure up to and including 500 mg/kg bw/day in young castrated male rats in a Hershberger assay (Lee and Koo 2007). The authors did note a small but statistically significant decrease in serum testosterone levels and a slight increase in serum luteinizing hormone levels at 100 mg/kg bw/day and above.

Table 9-27. Effects from exposure to BBP in prepubertal/pubertal males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
SD rats; 0, 500 BBP; gavage; 4 wks (Kwack et al. 2009)	Prepubertal (PND35)	NM	500[e] (↓ sperm count [31%], motility [40%])	NM	500[e] (BW) NE (ROW) 500[e] (ST- ↑ liver wt)
SD rats; 0, 20, 100, 500 BBP; gavage; 10 days (Lee & Koo 2007) (CAS not defined)	Pubertal (PND49)	NM (T) 100 (S) 100 (↑LH)	NM	NM	NE (BW) NE (ROW) NE (ST)
B6C3F1 mice: 0, 1600, 3100, 6300, 12500, 25000; est. 0, 240, 464, 946, 1875, 3750 (diet) 14 days (NTP 1982)	PND35	NM	NM	NP	NE (BW) NP (ROW) NE (ST)

[a] Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S) or luteinizing hormone (LH).
[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis or reproductive success at adult stage after *in utero* exposure.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] Lowest dose tested in the study.
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
NS = not statistically significant
NDR = no dose relationship
NP = not reported

Overall, the lowest LOEL for reproductive toxicity identified for BBP at the prepubertal/pubertal life stage was 500 mg/kg bw/day based on decreased sperm count and sperm motility in young male rats, effects that could potentially have been secondary to systemic effects (Kwack et al. 2009). As described in Section 9.2.7.1, the lowest LOEL for reproductive toxicity identified for MBzP at the prepubertal/pubertal life stage was 250 mg/kg bw/day based on decreased sperm counts after four weeks of exposure (Kwack et al. 2009). Therefore, the lowest LOEL of 250–500 mg/kg bw/day will be used as the critical effect level range for the reproductive toxicity of B84P for this life stage based on the effects observed after exposure to MBzP and BBP, respectively.

9.2.8.1.3 Oral exposure at the mature male adult stage

As with the previous life stages, no studies examining the potential reproductive toxicity of B84P at the adult male life stage (PND55+) were identified. Studies conducted with BBP were reviewed to characterize the health effects of B84P for this life stage (Health Canada 2015a). Summaries of the studies are described in Table 9-28 below. As mentioned in previous sections, no studies examining the potential reproductive toxicity of DIBP and MBzP at the adult male life stage were identified.

Overall, the reproductive effects of BBP in adult male rats have included reduced mating and fertility, decreased testes weights, histopathological effects in the testes as well as decreases in serum testosterone levels. See Table 9-28 below for a summary of the effects in adult male rodents after oral exposure to BBP. In an NTP ten-week modified mating study, male F344 rats were exposed to BBP in the diet at levels of 0, 300, 2800 or 25 000 ppm (0, 20, 200 or 2200 mg/kg bw/day) for ten weeks with a corresponding two-day recovery period (NTP 1997c). The rats were then mated with untreated females and necropsied with a full histological examination of the control and high-dose group only. However, the testis and epididymis, seminal vesicle and prostate were examined in all groups. Males in the high-dose group (2200 mg/kg bw/day) exhibited reduced absolute and relative testis and prostate weights, along with marked degeneration in the testis and epididymis. Epididymal sperm concentration was 87, 70, and 0.1% of the control in the 20, 200 and 2200 mg/kg bw/day groups, respectively. Reproductive success (pregnancies) and sperm motility and morphology were comparable between the controls and the low- and mid-dose groups, but these parameters were not measured in the high-dose group due to the absence of sperm; no females were pregnant after mating with the males. The significant reduction in sperm count observed in the 200 mg/kg bw/day group was not considered adverse by the NTP Expert Panel (2002), as sperm counts might have been affected by the shorter recovery period from the time between mating to necropsy in this group compared to the other dose groups. Further, a European Union risk assessment on BBP (2007) performed a covariate analysis of variance taking into account days of recovery and concluded that the decrease in spermatozoa concentration was not statistically significant at 200 mg/kg bw/day (at the 5% level; $p = 0.07$) (ECJRC 2007), although the response was still dose-dependent.

A more recent 2-generation study in Crj:CD Sprague–Dawley IGS rats administered 0, 100, 200 and 400 mg/kg bw/day of BBP by gavage starting at five weeks of age (F0)

and three weeks of age (F1) for ten weeks prior to mating through weaning (Aso et al. 2005). Effects in F0 males included reduced absolute epididymal weight, hyperplasia of the Leydig cells in the testes and decreased spermatozoa in the lumina of the epididymis at the 400 mg/kg bw/day dose level.

Table 9-28. Reproductive effects from exposure to BBP in adult males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Age at the start of study	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
F344 rats; 0, 300, 2800, 25000 ppm, est. 0, 20, 200, 2200; diet; 10 wks (NTP 1997c)	Not specified	NM	200 (epidid. sperm concentration)	2200 (degeneration of seminiferous tubule germinal epithelium)	2200 (BW) 2200 (ROW) 2200 (ST- ↓ prostate glands)
SD rats; 0, 100, 200, 400; gavage; F0: 4 wks before mating – PND21 of offspring (Aso et al. 2005)	PND35	NM (T) NE (S) NE (LH)	NE	400 (Leydig cell hyperplasia and decreased spermatozoa in epididymis)	NE (BW) 400 (↓ abs. epididymal wt) 400 (ST- ↑ liver and kidney wt)
SD rats; 0, 160, 480, 1600; gavage; 14 days (Lake et al. 1978)	Not specified	NP	NP	480 (testicular atrophy)	1600 (BW) 1600(ROW) 1600 (ST-↑ liver and kidney wt, liver histopathology and peroxisome prol.)
SD rats; F0: 0, 20, 100, 500; diet; 10 wks prior to mating – PND21 (Nagao et al. 2000)	PND42	NM (T) 500(↓S) NE (LH)	NE	NE	500 (BW) NE(ROW) 500 (ST- ↑ liver and other organ wt)
SD rats; F1: 0, 750, 3750, 11250 ppm, est. 0, 38, 188, 563 (HC	Not specified	NM	38^{NDR} (↑ sperm production, NS	NE	NE (BW) NE (ROW) 563 (ST-)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Age at the start of study	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
1994); diet; 10 wks prior to mating – PND21 (Tyl et al. 2004)			at 563)		
Cpb:WU rats; 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100; gavage; 28 days (Piersma 2000)	PND28	NM (T) 450 (↓S) 1250 (↑LH)		**970** (severe testicular atrophy)	1250^{NS}(BW) 1250 (ROW) 750 (ST- ↑ rel liver wt)
Wistar rats: 0, 250, 500, 1000 (gavage) 8 wks (Piersma et al. 1995)	PND84	NP	NP	1000 (testicular degeneration, Leydig cell hyperplasia)	1000 (BW) NP (ROW) NP (ST)
F344 rats; 0, 300, 900, 2800, 8300, 25000 ppm, est. 0, 30, 60, 180, 550, [1650] (HC 1994); diet; 26 wks (NTP 1997b)	PND42	NM	1650 (sperm concentration)	1650 (hypospermia, seminiferous tubule atrophy)	1650(BW) 1650 (ROW) NE (ST)
F344 rats; 0, 0.625, 1.25, 2.5, 5.0%, est. 0, 313, 625, 1250, 2500 (HC 1994); diet; 14 days (Agarwal et al. 1985)	PND105	NM (T) 2500 (↓S) 1250 (LH-insuff. sample volume at 2500)	1250 (immature spermatogenic cells)	1250 (testicular atrophy)	1250(BW) 1250 (ROW-epididymis, seminal vesicle) 313[e] (ST- ↑ kidney wt)
F344 rats; 0, 3000, 6000, 12000 ppm, est. 0, 120, 240, 500; diet; 2 years (NTP 1982 in NTP 1997)	Not specified	NM (T) NP (S) NM (LH)	NM	NM	500 (BW) NM (ROW) 120[e] (ST- ↑ kidney wt)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Age at the start of study	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
B6C3F1 **mice**; 0, 1600, 3100, 6300, 12500, 25000, est. 0, 240, 464, 946, 1875, 3750; diet; 14 days (NTP 1982)	PND35	NM	NM	NP	NE (BW) NP(ROW) NE (ST)
B6C3F1 **mice**; 0, 1600, 3100, 6300, 12500, 25000, est. 0, 240, 464, 946, 1875, 3750; diet; 90 days (NTP 1982)	PND35	NM	NM	NP	240[e](BW) NP(ROW) NE (ST)
B6C3F1 **mice**; 0, 6000, 12000 ppm, est. 0, 1000, 2000 (NICNAS); Diet; 2 years (NTP 1982)	PND35	NM	NM	NE	1000 [e] (BW) NP(ROW) NP (ST)

[a] Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S) and/or luteinizing hormone (LH).
[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis or reproductive success after mating.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] Lowest dose tested.
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
NP = not reported, but indicated effect was examined in the methods section of the study
NM = not measured

Overall, the highest NOAEL for reproductive toxicity identified for BBP was 200 mg/kg bw/day based on histopathological effects in testes of adult F0 males, which included reduced absolute epididymal weight, hyperplasia of the Leydig cells in the testes and decreased spermatozoa in the lumina of the epididymis at 400 mg/kg bw/day (Aso et al. 2005). A NOAEL of 200 mg/kg bw/day was also determined from an earlier study in F344 rats, where a high rate of infertility (decreased numbers of pregnancies), marked

histopathology in the testes and epididymis, and lower sperm counts were observed at 2200 mg/kg bw/day (NTP 1997b). These endpoints were selected, as they represent reproductive effects in adult male animals that were exposed specifically during this life stage. Systemic effects appeared to be mostly limited to increased kidney and liver weights, with the lowest LOAEL at 313 mg/kg bw/day based on a significant increase in relative liver and kidney weights, accompanied by histological changes in the liver at higher doses in male F344 rats administered BBP for 14 days (Agarwal et al. 1985). No studies were identified for B84P on any other species via any other route of exposure (dermal, inhalation) at this life stage. Therefore, the NOAEL of 200 mg/kg bw/day will be used as the critical effect level for the reproductive toxicity of B84P for this life stage.

9.2.8.2 Oral exposure in females

The potential reproductive/developmental effects of DIBP and DBzP (MBzP) in females were summarized in sections 9.2.2.2 and 9.2.7.2 above, respectively.

As previously noted, there was many studies identified examining the reproductive and developmental effects of BBP. Over 20 studies were performed in rats and 3 studies in mice. The route of exposure was oral in all instances, either gavage or feed. The lowest LOAEL identified for developmental toxicity of BBP in females was 100 mg/kg bw/day and was determined from the previously described 2-generation studies in Section 9.2.8.1 (Aso et al., 2005; Nagao et al., 2000). In the first study (Aso et al., 2005), effects included altered reproductive development (statistically significant increase of AGD in F1 and decreased pup weight on PND0 in F2 female offspring at 100 mg/kg bw/day and above, the lowest dose tested). Maternal effects were reported as a statistically significant increase in absolute and relative liver and kidney weights in F0 females at 400 mg/kg bw/day (NOAEL of 200 mg/kg bw/day).

In the second study (Nagao et al., 2000), altered growth and functional deficits (thyroid) included a statistically significant decrease in mean body weights (on PND0) and of serum T3 (at weaning) at 100 mg/kg bw/day BBP and above in F1 offspring only (NOAEL of 20 mg/kg bw/day). Maternal effects included a statistically significant decrease in relative ovary weights in F0 females and decreased body weights in F1 at 500 mg/kg bw/day (NOAEL of 100 mg/kg bw/day).

The lowest LOAELs identified for the reproductive toxicity of BBP in adult females ranged from 500 to 590–2330 mg/kg bw/day, with NOAEL ranging from 100 to 1100 mg/kg bw/day. The critical effects referred principally to pregnancy outcomes, but also to alterations in reproductive organ weights and hormone levels (serum prolactin).

In summary, studies that examined the reproductive/developmental effects of BBP in females were principally performed at high doses of exposure. Their results suggest that BBP is a reproductive and developmental toxicant at 100 mg/kg bw/day and above, at the same dose level as that for which effects were observed in male offspring. The critical endpoints were related to growth alteration, lethality, altered reproductive organ weights, delay of puberty and teratogenicity (variations and skeletal or visceral malformations). The critical reproductive endpoints were related to pregnancy

outcomes, alterations of reproductive organ weights, hormone levels (progesterone and prolactin) and reproductive-related organ visual examination and histopathology (mammary gland). Gender-related differences were reported (males are apparently more sensitive than females).

9.2.8.3 Endocrine studies

One targeted study by Clewell et al. (2010) examined the effects of MBzP on progesterone and testosterone synthesis in the immortalized mouse Leydig cell tumour (MA-10) assay system. MBzP was a weak inhibitor of testosterone synthesis because, according to the authors, this inhibition was statistically significant at concentrations of 3, 30 and 100 µM, and none of the treatment concentrations caused more than a 35% decrease in testosterone. A more recent study by the same group using a rat Leydig cell line (R2C) also showed that this monoester slightly reduced testosterone production at concentrations equal to and greater than 30 µM (Balbuena et al. 2013).

In the same study described in Section 9.2.8.1 by Saillenfait et al. (2003), mouse and rat whole embryos were cultured at comparable developmental stages and exposed to 0 to 5 mM MBzP for 48 hours. It appeared as though the mouse embryo was not intrinsically more sensitive to MBzP than the rat embryo. Similar to *in vivo* observations, the central nervous system was a target of MBzP, as indicated by the occurrence of open neural tubes (Saillenfait et al. 2003).

9.2.8.4 Reproductive and developmental toxicity: evidence in humans

No information is available on the potential reproductive/developmental effects of B84P in humans.

9.2.8.5 Other systemic effects[29]

9.2.8.5.1 Repeated-dose studies

No short-term and subchronic studies have been identified in the literature for B84P. Studies conducted on its closest analogues DIBP, MBzP and BBP (as described in sections 9.2.2.4 and 9.2.7.4, respectively) were used to characterize the health effects of B84P.

Common systemic effects of these analogues are organ changes (organ weight changes, histopathological changes) and decreases in body weight gain in exposed dams.

[29] This section presents studies examining effects other than reproductive effects.

The lowest LOAEL for short-term exposure was 167 mg/kg bw/day based on dose-dependent decreases in body weight gain (22% decrease for adjusted weight gain) associated with a decrease in food consumption (8–15%) in dams in a developmental toxicity study in rats after exposure to MBzP (Ema et al. 2003, as described in Section 9.2.8.1).

Short-term and subchronic oral studies looking at the effects of DIBP on rodents have also been identified in the literature. Refer to Section 9.2.2.4 for summaries of the studies for this analogue.

Short-term and subchronic studies were also identified for BBP. Most of the repeated-dose studies for this phthalate have been conducted in rats. Only one study in mice and one study in dogs were reported. Also, most studies have used the oral route to study the potential effects of BBP exposure. However, a few inhalation studies and one dermal study were identified. The main effects reported are decreases in body weights and increases in organ weights. The available studies are summarized below. Critical effect levels identified from these studies are presented in Table 9-29.

In a short-term study in which male F344 rats were exposed to 0, 0.625, 1.25, 2.5 or 5.0% BBP (0, 313, 625, 1250 or 2500 mg/kg bw/day) through diet for 14 days, a LOAEL of 313 mg/kg bw/day was identified based on increased LH levels and an increase in relative liver and kidney weights, accompanied by histological changes in the liver (mild multifocal hepatitis) at the highest dose tested. At the two highest doses, a relative decrease in testes, seminal vesicle and thymus weight were observed, and dose-related histopathological changes in seminal vesicles, testes and prostate were noted, as were a decrease in bone marrow cellularity and an increase in FSH. A relative decrease in epididymal weight and cortical lymphocytololysis in the thymus was also observed at the highest dose tested, as well as an increase in testosterone levels (Agarwal et al. 1985). In a 14-day gavage study in male Sprague–Dawley rats, historical changes in the testes were observed in animals administered 480 mg BBP/kg bw/day. Testicular atrophy, a decrease in body weight, liver enlargement and ultrastructural changes with increased peroxisome numbers in the liver were observed at 1600 mg/kg bw/day, the highest dose tested (Lake et al. 1978). In another two-week gavage study in which Wistar rats were given similar doses of BBP (0, 480 or 1600 mg/kg bw/day), no effects were reported at 480 mg/kg bw/day, and decreased body weight and testicular atrophy were observed at the highest dose tested. Microscopic changes in the liver were not determined (Hammond et al. 1987).

In a four-week range finding study, Sprague–Dawley rats of each sex were exposed to 0, 500, 1000, 1500, 2000, 3000 and 4000 mg/kg bw/day of BBP in feed. A NOAEL of 1000 mg/kg bw/day and a LOAEL of 1500 mg/kg bw/day were identified based on dose-related decrease in body weight gain in both sexes (more pronounced in males), increased mortality in males and a dose-related increase in histopathological changes in the testes. Stiffness while walking was noted in exposed animals from 2000 mg/kg bw/day, as was bleeding around the nares in animals exposed to the highest dose. Rats exposed to the highest dose that died during the study exhibited testicular atrophy,

dehydration and blue discoloration and/or inflammation of the extremities and had gross and microscopic evidence of widespread haemorrhaging in body tissues (Hammond et al. 1987). When young male Cpb:WU rats were exposed for the same duration (28 days) via gavage at doses up to 2100 mg/kg bw/day, the NOEL and the LOEL for systemic toxicity were 580 and 750 mg/kg bw/day, respectively, based on statistically significantly increased relative liver weight and liver palmitoyl CoA (PCoA), an index of peroxisome proliferation, at 750 mg/kg bw/day and above. A dose-dependent increase trend in relative kidney weight and a trend toward a decrease in thymus and thyroid weight were reported from 750 mg/kg bw/day, but none of these changes were statistically significant. A statistically significant decrease in testosterone levels was reported from 450 mg/kg bw/day, severe atrophy of the testes was noted from 970 mg/kg bw/day and a significant decrease in relative testes weight and a significant increase in FSH were reported from 1250 mg/kg bw/day (Piersma et al. 1999).

In a six-week range finding investigation studying the neurotoxicity of BBP after oral administration in feed, there were no adverse histopathological effects on the nervous system of rats exposed to up to 3000 mg/kg bw/day, although reversible clinical signs were observed (Robinson 1991).

In a subchronic diet study, Wistar rats of each sex were exposed to 0, 151, 381 and 960 mg BBP/kg-bw/d in feed for three months. A reduction in body weight gain was reported in low-, mid- and high-dose groups. However, only the reduction at the highest dose was considered compound-related since food consumption was decreased in the low- and mid-dose groups but not in the highest-dose group. Slight anaemia at the highest dose and decreased urinary pH at mid and high doses were reported in males. A significant increase in relative liver weights was observed at all dose levels in females (small increases at the low and mid doses) and at the highest dose in males. A significant increase in relative kidney weight was noted in both sexes at the mid and high doses. While the relative cecum weight was unchanged in males, a dose-related increase was observed at all dose levels in females.

Gross pathological lesions were limited to increased incidence of red spots on the liver at 381 mg/kg bw/day and higher in males. Histopathological changes were reported in the pancreas of males exposed at mid and high doses, and included islet enlargement with cell vacualoation and peri-islet congestion. Small areas of cellular necrosis were also observed in the liver of males exposed at the highest dose. No histopathological changes were reported in females. In this study, a NOAEL of 151 mg/kg bw/day and a LOAEL of 381 mg/kg bw/day was identified for males based on histopathological changes in the pancreas, gross pathological alterations in the liver and a significant increase in relative kidney weight. For females, a LOEL of 151 mg/kg bw/day was identified based on marginal increases in relative liver and cecum weights in the absence of gross and histopathological changes (Hammond et al. 1987).

In another three-month study reported in Hammond et al. 1987, Sprague–Dawley rats of both sexes were administered 0, 188, 375, 750, 1125 and 1500 mg BBP/kg-bw/d for three months. A NOEL of 375 mg/kg bw/day and a LOEL of 750 mg/kg bw/day were

identified based on a significant increase in relative liver and kidney weights in females. In males, no increase in kidney weight was noted but a significant increase in relative liver weight was reported at 1125 mg/kg bw/day. No compound-related lesions were observed in this strain of rats upon histopathological examination in the organ tissues (liver, testes, and pancreas) (Hammond et al. 1987).

In a subchronic study in dogs (three per sex per group) given BBP through diet for three months, no adverse effects were reported at doses up to 50 000 ppm (equivalent to 1850 mg/kg bw/day in males and 1973 mg/kg bw/day in females). The only effect reported was a decrease in body weight gain in the highest-dose group in males and in the two highest-dose groups in females, but these decreases were associated with a decrease in food consumption (Hammond et al. 1987).

When mice were exposed for 90 days to 0, 240, 464, 946, 1875 and 3750 mg BBP/kg-bw/d through diet, no adverse effects were observed again at any BBP doses studied. While a decrease in body weight gain was observed at all doses tested in male mice and at 1875 mg/kg bw/day and higher in females, food consumption was not reported. Due to this, the author identified a LOEL for male mice at 240 mg/kg bw/day and a LOEL for female mice at 1875 mg/kg bw/day (NOEL at 946 mg/kg bw/day) based on decreased body weight gain (NTP 1982b).

In a NTP study in which F344 male rats were exposed for 26 weeks to 0, 300, 900, 2800, 8300 and 25 000 ppm DIDP (approximately 0, 30, 60, 180, 550 and 1650 mg/kg bw/day) through diet, a NOAEL of 180 mg/kg bw/day and a LOAEL of 550 mg/kg bw/day were identified based on increase in the mean cell hemoglobin found on days 60–180, which may be associated with macrocytic anemia found at the next dosing level (1650 mg/kg bw/day) on days 30–180, and an increase in relative liver and kidney weights. At the highest dose, a decrease in total body weight was observed, presumably due to a reduction in food consumption. This reduction in actual food consumption made it difficult for the dose to be calculated; the 1650 mg/kg bw/day dose is estimated from the intake levels of the lower doses. Since the dose is based on the amount of food intake, the results seen may be due to a lower dose than what was calculated. Testicular effects (hypospermia, atrophy) were also reported at that dose level (NTP 1997b).

In a short-term inhalation study in which Sprague–Dawley rats were exposed to 0, 360, 1000 and 2100 mg/m^3 BBP given through aerosol/vapour for six hours per day, five days per week for four weeks, toxicological effects such as a statistically significant decrease in body weight gain (33% for males and 13% for females), death (3/20 males and 4/20 females) and atrophy of the spleen and reproductive organs (in males only) were observed in animals in the highest-dose groups. The NOAEC was 1000 mg/m^3 and the LOAEC was 2100 mg/m^3 based on decreased body weight gain and atrophy of the spleen and testes (Monsanto 1981). In another similar four-week study, BBP (0, 49, 144 and 526 mg/m^3) was also given as an aerosol/vapour to Sprague–Dawley rats for six hours per day, five days per week. A reduction in body weight gain was noted in both sexes exposed at the highest dose. No changes in clinical parameters, organ

weights or microscopic abnormalities were observed. In this study, the NOAEC was 144 mg/m^3 and the LOAEC was 526 mg/m^3 based on decreased body weight gain (Hammond et al. 1987).

In a subchronic inhalation study, a group of 25 male and female Sprague–Dawley rats was exposed to concentrations of 0, 51, 218 or 789 mg/m^3, six hours per day, five days per week for 13 weeks. Significant increases in absolute and/or relative liver and kidney weights were observed in both sexes. In males, a marked decrease in serum glucose was observed at 789 mg/m^3. No such increase was noted in females. No compound-related macroscopic or microscopic lesions were detected in any tissues. The NOEC was 218 mg/m^3 and the LOEC was 789 mg/m^3 based on an increase in liver and kidney weights (both sexes) and an increase in serum glucose in males (Monsanto 1982; Hammond et al. 1987).

Finally, in a dermal study, only local irritation was reported after repeated skin applications of BBP at doses of 1, 5, 10 and 100 mg/kg-bw for five months. However, this study was poorly reported and no information regarding the species used was provided (Statstek 1974).

Table 9-29. Short-term and subchronic studies in rodents exposed to BBP

Strain and species; duration; route; dose [mg/kg bw/day] reference	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Result
Male F344 rats; Short-term, 14 days, Diet 0, 0.625, 1.25, 2.5, or 5.0%; est. 0, 313, 625, 1250 or 2500 Agarwal et al. 1985	313	-	Significant increase in relative liver and kidney weights, accompanied by histological changes in the liver at the highest dose and increased LH levels.
Male Sprague–Dawley rats; Short-term, 14 days, Gavage 0, 160, 480, 1600 Lake et al. 1978	480 (repro) 1600 (systemic)	160 (repro) 480 (systemic)	Historical changes in the testes at 480 mg/kg bw/day. Testicular atrophy, a significant decrease in body weight, liver enlargement and ultrastructural changes with increased peroxisome numbers in the liver were observed at the highest dose tested.
Wistar rats; Short -term, 2 weeks, Diet 0, 480 or 1600 Hammond et al. 1987	1600	480	A significantly decreased body weight and testicular atrophy were observed at the highest dose tested.

Sprague–Dawley rats; Short-term, 4 weeks, Diet 0, 500, 1000, 1500, 2000, 3000, 4000 Hammond et al. 1987	1500	1000	A dose-related decrease in body weight gain in both sexes (more pronounced in males), increased mortality in males (2/5, 8/10, 7/10 and 9/10 at 1500, 2000, 3000 and 4000 mg/kg bw/day, respectively) and a dose-related increase in histopathologic changes in the testes.
Cpb:WU rats; Short-term, 28 days, gavage 0, 270, 350, 450, 580, 750, 970, 1,250, 1,600, 2,100; Piersma 2000	450 (repro) 750 (LOEL; systemic)	350 (repro) 580 (NOEL; systemic)	A significant decrease in testosterone levels from 450 mg/kg bw/day and testicular atrophy from 970 mg/kg bw/day. Relative liver weight was statistically significantly increased at 750 mg/kg bw/day and above. Liver palmitoyl CoA (PCoA), an index of peroxisome proliferation, showed a similar response.
CD rats; Short-term, 6 weeks, Diet 0, 500, 15000, 3000 Robinson 1991	-	3000	No mortality was reported and no histopathological changes were detected in the central nervous system. A transient stiffness when walking was observed at 3000 mg/kg bw/day.
Sprague–Dawley rats; Subchronic, 3 months, Diet 0, 188, 375, 750, 1125, 1500 Hammond et al. 1987	M: 1125 (LOEL) F: 750 (LOEL)	M: 750 (NOEL) F: 375 (NOEL)	M: Significant increase in relative liver weight. F: Significant increase in relative liver and kidney weights.
Wistar rats; Subchronic, 3 months, Diet 0, 151, 381, 960 Hammond et al. 1987	M: 381 F: 151 (LOEL)	M: 151 F: -	M: Significant increases in relative kidney weight, histopathological changes in the pancreas and gross pathological alterations in the liver. F: Marginal increases in relative liver and cecum weights. No histopathological or gross pathological changes were reported.
Male F344 rats; Subchronic, ad lib for 26 weeks, Diet 0, 300, 900, 2800, 8300,	550	180	A significant increase in the mean cell hemoglobin found on days 60–180, likely associated with macrocytic anemia found at

25 000 ppm; est. 0, 30, 60, 180, 550, 1650 NTP 1997b			1650 mg/kg bw/day on days 30–180, and an increase in relative liver and kidney weights.
Beagle dogs; Subchronic, 3 months, Diet 0, 10000-50000 ppm; est. 0, 400, 1000, 1850 (males); 0, 700, 1270, 1973 (females) Hammond et al. 1987	M: - F: -	M: 1850 F: 1973	No adverse effects.
B6C3F1 mice; Subchronic, 90 days, Diet 0, 240, 464, 946, 1875 and 3750 NTP 1982b	M: 240 (LOEL) F: 1875 (LOEL)	M: - F: 946 (NOEL)	No adverse effects. Decrease in body weight gain. Food consumption was not reported.
Subchronic, 5 months, Dermal; 1, 5, 10 and 100 mg/kg-bw Statsek 1974	100 (LOEL)	10 (NOEL)	Local irritation. No mortality.
Sprague–Dawley rats; Short-term, 4 weeks, Inhalation 0, 360, 1000, 2100 mg/m^3 Monsanto 1981	2100 (LOAEC)	1000 (NOAEC)	Significant decrease in body weight gain in both sexes and atrophy of the spleen and of the reproductive organs in males.
Sprague–Dawley rats; Short-term, 4 weeks, Inhalation 0, 349, 144, 526 mg/m^3 Hammond et al. 1987	526 (LOAEC)	144 (NOAEC)	Significant decrease in body weight gain in both sexes.
Sprague–Dawley rats; Subchronic, 13 weeks, Inhalation 0, 51, 218, 789 mg/m^3 Monsanto 1982, Hammond et al. 1987	789 (LOEC)	218 (NOEC)	Significant increase in absolute and relative liver and kidney weights in both sexes and marked decrease in serum glucose in males only.

Overall, the lowest LOAEL for short-term oral exposure was 167 mg/kg bw/day based on a dose-dependent decrease in body weight gain and a decrease in food consumption in dams in a developmental toxicity study in rats exposed to MBzP (Ema et al. 2003). For DIBP, the lowest LOAEL for short-term oral exposure was at 900 mg/kg bw/day based on decreased body weight gain in dams in a developmental toxicity study in rats (Howdeshell et al. 2008). For BBP, the lowest LOAEL for short-term oral exposure was 313 mg/kg bw/day based on an increase in relative liver and kidney weights, accompanied by histological changes in the liver and increased LH levels in male rats (Agarwal et al. 1985).

The lowest LOAEL for subchronic oral exposure for DIBP was 4861–5960 mg/kg bw/day based on a decrease in body weight gain in male and female rats in a 16-week study (Hodge 1954). For BBP, the lowest oral LOAEL was 381 mg/kg bw/day (NOAEL of 151 mg/kg bw/day) based on histopathological changes in the pancreas, gross pathological alterations in the liver and a significant increase in relative kidney weight in male Wistar rats exposed for three months (Hammond et al. 1987). However, it is important to note that those histopathological effects were not observed in other strains of rats exposed orally to BBP for a similar or longer-term duration (Sprague–Dawley and F344, respectively). Also, no adverse effects were observed in mice and dogs exposed to high doses of BBP for three months.

Three inhalation studies were available for BBP. Among these studies, the lowest LOAEC for short-term exposure was 526 mg/m^3 (NOAEC was 144 mg/m^3) based on decreased body weight gain in rats (Hammond et al. 1987). In a subchronic inhalation study, the NOEC was 218 mg/m^3 and the LOEC was 789 mg/m^3 based on an increase in liver and kidney weights (both sexes) and an increase in serum glucose in male rats (Monsanto 1982; Hammond et al. 1987).

Finally, in a dermal study identified for BBP, a LOEL of 100 mg/kg bw/day was identified based on local irritation. However, this study was poorly reported (Statstek 1974).

9.2.8.5.2 Carcinogenicity

B84P has not been classified for its potential carcinogenicity by other international agencies.

No chronic toxicity/carcinogenicity studies were available for this phthalate or for its closest analogues MBzP or DIBP.

Chronic toxicity and carcinogenicity data have been identified in the literature for another analogue of B84P, BBP. The available data for BBP have been reviewed previously in a Priority Substances List (PSL) Assessment Report published by Environment Canada and Health Canada in 2000. Complete information from this report is available in Appendix I: Supporting information on the chronic toxicity and carcinogenicity of butylbenzylphthalate (BBP).

No new chronic studies on the carcinogenicity of BBP have been published since the PSL Assessment Report. This review has shown that no liver tumours were found to be associated with BBP oral exposure. An increase in mononuclear cell leukemias observed in female rats in a 1982 study was not confirmed in a 1997 repeat study (NTP 1982, 1997a). BBP induced an increase in pancreatic tumours (pancreatic acinar cell adenoma and combined adenoma and carcinoma) primarily in male rats, the full expression of which was prevented in a dietary restriction protocol (NTP 1997a). Also, a marginal increase in bladder tumours was observed in female rats, which was delayed upon dietary restriction (NTP 1997a). There was no evidence of carcinogenicity in mice (NTP 1982). Since the weight of evidence of genotoxicity was negative, it was suggested that BBP can be considered, at most, possibly carcinogenic to humans, likely inducing tumours through a non-genotoxic (albeit unknown) mechanism (Environment Canada and Health Canada, 2000). Non-cancer effects were observed in exposed rats (both sexes) but not in exposed mice. The lowest non-neoplastic LOAEL was 300 mg/kg bw/day based on a significant increase in incidence of nephropathy noted in all groups of exposed females (NTP 1997a; Environment Canada and Health Canada 2000).

Since the publication of the PSL Assessment Report (Environment Canada and Health Canada 2000), data on the carcinogenicity of BBP have also been reviewed by the International Agency for Research on Cancer (IARC 1999), the European Chemicals Bureau (ECB 2007), and the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency (EPA). IARC has classified BBP as Group 3 “Not classifiable as to its carcinogenicity to humans” based on inadequate evidence of the carcinogenicity of BBP in humans and limited evidence in experimental animals (IARC 1999). ECB published a risk assessment report on BBP (ECB 2007) and concluded that BBP is not mutagenic. ECB suggested that BBP may be a borderline case between being not classifiable with respect to its carcinogenicity and being classified as a Category 3 carcinogen. In the end, no classification was proposed by ECB (ECB 2007). More recently, the OEHHA of the California EPA developed a document on evidence of the carcinogenicity of BBP. Members of the Carcinogen Identification Committee (CIC) concluded that BBP has not been clearly shown to cause cancer and should not be listed under Proposition 65 as a carcinogen (OEHHA 2013a).

Information on the mode of action and human relevance of the different types of tumours observed in BBP-treated animals is available in Health Canada (2015c).

9.2.8.5.3 Genotoxicity

B84P was not mutagenic in an OECD Guideline 471 study at doses < 10 µg/plate (0.01, 0.04, 0.2, 1.0, 3.0 and 10.0 µl/plate) in *Salmonella* strains TA98, TA100, TA1535, TA1537 and TA1538, with or without metabolic activation. No microbial toxicity was observed in any of the five strains at 10 µg/plate (with or without metabolic activation), although levels of 3 µg/plate and higher exceeded the solubility of the test material (Monsanto Research Corporation 1982 cited in US EPA 2006, 2010).

9.2.8.5.4 Evidence of systemic toxicity in humans

No information is currently available on the potential effects of B84P in humans.

9.2.9 DIHepP

9.2.9.1 Reproductive and developmental effects in males

9.2.9.1.1 Early development: *in utero* exposure

A literature search identified three oral studies examining the effect of DIHepP when administered during gestation in pregnant rats and the potential toxicity of DIHepP during gestation in rats, all focusing on male reproductive effects during the foetal masculinization programming window (GD15–17). Summaries of the studies are described in Table 9-30 below. No other developmental studies were identified examining gestational exposure to DIHepP via other routes of exposure or using other species.

In a 2-generation reproductive toxicity study, DIHepP appears to cause a multitude of effects in the male foetus related to RPS. A critical study by McKee et al. (2006) administered 0, 1000, 4500 or 8000 ppm of DIHepP in diet to Sprague–Dawley rats 70 days prior to mating, through the mating period, and during gestation and lactation (or until the termination period for males) (approximately 64–168, 304–750 and 532–1360 mg/kg bw/day for F0 and F1). Developmental effects in the F1 generation, observed primarily at 532–1289 mg/kg bw/day, included a significant reduction in AGD, a significant increase in incidence of NR and testicular abnormalities (HYP and CRY), a significant reduction in weights of testes and male accessory reproductive organs, a significant decrease in testicular sperm counts and daily sperm production, significant delays in PPS and a significant decrease in fertility. Reduction in AGD was also observed in the F2 generation at 309–750 mg/kg bw/day. Additional effects observed in the study included reductions in body weights, along with increased liver and kidney weights (mid dose and above) in both generations and increased pituitary weights in F1 males at the highest dose. The NOAEL for parental systemic toxicity in the F0 and F1 generations was 50–168 mg/kg bw/day (male and female dose level ranges) based on liver and kidney effects (see Section 9.2.9.5). The LOAEL for reproductive/developmental toxicity was 309–750 mg/kg bw/day, based on a significant reduction in AGD in male F2 pups exposed at the mid dose and above (Wil Research Laboratories Inc., 2003; McKee et al. 2006).

An oral developmental toxicity study was also performed by McKee et al. (2006), where pregnant rats were administered DIHepP by gavage at doses of 0, 100, 300 or 750 mg/kg bw/day during GD6–20. Offspring were examined on GD21. A significant decrease in maternal body weight gain resulting from a lower mean body weight was noted at the highest dose (750 mg/kg bw/day) and was primarily due to uterine content. There were also statistically significant dose-related increases in mean absolute and relative maternal liver weights in the 300 and 750 mg/kg bw/day dams compared with controls. Developmental effects included a significant reduction in the number of viable

foetuses/dam and significant increases in post-implantation loss and resorptions/dam, a reduction in mean foetal weights and a significant increase in external, visceral and skeletal malformations and variations in foetuses at 750 mg/kg bw/day. The principal external malformations in the high-dose group included stunting and anophthalmia; the visceral observations included ectopic testes, ectopic ovaries, and elongated and malformations of the subclavian and innominate arteries. The skeletal variations and malformations included both rib and vertebral anomalies. The NOAEL for maternal toxicity in this study was 750 mg/kg bw/day. While a significant increase in relative and absolute liver weight was observed in dams treated at the mid and high doses in comparison with controls, the increase, consistent with the occurrence of peroxisomal proliferation, is not considered an adverse effect (LOEL = 300 mg/kg bw/day) (McKee et al. 2006). In this study, the developmental NOAEL was established at 300 mg/kg bw/day, with a LOAEL of 750 mg/kg bw/day based on increased resorptions, viability and malformations.

A more recent study presenting the potential for DIHepP and other phthalates to perturb foetal testosterone production (*ex vivo*) in pregnant SD rats showed that this phthalate disturbed testicular testosterone production during gestation at 750 mg/kg bw/day (only dose tested) with a calculated ED_{50} value of 361.6 mg/kg bw/day (Furr et al. 2014). Further details were not provided.

Table 9-30. Effects from gestational exposure to DIHepP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[b]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
Crl:CD (SD) IGS BR rats; 0, 1000, 4500, 8000 ppm; est. F1 female intake during gestation; 0, 64–168, 309–750, 543–1360; diet; 70 days prior to mating – PND21 (McKee et al. 2006)	NM	**309–750** (AGD) NM (NR) NM (PPS)	NM	**309–750** (BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	LOEL = 309–750 (↑ kidney and liver wt)
Crl:CD (SD) IGS BR rats; 0, 1000, 4500, 8000 ppm; est. F0 female	NM	532–1289 (AGD) 532–1289 (NR)	532–1289 (CRY) 532–1289 (HYP)	NE (BW) 532–1289 (ROW) NE (FV)	LOEL = 304–716 (↑ kidney

intake during gestation; 0, 64–162, 304–716, 532–1289; diet; 70 days prior to mating – PND21 (McKee et al. 2006)		532–1289 (PPS)	NM (TP) 532–1289 (FER)	NM (EMB) NM (ESV)	and liver wt)
SD rats; 0, 100, 300, 600, 900; gavage; GD14–18 (Hannas et al. 2011)	**300,** EC_{50}= 443 (T- *ex vivo*) NM (S)	NM	NM	NM	NE
CR SD rats; 0,750; GD14–18; (Furr et al. 2014)	750 (T) ED_{50} = 361.6 [*ex vivo*] NM (S)	NM	NM	NM (BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	NE
Crl:CD BR VAF/Plus rats; 0, 100, 300, 750; gavage; GD6–20 (McKee et al. 2006)	NM	NM	750 (CRY-ectopic testes) NM (HYP) NM (TP) NM (FER)	750 (BW) NM (ROW) 750 (FV) 750 (EMB) 750 (ESV)	LOEL = 300 (↑liver wt)

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone
[b] Feminization parameters can include anogenital distance (AGD), nipple retention (NR) and preputial separation (PPS).
[c] Malformations can include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration
[d] Other developmental effects include decreases in overall foetal body weight at PND1 (BW), decreases in reproductive organ weight (ROW), embryo/foetal viability (FV) and embryotoxicity (EMB), or effects on the incidence of external, skeletal or visceral malformations (ESV).
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.
NDR = no dose relationship
[f] Lowest dose measured in the study.

Overall, the highest oral NOAEL for developmental toxicity of DIHepP at the *in utero* life stage was 64–168 mg/kg bw/day based on effects on the developing male reproductive system, as seen by decreased AGD at the next highest dose (309–750 mg/kg bw/day; McKee et al. 2006). The same effect level from this study was set by NICNAS (2008). No marked maternal toxicity that would affect the reproductive development of offspring

was reported, as effects included increases in liver and kidney weight occurring at 304–750 mg/kg bw/day (LOAEL; McKee et al. 2006).

9.2.9.1.2 Exposure at prepubertal/pubertal life stages

No reproductive toxicity studies with exposure to DIHepP for this life stage have been found in the literature. Therefore, results from the 2-generation study described in Section 9.2.9.1.1 above were used, particularly those from the F1 males that were exposed *in utero*, through lactation to DIHepP and until PND54.

In the 2-generation study, significant decreases (with or without analysis relative to the cube root of pup body weight; only measured in high-dose group) in AGD, an increase in retained thoracic nipples, external genitalia disorder such as hypospadias (7/30), lacking testes (2/30) and undescended testes (2/30) were observed in F1 males at 8000 ppm (419–764 mg/kg bw/day). Increased balanopreputial separation was also statistically delayed compared to the control (46.1 vs. 50.3 days) in the high-dose group. Observation of the F1 generation at the adult stage also showed effects on reproductive organs (severe degeneration of seminiferous tubules) and decreased fertility at high doses (McKee et al. 2006).

Overall, the NOAEL for reproductive toxicity identified for DIHepP for this life stage was 227–416 mg/kg bw/day. However, it is difficult to determine whether the effects observed were due to *in utero* exposure of DIHepP or during postnatal and lactation exposure of F1 males. The same effect level from this study was set by NICNAS (2008).

9.2.9.1.3 Oral exposure at the mature adult stage

No reproductive toxicity studies with exposure to DIHepP for this life stage were identified in the literature. Effects from exposure of adult F0 males to DIHepP are reported in this section.

Reproductive effects in this 2-generation study, described above, showed that there were no significant differences in body weights in either males or females during the study (McKee et al. 2006). There were no significant differences in mating success or in gestational period length. Weights of the reproductive organs were not significantly different from the concurrent control values in the F0 generation and there were no histological changes suggestive of treatment-related effects in any of these organs. There were no differences in sperm parameters among the males. No effect on reproduction was noted in F0 males. A NOAEL of 404–623mg/kg bw/day was therefore established for this life stage.

9.2.9.2 Oral exposure in females

Three studies on the reproductive and developmental effects of DIHepP in females were identified. They include a reproductive (2-generation) and developmental toxicity study in rats administered DIHepP through continuous breeding or during gestation (GD6–20), respectively (McKee et al. 2006).

The lowest LOAEL identified for developmental toxicity in females, obtained from the 2-generation study described in previous sections, was 404–1289 mg/kg bw/day for F1 offspring and 404–1360 mg/kg bw/day for F2 offspring (8000 ppm in diet) based on reduced body weight on PND4–21 in F1 and PND14–21 in F2 offspring (McKee et al., 2006). A significant reduction in the female mating and fertility index, and a statistically significant reduction of ovarian weight at 404–1360 mg/kg bw/day (8000 ppm) were also observed in F1 parents (NOAEL of 222–750 mg/kg bw/day). No reproductive adverse effects were observed in F0 parents.

Overall, the few available studies available indicate that DIHepP induced reproductive (alterations of reproductive performance and pregnancy outcomes) and developmental (alterations of growth, functional deficit, lethality and teratogenicity) adverse effects at high doses (404–1360 mg/kg bw/day and above). Alterations of reproductive performance were observed in F1 parents only (after *in utero* and subsequent exposures).

9.2.9.3 Endocrine studies

DIHepP was inactive in *in vitro* screening tests for competitive binding and gene expression using the estrogen receptor. The test concentrations used were up to 2000 mg/kg. McKee et al. (2004) reported that the monoester corresponding to DIHepP (MHepP) was inactive in *in vitro* assays to assess androgen receptor activity.

DIHepP did not exhibit any estrogenic activity when tested in most *in vitro* and *in vivo* assays, with only an isomeric mixture demonstrating weak estrogenic activities in a human oestrogen receptor (ER) α (but not β) reporter gene assay (Zacharewski et al. 1998; McKee et al. 2004; Nishihara et al. 2000; Takeuchi et al. 2005; and Toda et al. 2004).

9.2.9.4 Reproductive and developmental toxicity: evidence in humans

No information is currently available on the potential reproductive/developmental effects of DIHepP in humans.

9.2.9.5 Other systemic effects[30]

9.2.9.5.1 Repeated-dose studies

Although no long-term studies have been identified, the toxicity of DIHepP has been investigated in a shorter term study in which male rats and mice were exposed to DIHepP through diet (0, 50 or 600 mg/kg bw/day in rats; 0, 65 or 780 mg/kg bw/day in mice) for two or four weeks (Smith et al. 2000). However, only the livers were examined.

[30] This section presents studies examining effects other than reproductive effects.

In both species, effects indicative of peroxisome proliferation were observed. In rats, elevated relative liver weight and increased periportal DNA synthesis in liver were observed after two or four weeks of treatment at 50 mg/kg bw/day and higher. In mice, increased periportal DNA synthesis in liver was observed after two weeks of treatment at 65 mg/kg bw/day and higher. In both rats and mice, increased peroxisomal beta-oxidation (PBOX) in liver was also observed at two and four weeks at the highest dose. The LOEL for repeated-dose oral exposure was 50 mg/kg bw/day, based on elevated relative liver weight and increased periportal DNA synthesis in the liver of male rats.

Results of the 2-generation reproductive toxicity study described above can also be used to evaluate this endpoint (McKee et al. 2006; Section 9.2.9.1.1). No treatment-related changes were observed in body weights, clinical observations or food consumption. Dose-related increases in liver and kidney weights were seen in both sexes of parental F0 rats treated with doses of 222–716 mg/kg bw/day. Histopathological findings observed at mid and high doses in the liver, kidney and pituitary gland included centrilobular hepatocellular hypertrophy and vacuolation, dilated renal pelvis/hydronephrosis and hypertrophy of the pars distalis of the pituitary gland. The NOAEL for systemic toxicity in F0 animals was determined to be approximately 50–168 mg/kg bw/day, with a LOAEL of 222–716 mg/kg bw/day based on liver and kidney effects (McKee et al. 2006).

9.2.9.5.2 Carcinogenicity

DIHepP has not been classified for its potential carcinogenicity by other international agencies, and no chronic toxicity/carcinogenicity studies were identified for this phthalate. In the multigenerational study described above, when SD rats (30/sex/group) were given DIHepP at up to 8000 ppm in diet (419–764 mg/kg bw/day for males and 833–1360 mg/kg bw/day for females), the systemic effects reported in F1 adults (exposed for a significant period of their lifetime) were increases in liver and kidney weights associated with centrilobular hypertrophy in males and females in mid-dose animals (227–750 mg/kg bw/day; McKee et al. 2006). Hepatocellular vacuolation was also noted in male at high doses. Based on this, the carcinogenic potential of DIHepP is likely limited. However, in a repeated-dose where rats and mice were exposed to DIHepP for two or four weeks (Smith et al. 2000; described above), effects indicative of peroxisome proliferation were observed, which could potentially result in the increased incidence of hepatocellular tumours. However, this has been mostly observed at high doses.

9.2.9.5.3 Genotoxicity

In *in vitro* assays, DIHepP was not mutagenic in a bacterial mutation assay using *Salmonella typhimurium*, with and without activation (Exxon Biomedical Sciences, Inc. 1995). Similarly, a negative response was observed in an assay for chromosomal aberration in Chinese hamster ovary cells in the presence and absence of metabolic activation (Hazleton Laboratories America, Inc. 1991). *In vivo* genotoxicity studies for DIHepP have not been identified in the literature.

9.2.9.5.4 Evidence of systemic toxicity in humans

No information is currently available on the potential effects of DIHepP in humans.

9.2.10 BIOP

No studies examining the potential reproductive/developmental health effects of BIOP were identified for any species or gender. DIOP (1,2-Benzenedicarboxylic acid, diisooctyl esters, C7-rich: CAS RN 27554-26-3) and MBz (1,2-Benzenedicarboxylic acid, mono[phenylmethyl] ester: CAS RN 2528-16-7) were identified as the "closest analogue" phthalates to BIOP within the subcategory based on consideration of similarities in monoester metabolism as well as the length and nature of the ester chains (Section 2.3.2; Health Canada 2015a).

Based on health effects information on the analogues MBzP and DIOP, a potential health effect of concern may be associated with BIOP. A review of the potential developmental and reproductive toxicity of the analogue(s) showed that this medium-chain phthalate could have adverse effects on the reproductive system of the developing male, in addition to systemic effects (liver, kidney).

Given the absence of reporting to the section 71 industry survey and the absence of information as to BIOP presence in product databases, general population exposure to BIOP from environmental media and products used by consumers is expected to be negligible. Therefore, risk to human health for this substance is not expected.

9.2.11 B79P

9.2.11.1 Reproductive and developmental effects in males

9.2.11.1.1 Early development: *in utero* exposure

Only one oral rat study was found focusing on the effects of B79P during development. This study examined the effects of B79P when administered during gestation in pregnant rats during the foetal masculinization programming window (GD15–17). Summaries of the studies are described in Table 9-31 below.

In the extended 1-generation reproductive and developmental toxicity study, parental female SD rats were administered 0, 750, 3750 or 7500 ppm of B79P in diet from GD6, through lactation to PND21. The dose for maternal rats was estimated to be 0, 50, 250 or 500 mg/kg bw/day based on food consumption. In male pups, a statistically significant reduction in AGD on PND21 was observed at 250 mg/kg bw/day and above. It was noted that a statistically significant reduction in AGD was seen in all treatment groups in both males and females at birth. A dose-related and statistically significant increase in the percentage of male pups with a defect of the penis (epispadias) was observed on PND21 at mid dose and above (0, 1.5, 14 and 21% at 0, 50, 250 or 500 mg/kg bw/day, respectively). Also, the percentage of male pups with one or more retained areolae at PND11–13 was statistically significantly increased at 500 mg/kg

bw/day only (27% compared with 2.8% in the controls). No differences in AGD, epispadias or areolae were observed in F1 males of any of the dose groups assessed at PND75, suggesting transient effects. Treatment-related histopathological lesions of the left testis (dilated seminiferous tubule lumina) were observed in the 500 mg/kg bw/day group at PND75 (no histopathology performed on other groups). A slight increase in the incidence of undescended testes (cryptorchidism, CRY) was also observed at PND21, but not at PND75, in F1 males from all treated groups. During the lactational period only, F1 males and females showed reduced body weight gain in all treatment groups.

Maternal toxicity for the study was noted at 250 mg/kg bw/day and above based on treatment-related reductions in body weight changes seen on GD6–9 only (with no effects on final body weights at PND21) and increased organ weights (liver and kidneys) reported at PND21. Maternal reproductive and lactational parameters (including fertility and gestational indices, and number of live births) indicated no treatment-related effects at any dose level. The NOAEL for F0 maternal systemic toxicity was considered to be 50 mg/kg bw/day based on decrease body weight gain during gestation and liver and kidney effects at 250 mg/kg bw/day. For F1 male developmental toxicity, 250 mg/kg bw/day was considered the LOAEL based on a significant reduction in AGD and increased epispadias, particularly in the mid-dose group and above (REACH dossier; ECHA 2013b).

Since only one study was identified for B79P, MBzP (1,2-Benzenedicarboxylic acid, mono[phenylmethyl] ester: CAS RN 2528-16-7) and DINP (1,2-Benzenedicarboxylic acid, diisononyl ester: CAS RN 68515-48-0) were identified as the “closest analogue” phthalates to B79P within the subcategory based on consideration of similarities in monoester metabolism as well as the length and nature of the ester chains (Section 2.3.2; Health Canada 2015a).

Refer to Section 9.2.2.1.1 of the assessment for DINP (Environment Canada and Health Canada 2015b) for a review of the potential reproductive/developmental effects of DINP, and Section 9.2.7.1 of this assessment for MBzP (CAS RN 2528-16-7; included in health effects of DBzP) for all life stages.

Table 9-31. Effects from gestational exposure to B79P, MBzP and DINP in male offspring (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration (reference) CAS RN	Testosterone levels[a] (T, S)	Feminization parameters[b]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
B79P		50 (at	50 (CRY,	NM (BW)	250 (↑

SD rats: 0, 750, 3750, 7500 ppm; est. 0, 50, 250, 500 (diet) GD6–PND21 Cited in REACH Dossier; ECHA 2013b		PND1 both sexes) (AGD) **250** (at PND21 for males) **500** (NR) NR (PPS)	epispadias) NM (HYP) 500** (TP) NM (FER)	NM (ROW) NE (FV) NE (EMB) NR (ESV)	liver & kidney wts, ↓ body wt)
DINP SD rats; 0, 0.2, 0.4, 0.8%, est. F0 (gestation): 0, 133–153, 271–307, 543–577 (postpartum): 0, 159–395, 347–758, 673–1541 by EURAR (2003); diet; 10 wks to prior to mating – PND21 (Waterman et al. 2000) 68515-48-0	NM	NR (AGD) NM (NR) NR (PPS)	NR (CRY) NR (HYP) NE (TP) NE (FER-mating test)	159–395[e] (10%, BW–PND21) NR (ROW) NE (FV) NM (EMB) NR (ESV)	LOEL= 159–395[e] (↑ kidney wt; liver wt @ 347–750); 673–1541 (↓ BW on PND14, 21)
DINP SD rats; 0, 0.2, 0.4, 0.8%, est. F1 (gestation): 0, 133–153, 271–307, 543–577 (postpartum): 0, 159–395, 347–758, 673–1541 by ECJRC (2003); diet; 10 wks to prior to mating – PND21 (Waterman et al. 2000) 68515-48-0	NM	NR (AGD) NM (NR) NR (PPS)	NR (CRY) NR (HYP) NE (TP) NE (FER-mating test)	347–758 (BW – PND7, 14, 21) NR (ROW) 347–758[NDR] (FV – PND7) NM (EMB) NR (ESV)	LOEL= 673–1541 (↑ liver wt, ↓ BW)
DINP SD rats; 0, 50, 250, 750; gavage; GD12–19	250, NE (T-GD19: 2 hrs	NE (AGD-PND1) NM (NR) NM (PPS)	NM (CRY) NM (HYP) 250 (TP-MNGs) NM (FER)	NE (BW-GD19) NR (ROW) NM (FV) NM (EMB)	LOEL= 250 (↑ liver wt)

(Clewell 2011 in ECHA 2013a) 68515-48-0	after, 24 hrs) NM (S)			NM (ESV)	
DINP SD rats: 0, 760, 3800, 11400 ppm, est. 0, 50, 250, 750; diet; GD12–PND14 (Clewell et al. 2013) 68515-48-0	NE (T-PND49, large variation) NM (S)	NE, 750, NE (AGD-PND2, 14, 49) 750[NS] (NR-increasing trend) 750[NS] (PPS- one animal)	750[NS] (CRY- 2 males at high dose) 750[NS] (HYP- 2 animals at PND49, 1 male from same litter at 56 and 288) 250 (TP-MNGs, LC aggregates) NM (FER)	250[f] (10%, BW) (@ PND14; 750 @ PND2) NE (ROW) NE (FV) NM (EMB) NM (ESV)	LOEL = 750 (↓BW, ↓food consump.) @ 250 (↓food consump. but not BW PND2–14)
DINP Harlan SD rats; 0, 750; GD14–18 (Furr et al. 2014)	750 (T) NM (S)	NM	NM	NM (BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	NE
MBzP Wistar rats; 0, 167, 250, 375; gavage; GD15–17 (Ema et al. 2003)	NM	250 (AGD) NM (NR) NM (PPS)	250 (CRY) NM (HYP) NM (TP) NM (FER)	NM (ROW) 375 (BW) NE (FV) NE (EMB) NM (ESV)	167 (↓food consumption, ↓BW, no embryolethality)

[a] Testosterone levels measured (can include quantity/production) at varying days post-birth. T = testicular testosterone; S = serum testosterone

[b] Feminization parameters can include anogenital distance (AGD), nipple retention (NR) and preputial separation (PPS).

[c] Malformations include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP) and/or reproductive effects, such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after *in utero* exposure. TTM = transabdominal testicular migration

[d] Other developmental effects include decreases in overall fetal body weight at PND1 (BW), decreases in reproductive organ weight (ROW), fetal viability (FV) and embryotoxicity (EMB), or effects on the incidence of external, skeletal or visceral malformations (ESV).

[e] Lowest dose tested in the study.

[f] Clewell et al. (2013a): Reduced pup weight is attributed to reduced palatability of milk and feed of the PND14 pups. The authors concluded that in this study, there was no evidence of the rat phthalate syndrome with DINP at doses up to 11,400 ppm (~750 mg/kg-day).

NR = results not recorded (but measurement was stated in the methods and materials)

NM = not measured

NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns of effects, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.

NDR = no dose relationship

MNG = multinucleated gonocytes

Overall, the highest NOAEL for developmental toxicity of B79P at the *in utero* life stage was 50 mg/kg bw/day based on decreased AGD in males and an increased incidence of

epispadias at mid-dose and above at the next dose tested (250 mg/kg bw/day) (REACH dossier; ECHA 2013b). Evidence of retained nipples was also reported, but at higher doses. The NOAEL for maternal systemic toxicity was considered to be 50 mg/kg bw/day based on decreased body weight gain during gestation and liver and kidney effects at 250 mg/kg bw/day.

For the analogues MBzP and DINP, the lowest oral LOAEL for developmental toxicity of DINP at the *in utero* life stage was 159–395 mg/kg bw/day based on decreased pup weight after birth in two diet studies (Watermann et al. 2000; Clewell et al. 2013). Other effects at that dose included significantly reduced foetal testicular testosterone levels and evidence of testicular pathology (MNGs) (Clewell 2011 in ECHA 2013a; Clewell et al. 2013). For MBzP, the lowest oral LOAEL for developmental toxicity at the *in utero* life stage was also 250 mg/kg bw/day based on an increased incidence of cryptorchidism and decreased AGD in male foetuses (Ema et al. 2003).

Therefore, the critical effect level of 250 mg/kg bw/day will be used to characterize the risk of developmental toxicity of B84P for this life stage.

9.2.11.1.2 Exposure at prepubertal/pubertal life stage

There were no repeated-dose oral exposure studies in sexually immature animals (PND1–55) with B79P via any route of exposure. As with the previous life stage, MBzP and DINP were identified as the most appropriate candidates. Refer to Section 9.2.2.1.2 of the assessment for DINP (Environment Canada and Health Canada 2015b) for a review of the potential reproductive/developmental effects of DINP, and Section 9.2.7.2 of this assessment for MBzP.

Overall, the LOEL for the reproductive toxicity of MBzP and DINP at the prepubertal/pubertal life stage was 250 and 500 mg/kg bw/day based on decreased sperm counts and motility (for DINP only) after four weeks of exposure, respectively (Kwack et al. 2009). Therefore, the LOEL of 250 mg/kg bw/day will be used as the critical effect level for the reproductive toxicity of B79P for this life stage.

9.2.11.1.3 Oral exposure at the mature male adult stage

A search of the public literature identified only one study examining the potential reproductive toxicity of B79P at the adult male life stage. In a three-week feeding study in which male Sprague–Dawley rats were given two different formulations of B79P (one EU and one US) at around 60, 600 and 1200 mg/kg bw/day, minimal testicular degeneration was observed at 1200 mg/kg bw/day in several rats given the different B79P versions (ECHA 2013b). Neither compound affected absolute weights of the epididymis, testis or brain, whereas both test materials produced statistically significant increases in relative liver weight at 600 and 1200 mg/kg bw/day. The test materials produced a statistically significant and dose-related reduction in body weight gain from 600 mg/kg bw/day, particularly during the first week. The LOAEL for this study was 600 mg/kg bw/day based on reduced body weight gain and increases in liver weight and

acyl-CoA oxidase activity. The EU version of the test material had a slightly greater effect, but the difference between the two versions was minimal.

No studies were available where MBzP was administered to adult males starting after PND55. Toxicological studies conducted with DINP were examined to characterize the health effects of B79P. Refer to Section 9.2.2.1.3 of the screening assessment for DINP for a review of the studies available (Environment Canada and Health Canada 2015b).

Table 9-32. Reproductive effects from exposure to B79P and from exposure to DINP in adult males (mg/kg bw/day)

Strain and species; dose (mg/kg bw/day); route; duration **(reference)** **CAS RN**	**Life stage at the start of dosing (age)**	**Hormone levels[a]** **(T, S, LH)**	**Fertility[b]**	**Reproductive tract pathology[c]**	**Other effects[d]**
B79P SD male rats: 0, 60, 600, 1200 (diet) 3 wks Cited in REACH Dossier (ECHA 2013b)	11 wks	NM	NM	1200 (minimal testicular degeneration)	600 (BW) 742 (ROW) 600(ST- ↑ liver wts)
DINP F344 rats; 0, 0.03, 0.3, 0.6%, est. 0, 15, 152, 307; Diet; 2 years (Exxon Biochemical 1986; Hazleton et al. 1986a; Lington et al. 1987; Lington et al. 1977 in ECJRC 2003) 68515-48-0	6 weeks	NM	NM	NR	307 (BW) 307 (ROW) 152 (ST- ↑ kidney & liver wt and pathology)
DINP SD rats; 0, 500, 5000, 10 000 ppm, est. 0, 27, 271, 553; Diet; 2 years (Bio/dynamics 1986 in ECJRC 2003) CAS not defined but reported as 71549-	Not specified	NM	NM	553 (testicular interstitial cell hyperplasia)	NE (BW) NR (ROW) 271 (ST- liver lesions)

Strain and species; dose (mg/kg bw/day); route; duration (reference) CAS RN	Life stage at the start of dosing (age)	Hormone levels[a] (T, S, LH)	Fertility[b]	Reproductive tract pathology[c]	Other effects[d]
78-5 by US CPSC as never produced commercially (Babich, 1998)					

[a] Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S) or luteinizing hormone (LH).
[b] Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success at adult stage after *in utero* exposure.
[c] Reproductive tract pathology includes any observations based on histopathological examination of the testes, such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, increase in Leydig cell size, focal dysgenesis and/or seminiferous tubule atrophy.
[d] Other effects include decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).
[e] Lowest dose tested in the study.
NR = results not recorded (but measurement was stated in the methods and materials)
NM = not measured
NE = no effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured, and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOEL for reproductive toxicity identified for DINP was 276 mg/kg bw/day based on reduced relative and absolute reproductive organ weights at the next dose (LOEL = 742 mg/kg bw/day) (Moore 1998b) in adult male mice. This endpoint was selected in other international assessments (NICNAS 2008; EURAR 2003; ECHA 2013a). In a two-year study, testicular interstitial cell hyperplasia was also observed at the highest dose of 553 mg/kg bw/day (Babich 1998). However, the DINP CAS number was not provided in the study and was reported as 71549-78-5 (Babich, 1998). Therefore, the NOEL of 276 mg/kg bw/day will be used as the critical effect level for the reproductive toxicity of B79P for this life stage.

9.2.11.2 Oral exposure in females

No studies addressing female reproductive and developmental effects of B79P were identified. Data indicate that DINP is a developmental and reproductive toxicant at higher doses (600 mg/kg bw/day and above) in females more so than in males.

9.2.11.3 Reproductive and developmental toxicity: evidence in humans

No information is currently available on the potential reproductive/developmental effects of B79P in humans.

9.2.11.4 Other systemic effects[31]

9.2.11.4.1 Repeated-dose studies

One repeated-dose study has been identified in the literature for B79P.

In a three-week feeding study in which male Sprague–Dawley rats were given two different formulations of B79P (one EU and one US) at around 60, 600 and 1200 mg/kg bw/day, effects observed from 600 mg/kg bw/day included reduced body weight gain and increases in relative liver weight and acyl-CoA oxidase activity (an indication of peroxisome proliferation) (ECHA 2013b). Neither compound affected absolute weights of the epididymis, testis or brain. There were apparently no gross necropsy findings at sacrifice. An initial decrease in food consumption was observed during the first two weeks at the highest dose (and returned to normal thereafter). In conclusion, no statistically significant adverse effects were seen in male rats ingesting 60 mg/kg bw/day (considered the NOAEL for this study) for three weeks. The LOAEL was 600 mg/kg bw/day based on reduced body weight gain and increases in liver weight and acyl-CoA oxidase activity.

Studies conducted with DINP were also examined to characterize the health effects of B79P. Refer to Section 9.2.1.2 for a complete summary of the available repeated-dose studies for DINP (Environment Canada and Health Canada 2015b).

The lowest LOAEL for short-term oral exposure identified for DINP was 200 mg/kg bw/day, based on histopathological changes in the liver and kidney of mice exposed for 14 days (Ma et al. 2014).. No systemic effects were noted in rats exposed to DINP in one dermal study (six-week duration) (Hazleton 1969). The lowest LOAEL for subchronic oral exposure was 60 mg/kg bw/day, based on an increased frequency of kidney lesions in all exposed males in a 13-week study in rats (Hazleton 1981a). In dogs, the NOAEL for subchronic exposure was 37 and 160 mg/kg bw/day based on increases in liver and/or kidney weights, accompanied by histopathological changes in males and females at 160 and 2000 mg/kg bw/day, respectively, in a 13-week study (Hazleton Laboratories 1971b).

The NOAEL of 500 mg/kg bw/day identified from a short-term and a subchronic study in monkeys indicates that monkeys and probably humans are less sensitive than rodents and dogs to liver effects, which is consistent with the hypothesis that species differences in the activation of PPARα or its signaling network by peroxisome proliferation may exist.

9.2.11.4.2 Carcinogenicity

[31] This section presents studies examining effects other than reproductive effects.

B79P has not been classified for its potential carcinogenicity by other international agencies and no chronic toxicity/carcinogenicity studies were available for this phthalate. There was also no study available for the closest analogue MBzP. The OEHHA has recently reviewed evidence of the potential carcinogenicity of the analogue DINP and it has been concluded that DINP has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer and should be listed under Proposition 65 (OEHHA 2013b). Accordingly, DINP has been listed at the end of 2013 (OEHHA 2013c). DINP has not been classified for its potential carcinogenicity by other international agencies.

Refer to Section 9.2.2.1 for a summary of the available studies for the closest analogue DINP (Environment Canada and Health Canada 2015b).

Chronic studies conducted with DINP were examined to characterize the health effects of B79P. The most relevant studies are presented in Table 9-33.

Table 9-33. Carcinogenicity studies in rodents exposed to DINP

Strain and species; dose [mg/kg bw/day]; route; duration (reference)	Result
Fischer 344 rats; 0, 500, 1500, 6000, and 12000 ppm; est. 0, 29, 88, 359, 733 (males); 0, 36, 109, 442, 885 (females); Diet; 2 years Recovery study; 0, 12000 ppm; est. 0, 637.3 (males); 0, 773.6 (females); Diet; 78 weeks, followed by 26 weeks recovery (Moore 1998a) **DINP-1 68515-48-0**	Dose-related increase in incidence of MNCL in both sexes from 6000 ppm (males: 22/65, 23/55, 21/55, 32/65, 30/65; females: 17/65, 16/49, 9/50, 30/65, 29/65 at 0, 29–36, 88–109, 359–442, 733/885 mg/kg bw/day, respectively). Significant increase in hepatocellular carcinoma in males at the highest dose tested (1/65, 0/50, 0/50, 1/65, 12/65 at 0, 29, 88, 359, 733 mg/kg bw/day, respectively) but not in females (1/65, 0/49, 0/50, 1/65, 5/65 at 0, 36, 109, 442, 885 mg/kg bw/day, respectively). Significant increase incidence of carcinoma or adenoma in both sexes at the highest dose (males: 5/65, 3/50, 2/50, 7/65, 18/65; females: 1/65, 1/49, 0/50, 2/65, 8/65 at 0, 29–36, 88–109, 359–442, 733–885 mg/kg bw/day, respectively). LOAEL (non-neoplastic): 358–442 mg/kg bw/day (increase in absolute and relative liver and kidney weights, increase in serum ALT and AST, and histopathological findings in both organs) (males/females) Recovery study: Significant increase in MNCL in both sexes and significant increase in renal tubular

	carcinomas in exposed males (0/65, 4/50 at 0, 637 mg/kg bw/day, respectively).
Fischer 344 rats; 0, 0.03, 0.3, 0.6%; est. 0, 15, 152, 307 (males); 0, 18, 184, 375 (females); Diet; 2 years (Lington et al. 1997) **DINP-1 68515-48-0**	Increase in incidence of MNCL at the two highest doses tested in both sexes (males: 33/81, 28/80, 48/80, 51/80; females: 22/81, 20/81, 30/80, 43/80 at 0, 15–18, 152–184, 307–375 mg/kg bw/day, respectively). LOAEL (non-neoplastic): 152–184 mg/kg bw/day (increase in absolute and relative liver and kidney weights, and increase in histopathological changes in both organs at the two highest doses) (males/females)
Sprague–Dawley rats; 0, 500, 5000, 10,000 ppm; est. 0, 27, 271, 553 (males); 0, 33, 331, 672 (females); Diet; 2 years (Bio/dynamics 1986) **DINP-A 71549-78-5**	Increase in incidence of hepatocellular carcinoma in females treated with the two highest doses (males: 2/70, 5/69, 6/69, 4/70; females: 0/70, 0/70, 5/70, 7/70 at 0, 27–33, 271–331, 553–672 mg/kg bw/day, respectively). Increased incidence of neoplastic liver nodules at all doses (not significant) (males: 2/70, 5/69, 6/69, 5/70; females: 1/70, 1/70, 5/70, 2/70 at 0, 27–33, 271–331, 553–672 mg/kg bw/day, respectively). Significant increase in testicular interstitial cell hyperplasia in males at the highest dose. Non-significant increase in the incidence of testicular interstitial cell carcinoma (increase was outside the range of historical control) (2/59, 7/60 at 0, 553 mg/kg bw/day, respectively). Slight increase in pancreatic islet cell carcinoma (1/70, 4/70 at 0, 553 mg/kg bw/day, respectively) and parathyroid gland hyperplasia in males treated with the highest dose. Slight increase in endometrial hyperplasia and adenocarcinoma in high-dose females (hyperplasia: 2/70, 13/69; adenocarcinoma: 0/70, 2/69 at 0, 672 mg/kg bw/day, respectively). LOAEL (non-neoplastic): 27 mg/kg bw/day (histologic changes in the liver) (males)
B6C3F1 mice; 0, 500, 1500, 4000, 8000 ppm; est. 0, 90, 276, 742,1560 (males); 0, 112, 336, 910, 1888	Significant increase in incidence of hepatocellular carcinoma at the two highest doses in females and at the highest dose in males (males: 10/70, 8/67, 10/66, 17/65, 20/70; females: 1/70, 2/68, 5/68, 7/67, 19/70 at

(females); Diet; 2 years Recovery study; 0, 8000 ppm; est. 0, 1377 (males); 0, 1501 (females); Diet; 78 weeks, followed by 26 weeks recovery (Moore 1998b) **DINP-1 68515-48-0**	0, 90–112, 276–336, 742–910, 1560–1888 mg/kg bw/day, respectively). Significant increase in incidence of total liver neoplasms (carcinomas and adenomas) in females from 1500 ppm and in males at the two highest doses (males: 16/70, 13/67, 18/66, 28/65, 31/70; females: 3/70, 5/68, 10/68, 11/67, 33/70 at 0, 90–112, 276–336, 742–910, 1560–1888 mg/kg bw/day, respectively). LOAEL (non-neoplastic): 276–336 mg/kg bw/day (increase in absolute liver weights accompanied by histopathological changes in the liver at the highest dose and decreased body weight gain) (females); (increased incidence of liver masses and decreased absolute kidney weights) (males) Recovery study: increased incidence of total liver neoplasms in both sexes. Significant increased incidence of carcinoma in females only.

Overall, the lowest oral doses associated with a significant increase in the incidence of tumours are 331–336 mg/kg bw/day based on a significant increase in hepatocellular tumours in female rats and mice, respectively (Bio/dynamics 1986; Moore et al. 1998b).

The lowest oral dose associated with chronic non-cancer effects was 27 mg/kg bw/day based on histologic changes in the liver of male rats exposed to DINP in a two-year carcinogenicity study (Bio/dynamics 1986); however, the incidence of those changes was not dose-related.

DINP CAS number was not provided in the Bio/dynamics study; however, it was reported as DINP-A (71549-78-5) in a risk assessment report of the US Consumer Product Safety Commission (2010). DINP-A has an isomeric composition similar to DINP-2 (28553-12-0). In comparison, the LOAEL in the Lington study was 152–184 mg/kg bw/day based also on liver effects in both male and female rats exposed to DINP-1. According to US CPSC (2010b), the difference in the toxic potency between the Bio/dynamics and Lington studies may be due to differences in dose selection, differences in toxicity between the two forms of DINP, and/or the use of a different rat strain. Since effects in the Biodynamic study (1986) were not found to be dose-related, the LOAEL of 152–184 mg/kg bw/day (NOAEL of 15–18 mg/kg bw/day) from the Lington et al. (1997) study is considered more relevant.

9.2.11.4.3 Genotoxicity

In vitro, B79P was not mutagenic in a bacterial assay with *S. typhimurium* strains TA98, TA 100, TA 1535, TA 1537 and TA 15538, with or without metabolic activation (Monsanto 1982).

In the available genotoxicity studies for the closest analogue DINP, negative results were observed in *in vitro* and *in vivo* assays. Refer to Section 9.2.1.1 for a summary of the available studies for DINP (Environment Canada and Health Canada 2015b).

9.2.11.4.4 Evidence of systemic toxicity in humans

No information is currently available on the potential effects of B79P in humans.

9.3 Characterization of risk to human health

The health effects data for medium-chain phthalates shows that there is evidence of developmental, reproductive and systemic effects. Of these, the critical effects for risk characterization are developmental effects on males, as the information available at this time is strongest for effects on the development of the reproductive system, such as alterations of feminization parameters, reproductive tract malformations and effects on fertility. Below are the various aspects taken into consideration for the characterization of risk to human health.

Relevant sources and durations of exposure

Sources of exposure for medium-chain phthalates are predominantly from indoor air, dust, food and breast milk. Due to the identified presence of some of these substances in manufactured items that may come into contact with skin, two scenarios were conducted to evaluate dermal exposure of these substances from dermal contact (adults and infants). Finally, since DIBP may also be present in children's toys and articles, oral exposure from mouthing these products was also evaluated.

With respect to the use of adhesives, sealants and coatings which contain medium-chain phthalates, exposure would not be considered to be of concern for human health based on the following:

Dermal absorption of medium-chain phthalates in rats is low (2–10%), and evidence shows that human skin is less permeable than rat skin to phthalate diesters. Also, retention in skin is 3 to 6 fold higher in rat compared to human (Mint and Hotchkiss 1993; Mint et al. 1994). Distribution in tissues of rats is generally low, showing no accumulation, and excretion is rapid, within hours to days.

Exposure from use of these products would be of very short duration (acute) via the dermal route.

Phthalates in general are not considered acute toxicants, with LD_{50} levels from dermal exposure being at minimum 2 to 5 fold higher than oral values (Draize et al. 1948; Eastman Kodak 1978; David et al. 2001; Monsanto Company 1970, cited in US EPA 2006, 2010).

Acute dermal toxicokinetic information indicates that reproductive organs are not a target organ, and that presence and residence time in other tissues (adipose and muscle) is extremely low after 7 days (0.02 to 0.3% of applied dose) (Elsisi et al. 1989).

This is consistent with the assessments of other jurisdictions who have focused their assessment on repeated exposures (ECHA 2013a; US CPSC CHAP 2014).

Adversity of apical endpoints

Effects seen after *in utero* exposure to certain phthalates are similar to effects observed with other chemicals, such as vinclozolin, linuron, flutamide and finasteride, which cause decreased AGD at birth and retained nipples (NR), but also otherreproductive tract malformations, including, but not limited to, hypospadias (HYP) and undescended testes (CRY) in male rats (Gray et al. 1999; Mylchreest et al. 1999, 2000; McIntyre et al. 2000, 2001, 2002; Barlow et al. 2002; Bowmann et al. 2003).

Health Canada considers that both significantly reduced AGD and NR in male rats after exposure to certain phthalates during the critical developmental window in gestation are established indicators of androgen deficiency during prenatal development, which can have severe and irreversible effects on the male reproductive system and may, in turn, interfere with fertility based on the following:

1) Reduced AGD and NR have been demonstrated to persist into adulthood (McIntyre et al. 2001; Bowmann et al. 2003; Hotchkiss et al. 2004) and were found to be predictors of compromised reproductive capacity in adulthood (Hotchkiss et al. 2004). Decreased AGD was also a sensitive predictor of lesions in the male reproductive tract (Barlow et al. 2004);
2) The measurement of AGD is part of the OECD Guidance for mammalian reproductive toxicity testing and assessment and, further, the measurement of NR was also recommended, both being based on the same premise as (1) above (OECD 2008);
3) Several international regulatory agencies and scientific bodies have used AGD and NR as points of departure in characterizing the potential risk of phthalates on the developing male reproductive system (ECJRC 2007; NICNAS 2008; Danish EPA 2012; ECHA 2013a; Germany 2014; US CPSC CHAP 2014).

For these reasons, AGD and NR, along with other adverse effects related to RPS, will be considered in the characterization of risk for phthalates.

Human relevance of reproductive/developmental effects

The specific MOA of phthalate-induced effects on the male reproductive system has not been fully elucidated and the proposed mechanism(s) of action is reviewed elsewhere (section 9.2; NAS 2008). The effects seen in the developing reproductive tract of male rats show excellent concordance with the endpoints of concern in human males, namely infertility, decreased sperm count, cryptorchidism, reproductive tract malformations,

hypospadias and testicular tumours (germ-cell-derived in humans and Leydig-cell-derived in rats), which have been postulated to comprise the human testicular dysgenesis syndrome (TDS) (Health Canada 2015a; NAS 2008). It is noted, however, that there are no consistent human data directly linking the hypothesized syndrome with exposure to phthalates (NAS 2008). Regardless, several attempts have been made to determine whether these effects are observable in human tissues.

Overall, limited data on the effects on human foetal testes suggest effects such as a reduction in the number of germ cells and an increase in MNGs, with no consistent effects on testosterone biosynthesis (Hallmark et al. 2007; Lambrot et al. 2009; Yuan et al. 2012; Desdoits-Lethimonier et al. 2012). Recent reviews identified a number of limitations to the interpretation of recent xenograft studies (Mitchell et al. 2012; Heger et al. 2012; Spade et al. 2014), such as, but not limited to: 1) the substantial individual variability associated with the use of human biological material and the use of pooled testes at different ages; 2) the methods of material collection of human foetal testes, which are highly variable compared to animal models; 3) the potentially short exposure period being insufficient; 4) other sources of reproductive hormones not being considered; and 5) the potential difference in metabolizing capabilities of the animal hosts and humans (Albert et al. 2014; Habert et al. 2014).

This method was recently used with prepubertal primate testes xenographted into mice, showing that exposure to certain phthalates caused perturbations of steroidogenic gene expression, impaired tubule formation and germ cell differentiation as well as decreased spermatogonial numbers after subchronic exposure (Rodriguez-Sosa et al. 2014).

Habert et al. (2014) also cautioned that *in vitro* interspecies comparisons need to be carried out carefully by selecting appropriately comparable stages of gestation, using identical methods that can measure gametogenesis and steroidogenesis across the different species, and using non-contaminated explants of very similar size.

Similarly to the position presented by ECHA (2013a) in their assessment of DINP and DIDP, it is acknowledged that there are differences between human and rat steroidogenesis, but the processes involved in male reproductive development are similar. The critical enzymes involved in steroidogenesis are identical in rats and humans, and all mammals are believed to have parallel activation mechanisms for androgen-dependent processes. As ECHA (2013) stated, it is possible that a sufficient exposure may cause anti-androgenic effects in human foetuses similar to those observed in animals. Habert et al. (2014), in a report presented at the 7th Copenhagen Workshop on Endocrine Disrupters, supported by the Danish EPA and the Society for Reproduction and Fertility, also stated that the rat model is relevant and important to human health risk assessment when choosing a common effect in both species. This position was also supported by the US CPSC CHAP in their cumulative risk assessment (US CPSC CHAP 2014).

With respect to indicators of androgen deficiency in human males regardless of the cause, reduced AGD and penile size were reported in human boys with cryptorchidism

and hypospadias (Thankamony et al. 2014). Inverse associations with male AGD and environmental chemicals (phthalates and BPA) have been reported in boys from US, China and Japan, although consistency in methods and reproducibility of this endpoint has been a challenge (Swan et al. 2006; Miao et al. 2011; Suzuki et al. 2012). Although direct evidence of prenatal anti-androgen exposure and reduced adult reproductive capacity in humans is currently lacking, associations between AGD, decreased penile size, decreased semen quality, infertility and decreased serum levels of testosterone in adult men have been reported (Mendiola et al. 2011; Eisenberg et al. 2011, 2012a, 2012b; Bornehag et al. 2014; Bustamante-Montes et al. 2013). A recent review by Juul et al. (2014) stated that, like in animal studies, AGD measurements are a useful continuous gauge of androgen exposure *in utero* in humans.

Consideration of human relevance of other systemic effects

It is well documented that phthalates can induce peroxisome proliferation in the liver as well as increased liver weight in rats and mice. In some cases, liver cancer was also observed following longer-term oral administration of high doses of phthalates. It is well established that the peroxisome proliferator-activated receptor (PPAR) α plays a role in peroxisome proliferation-induced liver effects (Corton and Lapinskas 2005). However, the relevance of the hepatotoxic effects of phthalates observed in rodents is difficult to establish due to the species-specific differences in peroxisomal proliferation response (rodents being significantly more sensitive than humans to PPARα-mediated induction of peroxisome proliferation) (ECB 2008, NICNAS 2010, US CPSC 2010c). Several recent studies have suggested that the mechanisms of liver toxicity of peroxisome proliferators have not been entirely elucidated and that multiple pathways may exist, some of those likely PPARα-independent (Ito et al. 2007, Yang et al. 2007, Eveillard et al. 2009, Ren et al. 2010, IARC 2012). Based on this, liver effects cannot be precluded as an effect potentially relevant to humans and should be included in the characterization of the health effects of phthalates. More detailed information on the mode of action of liver carcinogenicity in rodents with peroxisome proliferators is available in Health Canada (2015c).

9.3.1 DIBP

Based principally on consideration of the weight-of-evidence-based classification of DIBP by the European Commission as Category 1B – reproductive toxicant (EC No 1272/2008) and consideration of the available information, critical effects associated with exposure to DIBP are developmental effects on the male reproductive system. Adverse effects in the parameters used to measure RPS after *in utero* exposure to DIBP included decreased testicular testosterone levels, decreased AGD, nipple retention, delayed preputial separation, reproductive tract malformations (cryptorchidism, hypospadias, exposed *os* penis, cleft prepuce), testicular pathology as well as potential effects on fertility through abnormalities in sperm. DIBP was also shown to have inhibitory effects on the expression of genes that are involved in testosterone production *in vivo*.

Based on the available information at this time, it appears as though the foetal male rat is the life stage most sensitive to the effects of exposure to DIBP. No conclusions can be made on whether the foetal mouse is less or more sensitive than the rat, as no studies examining the parameters used to measure RPS in this species using DIBP were available for this life stage. However, some evidence in the prepubertal/pubertal life stage and in the adult stage using DBP as an analogue indicated that mice were not as sensitive to the reproductive effects of DIBP later on in life. Rabbits appear to be as sensitive to the adverse reproductive effects of DBP as rats at similar doses. No studies were available identifying the potential reproductive/developmental toxicity of DIBP via any other route of exposure. See Table 9-34 for a summary of the critical effects of DIBP that will be used for risk characterization.

Developmental effects in female rats were identified at equal or higher doses than males after oral exposure with critical endpoints related to growth alterations, alterations of reproductive development, functional deficit, lethality and mild teratogenicity. Reproductive effects of DIBP in females (alterations of fertility and pregnancy outcomes) were observed at 750 mg/kg bw/day and above.

Table 9-34. Summary of critical effects levels for reproductive and/or developmental effects after oral exposure to DIBP

Life stage during which exposure occurred	Species	Effects	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
***in utero* (GD12–21)**	Rat	↓AGD, ↓NR, effects on fertility and other RPS effects; decreased testicular testosterone production	250	125	Saillenfait et al. 2008; Furr et al. 2014
(pre)pubertal	Rat	↑apoptotic spermatogenic cells, ↓ testes weight and vimentin filament disorganization in Sertoli cells	500	300	Zhu et al. 2010
adult	Rat (DBP)	Testicular pathology, effects on sperm count and motility, and decreased ROW	500	250	Srivastava et al. 1990b; Zhou et al. 2011

The potential sources of exposure to DIBP for the general population from environmental media and food is expected to be from food (oral ingestion), breast milk, indoor air (inhalation) and house dust (oral ingestion), with the major drivers of exposure being breast milk and indoor air. With respect to products used by consumers, potential sources of exposure may occur from oral mouthing of plastic toys and articles (infants 0

to 18 months), dermal contact with plastic articles (e.g., manufactured items such as exercise equipment and floor coverings) and DIBP presence in cosmetics. Finally, urinary metabolite concentrations of DIBP (MIBP and 2OH MIBP) were evaluated, and reverse dosimetry was used to calculate DIBP intakes. These intakes were derived from internal urinary concentrations and therefore represent exposure from all routes and sources at a given time.

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-35.

Table 9-35. Summary of margins of exposure to DIBP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)[c]
Children (male and female) 6 to 11 years of age: biomonitoring, CHMS	1.5 (5.3)	NOAEL = 300 Testicular pathology at 500 mg/kg bw/day (7 d)	200 000 (56 604)
Infants 0 to 0.5 year of age (breastfed): environmental media and food	1.6 (5.9)	NOAEL = 300 Testicular pathology at 500 mg/kg bw/day (7 d)	187 500 (50 847)
Infants/children (0 to 18 months of age)[a]: contact plastic articles, dermal	30.7[b] (245.3)	NOAEL = 300 Testicular pathology at 500 mg/kg bw/day (7 d)	9772 (1223)
Infants (0 to 18 months of age): mouthing toys, oral	62.8[b] (251.0)	NOAEL = 300 Testicular pathology at 500 mg/kg bw/day (7 d)	4777 (1195)
Adults (females) 20 to 49 years of age: biomonitoring, CHMS	0.56 (1.4)	NOAEL = 125 Reduced AGD, NR, effects on fertility and other TDS effects at the next highest dose (250 mg/kg bw/day)	223 214 (89 286)
Adults 20 to 59 years of age[a]: chronic body lotion, dermal	0.030	NOAEL = 125 Reduced AGD, NR, effects	Over 1 million

		on fertility and other TDS effects at the next highest dose (250 mg/kg bw/day)	
Adults (20+): contact plastic articles, dermal	30.8[b] (96.3)	NOAEL = 125 Reduced AGD, NR, effects on fertility and other TDS effects at the next highest dose (250 mg/kg bw/day)	4058 (1298)

[a] Estimate adjusted based on 10% dermal absorption of DBP.
[b] Estimated lower-end exposure.
[c] Margin of Exposure: central tendancy and (upper bounding)

The above MOEs are considered adequate to account for uncertainties in the exposure and health effects databases, and protective of the potential reproductive effects of phthalate toxicity not only in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Based on the information available, there is evidence that DIBP has effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the above MOEs are considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to DIBP and other phthalates exhibiting a similar mode of action.

9.3.2 DCHP

Based principally on the weight of evidence from the available information, critical effects associated with exposure to DCHP are developmental effects on the male reproductive system following exposure *in utero* as well as systemic effects on the liver and kidney after subchronic exposure.

Adverse effects in the parameters used to measure RPS after *in utero* exposure to DCHP included decreased foetal testosterone production, decreased AGD, retention of areole mammae and delayed preputial separation, along with testicular pathology. DCHP was also shown to have inhibitory effects on two enzymes that are involved in testosterone production *in vitro*, although this effect was not confirmed with confidence in *in vivo* studies.

Based on the available information from the 2-generation OECD Guideline study (Hoshino et al. 2005), it appears as though the foetal male rat is the most sensitive to adverse effects following exposure to DCHP compared to rats at other life stages; effects in F1 adult males, although occurring at the same dose levels of 1200 ppm, were less severe in nature and did not affect the overall reproductive success of the males. Further, there were no adverse reproductive effects when DCHP was administered to adult F0 males for 14 weeks (10 weeks prior to mating until 26 days after confirmed copulation). No conclusions can be made on whether the mouse is less or more

sensitive than the rat as no studies examining the parameters used to measure RPS in this species using DCHP were available. Further, no studies were available identifying the potential reproductive/developmental toxicity of DCHP via any other route of exposure. See Table 9-36 for a summary of critical effects of DCHP that will be used for risk characterization.

Developmental effects in female rats were identified at higher doses than males after oral exposure, with critical endpoints related to growth alterations (organs and body weights) and lethality. Reproductive effects of DCHP in adult females (pregnancy outcome alterations) were reported at high doses.

Table 9-36. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DCHP

Life stage	Species	Effects	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
in utero	Rat	Decreased AGD and retained nipples in F2 males (slight maternal toxicity); decreased testicular testosterone production (100 mg/kg bw/day)	107 (1200 ppm)	21 (240 ppm)	Hoshino et al. 2005; Furr et al. 2014)
(pre)pubertal	Rat	Testicular effects (tubular atrophy) in 1 out of 5 animals	2500 (LOEL)	1500 (NOEL)	Lake et al. 1982
adult	Rat	Slight focal seminiferous tubule atrophy in 1 male at highest dose, with decreased body weight gain	402 (6000 ppm LOEL)	80 (1200 ppm)	Hoshino et al. 2005

N/A = not applicable

The database for repeated-dose toxicity of DCHP suggests that liver and kidneys are also the main target organs for this phthalate. No effects were reported following chronic exposure of dogs and rats. Consequently, the carcinogenic potential of DCHP is considered limited. The lowest LOAEL identified from repeat-dose studies was 75 mg/kg bw/day (NOAEL of 25 mg/kg bw/day) based on increases in liver weight (females), accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses (200 and 500 mg/kg bw/day) in a subchronic feeding study in rats (de Ryke and Willems 1977).

The principal source of exposure to DCHP for the general population is expected to be from exposure to house dust and indoor air and from use of products used by consumers, such as sealants and adhesives. Although DCHP is present in food, intakes were calculated and exposure was estimated to be negligible.

Comparisons of upper-bounding estimates for oral exposure to DCHP from dust and indoor air for the most exposed age groups, with the appropriate critical effect levels, result in MOEs ranging from 166 667 to over 1 million, which are considered adequate to address uncertainties in the exposure and health effects databases. Further, these MOEs are considered protective of potential reproductive effects of phthalate toxicity not only in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-37 below.

Table 9-37. Summary of margins of exposure to DCHP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)[b]
Children 0.5 to 4 years of age: indoor air and dust, dermal and inhalation	0.0018 (0.15)	NOAEL = 25 Increased relative liver weight (females), accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses tested (subchronic)	Over 1 million (166 667 to)
Adolescents 12 to 19[a] years of age: indoor air and dust, dermal and inhalation	< 0.001 (0.065)	NOAEL = 21 Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F2 males after *in utero* exposure to DCHP at the next highest dose tested in rats (107 mg/kg bw/day)	Over 1 million (323 077)

[a] MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.
[b] Margin of Exposure: central tendancy and (upper bounding)

Based on the information available, there is evidence that DCHP has effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the above MOEs are currently considered adequate on an individual basis, this does not address the

potential risk of concurrent exposure to DCHP and other phthalates exhibiting a similar mode of action.

9.3.3 DMCHP

Based principally on the weight of evidence from the available information on its analogue, DCHP, the critical effects associated with exposure to DMCHP are developmental effects on the male reproductive system following exposure *in utero* as well as systemic effects on the liver and kidney after subchronic exposure. See above section and Table 9-36 for a summary of the critical health effects used for this phthalate.

A potential source of exposure for DMCHP for the general public is house dust; however, no other information as to monitoring of DMCHP in other media was identified.

A comparison of upper-bounding estimates for oral exposure to DMCHP from ingestion of dust for all age groups with the appropriate critical effect levels identified from studies conducted with DCHP (see Section 9.3.2) results in MOEs ranging from 462 963 to over 1 million. These MOEs are considered adequate to address uncertainties in the exposure and health effects databases, and protective of the potential reproductive effects of phthalate toxicity not only in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-38 below.

Table 9-38. Summary of margins of exposure to DMCHP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)[b]
Children 0 to 0.5 year of age: dust ingestion, oral	0.0027 (0.054)	$NOAEL_{DCHP}$ = 25 Increased relative liver weight (females), accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses tested (subchronic)	Over 1 million (462 963)
Adolescents 12 to 19[a] years of	< 0.001	$NOAEL_{DCHP}$ = 21	Over 1 million

age: dust ingestion, oral		Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F2 males after *in utero* exposure to DCHP at the next highest dose tested in rats (107 mg/kg bw/day)	
Adults 20+ [a] years of age: dust ingestion, oral	< 0.001	$NOAEL_{DCHP}$ = 21 Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F2 males after *in utero* exposure to DCHP at the next highest dose tested in rats (107 mg/kg bw/day)	Over 1 million

[a] MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.
[b] Margin of Exposure: central tendancy and (upper bounding)

Based on the information available for DCHP, there is evidence that DMCHP has potential effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the MOEs are currently considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to DMCHP and other phthalates exhibiting a similar mode of action.

9.3.4 DBzP

Based on an examination of the health effects database for the closest analogue to DBzP, MBzP (see Category Approach Document, Health Canada 2015a), the critical effects for the characterization of risk associated with exposure to DBzP are considered to be developmental effects on the male reproductive system following exposure *in utero* and systemic effects, such as decreased body weight gain and food consumption.

Adverse effects in the parameters used to measure RPS after *in utero* exposure to MBzP included decreased AGD and reproductive tract malformations (CRY). Based on the criteria used in selecting the appropriate analogue, it is considered appropriate to use the information on MBzP to characterize the toxicological profile of DBzP with respect to these reproductive/developmental effects.

Based on the limited available information, there appears to be no difference in sensitivity to the developmental effects of exposure to MBzP at different life stages. No conclusions can be made on whether the foetal mouse is less or more sensitive than the rat, as no *in vivo* studies examining the parameters used to measure RPS in this species using MBzP or DBzP were available for this life stage; however, there was some indication that MBzP was more toxic to pregnant mice and their offspring, but not

rats at similar doses. No studies were available identifying the potential reproductive/developmental toxicity of DBzP via any other route of exposure. See Table 9-39 for a summary of the critical effects of MBzP that will be used for risk characterization.

Based on the information extrapolated from studies using MBzP, developmental effects in female rats were identified at doses equal to those of males, as MBzP is teratogenic and embryolethal at maternally toxic doses. One rat study (Ema et al. 2003) reported a higher sensitivity in male offspring to the developmental toxicity of MBzP.

With regards to systemic effects, the lowest LOAEL for short-term exposure was 167 mg/kg bw/day based on a dose-dependent decrease in body weight gain (22% decrease for adjusted weight gain) associated with a decrease in food consumption (8–15%) in dams in a developmental toxicity study in rats (Ema et al. 2003).

Table 9-39. Summary of critical effect levels after oral exposure to DBzP using MBzP as closest analogue

Life stage	Species	Effects	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
in utero	Rat (MBzP)	↓ AGD and ↑cryptorchidism	250	167* (Systemic toxicity LOAEL based on ↓food consumption, ↓BW)	Ema et al. 2003
(pre)pubertal/adult	Rat (MBzP)	↓ sperm count (20%)	250 (LOEL)	NA	Kwack et al. 2009

* Maternal toxicity at this dose, but considered not a factor in selection of adverse effects in male offspring.

A potential source of exposure to DBzP for the general public is house dust; however, no other information as to DBzP monitoring in other media was identified. DBzP was identified as a potential food contact phthalate in the US; however, no monitoring as to its presence in food was identified (DBzP has been identified as a candidate for monitoring as part of future Health Canada total diet surveys). While association of potential DBzP use in products used by consumers was observed, no submissions as to its use, manufacturing and import in Canada were identified. Therefore, no direct consumer product exposure is expected.

A comparison of upper-bounding estimates for oral exposure to DBzP from ingestion of dust for all age groups with the appropriate critical effect levels results in MOEs over 1 million, considered adequate to address uncertainties in the exposure and health effects databases for DBzP on an individual substance basis. Further, these MOEs are considered protective of the potential reproductive effects of phthalate toxicity not only

in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-40 below.

Table 9-40. Summary of margins of exposure to DBzP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)
Children 0 to 0.5 year of age: dust ingestion, oral	0.016 (0.097)	$LOAEL_{MBzP}$ = 167 decrease in body weight gain and food consumption	Over 1 million
Adolescents 12 to 19[a] years of age: dust ingestion, oral	< 0.001 (0.0011)	$NOAEL_{MBzP}$ = 167 anti-androgenic effects *in utero* $LOAEL_{MBzP}$ = 167 decrease in body weight gain and food consumption	Over 1 million

[a] MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

Based on the information available, there is evidence that DBzP has effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the above MOEs are currently considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to DBzP and other phthalates exhibiting a similar mode of action.

9.3.5 B84P

Based on an examination of the health effects database for BBP, MBzP and DIBP as analogues, the critical effects for characterization of the risk associated with exposure to B84P are considered to be carcinogenicity and developmental effects on the male reproductive system.

No chronic/carcinogenicity studies were available for B84P. Its close analogue BBP has been classified by IARC as Group 3 “Not classifiable as to its carcinogenicity to humans” (IARC 1999). Also, the California EPA recently concluded that BBP should not

be listed under Proposition 65 as a carcinogen (OEHHA 2013a). Mononuclear cell leukemia was reported in female Fischer rats exposed to BBP in a 1982 study but not in a 1997 repeat study (NTP 1982, 1997a). It has been proposed that this type of lesion is specific to aging rats of this strain and is likely to be of no relevance to humans. BBP also induced an increase in pancreatic tumours primarily in male rats, the full expression of which was prevented in a dietary restriction protocol (NTP 1997a). There was no evidence of carcinogenicity in mice (NTP 1982). Pancreatic acinar cell carcinoma is rare in F344 male rats, having never been observed in untreated male F344 rats in NTP studies (NTP 1997a). Klaunig et al. has proposed a PPARα-dependent mode of action for the induction of pancreatic acinar cell tumours by BBP (Klaunig et al. 2003). However, there are data gaps in this proposed MOA and there are no existing data suggesting that PPARα is actually involved in the induction of pancreatic acinar cell tumours by BBP or in BBP tumorigenesis in general (Klaunig et al. 2003; OEHHA 2013a). Based on the little information available on the potential MOA involved in the increase in incidence of pancreatic tumours in rats and its potential occurrence in humans, it is considered that this type of tumour is of unclear relevance to humans.

In a Priority Substances List (PSL) report published by Environment Canada and Health Canada in 2000, it was suggested that BBP could be considered, at most, possibly carcinogenic to humans, likely inducing pancreatic tumours through a non-genotoxic (albeit unknown) mechanism (Environment Canada and Health Canada, 2000). Considering this and the available information for B84P regarding genotoxicity, which indicates that this phthalate is not likely to be genotoxic, a threshold approach is used to characterize risk to human health from exposure to B84P. An examination of chronic studies conducted on BBP indicates that potential pancreatic tumours would occur at doses higher than those at which developmental effects have been observed.

With respect to non-cancer effects, the lowest LOAEL for subchronic oral exposure was 381 mg/kg bw/day (NOAEL of 151 mg/kg bw/day) based on histopathological changes in the pancreas, gross pathological alterations in the liver and a significant increase in relative kidney weight in male Wistar rats exposed to BBP for three months (Hammond et al. 1987). No adverse effects were observed in mice and dogs exposed to high doses of BBP for three months (NTP 1982b; Hammond et al. 1987). The lowest LOAEL for chronic oral exposure was 300 mg/kg bw/day based on a significant increase in the incidence of nephropathy noted in all groups of exposed females in a two-year study in rats (NTP 1997a).

With regard to developmental effects, adverse effects in the parameters used to measure RPS after *in utero* exposure included decreased testicular testosterone levels, decreased AGD, NR, delayed PPS, reproductive tract malformations (CRY, HYP, exposed *os* penis, cleft prepuce), testicular pathology and potential effects on fertility through abnormalities in sperm. DIBP was also shown to have inhibitory effects on the expression of genes that are involved in testosterone production *in vivo*. MBzP also induced increased incidences of CRY and decreased AGD in the foetal rat at similar dose levels. Based on the criteria used in selecting the appropriate analogues, it is

considered appropriate to use the information on BBP to characterize the toxicological profile of B84P with respect to these reproductive/developmental effects, as it appears to be the most potent of the three analogues. BBP has been classified by the European Commission as Category 1B – reproductive toxicant (EC No 1272/2008).

Using BBP as an analogue for the adult life stage indicates that the adult appears to be less sensitive compared to younger animals, although no clear conclusions can be made with any confidence. Further, no conclusion can be made on whether the foetal mouse is less or more sensitive than the rat, as no *in vivo* studies examining the parameters used to measure RPS in this species using the three analogues were available for this life stage; however, there was some indication that MBzP was more toxic to pregnant mice and their offspring, but not rats at similar doses. No studies were available identifying the potential reproductive/developmental toxicity of B84P via any other route of exposure. See Table 9-41 for a summary of the critical effects of BBP that will be used for risk characterization of B84P.

Based on the information extrapolated from studies using MBzP, DIBP and BBP, developmental effects in female rats were identified at doses equal to or higher than those for male offspring and were based on growth alteration, lethality, altered reproductive organ weights, delay of puberty and teratogenicity (variations and skeletal and/or visceral malformations) after gestational exposure as well as pregnancy outcomes, alterations of reproductive organ weights, hormone levels (progesterone and prolactin) and reproductive-related organ visual examination and histopathology in adulthood.

Table 9-41. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to B84P using DIBP, MBzP and BBP as closest analogues

Life stage	Species	Effects	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
in utero	**Rat (BBP)**	Decreased body weight (F1/F2 males and females) and ↓AGD at birth in F2 males [a]; ↓ testicular testosterone	100	20	Aso et al. 2005; Nagao et la 2000; Furr et al. 2014
in utero	**Rat (DIBP)**	↓AGD, ↓NR, effects on fertility and other RPS effects at the next highest dose (500 mg/kg bw/day)	250	125	Saillenfait et al. 2008
in utero	**Rat (MBzP)**	↓ AGD and ↑cryptorchidism	250	167*	Ema et al. 2003

(pre)pubertal	**Rat (MBzP)**	↓ sperm counts and sperm motility	250 (LOEL)	NA	Kwack et al. 2009
(pre)pubertal	**Rat (BBP)**	↓ sperm counts and sperm motility	500 (LOEL)	NA	
(pre)pubertal	**Rat (DIBP)**	↑apoptotic spermatogenic cells, vimentin filament disorganization in Sertoli cells, and decreased reproductive organ weight	500	300	Zhu et al. 2010
adult	**Rat (BBP)**	reduced absolute epididymal weight, hyperplasia of the Leydig cells in the testes and decreased spermatozoa in the lumina of the epididymis	400	200	Aso et al. 2005
adult	**Rat (BBP)**	Severe testicular atrophy	480	160	Lake et al. 1978

[a] A statistically significant increase of AGD in F1 and decreased pup weight on PND0 in F2 female offspring at 100 mg/kg bw/day and above was also reported.

Potential exposure to B84P for the general population is expected to be from oral dust ingestion. However, dust intakes were calculated using B79P dust concentrations for B84P, as no laboratory standard is available for B84P. Uncertainty therefore exists with respect to estimating exposure from this source. Additionally, since B84P is a medium-volume chemical (> 100 000 kg, section 71 reporting) and has been notified to be used in textile applications in other jurisdictions, dermal exposure from handling plastic articles was assessed for infants (0 to 18 months) and adults (20+ years). The exposure estimates and respective margins of exposure are outlined in Table 9-42.

Comparisons of upper-bounding estimates for dermal exposure to B84P from contact with plastic articles (textiles, upholstery, etc.) for all age groups, with the appropriate critical effect levels, result in MOEs ranging from 2352 to 6991, which are considered adequate to address uncertainties in the exposure and health effects databases for B84P. Comparisons of upper-bounding estimates for oral exposure to B84P from dust ingestion for children 0 to 6 months of age result in MOEs over 1 million, which are also considered adequate to address uncertainties in the exposure and health effects databases for B84P. Further, these MOEs are considered protective of the potential reproductive effects of phthalate toxicity not only in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-42 below.

Table 9-42. Summary of margins of exposure to B84P for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Levels and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)[d]
Infants (0 to 18 months): exposure to plastic articles, dermal	2.7[c] (21.6)	NOAEL (BBP)= 151[b] Histopathological changes in the pancreas, gross pathological alterations in the liver and significant increase in relative kidney weight in male rats at next highest dose of 381 mg/kg bw/day (subchronic)	55 926 (6991)
Infants 0 to 6 months: dust ingestion, oral	0.0063 (0.047)	NOAEL (BBP)= 151[b] Histopathological changes in the pancreas, gross pathological alterations in the liver and significant increase in relative kidney weight in male rats at next highest dose of 381 mg/kg bw/day (subchronic)	Over 1 million
Adults (20+): exposure to plastic articles, dermal	2.7[c] (8.5)	$NOAEL_{(BBP)}$ = 20 Decreased pup body weight (male and female) and ↓AGD at birth in F2 males at next highest dose of 100 mg/kg bw/day; decreased foetal testosterone	7407 (2352)

[a] MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for these age groups.
[b] NOAEL (BBP prepubertal) = 300 (testicular pathology at 500 mg/kg bw/day [7d]) is at higher doses than the systemic effects.
[c] Estimated lower-end exposure, adjusted for dermal absorption (10%).
[d] Margin of Exposure: central tendancy and (upper bounding)

Based on the information available on DIBP, BBP and MBzP, there is evidence that B84P has potential effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the MOEs are currently considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to B84P and other phthalates exhibiting a similar mode of action.

9.3.6 DIHepP

Based principally on the weight of evidence from the available information, the critical effects associated with exposure to DIHepP are developmental effects on the male reproductive system following exposure *in utero* and liver and kidney effects following exposure at the adult stage. Adverse effects in the parameters used to measure RPS after *in utero* exposure to DIHepP included decreased foetal testicular testosterone production, decreased AGD, NR, delayed PPS, testicular pathology and potential effects on fertility through abnormalities in sperm.

Based on the available information at this time, it appears as though the foetal male rat is the life stage most sensitive to the developmental effects of exposure to DIHepP, although it should be noted that there is a lack of studies examining the effects of this substance in prepubertal/pubertal males. No conclusions can be made on whether the mouse is less or more sensitive than the rat, as no studies examining the parameters used to measure RPS in this species using DIHepP were available. Further, no studies were available identifying the potential reproductive/developmental toxicity of DIHepP via any other route of exposure. See Table 9-43 for a summary of critical effects of DIHepP that will be used for risk characterization.

Based on the limited information from studies using DIHepP, developmental effects in female rats were identified at doses higher than those for male offspring and were based on alterations of growth, functional deficit, lethality and teratogenicity after gestational exposure as well as alterations of reproductive performance and pregnancy outcomes in adulthood.

Table 9-43. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DIHepP

Life Stage	Species	Effects	LOAEL (mg/kg bw/day)	NOAEL(mg/kg bw/day)	Reference
in utero	Rat	Significant reduction in AGD in male F2 pups	309–750	64–168	McKee et al. 2006
(pre)pubertal	Rat	Significant reduction in AGD; delayed preputial separation, nipple retention, hypospadias and cryptorchidism in F1 pups	419–764	227–416	McKee et al. 2006
adult	Rat			404–623	McKee et al. 2006

No carcinogenicity studies were available for DIHepP. However, based on the results of the multigenerational study, the carcinogenic potential of DIHepP is likely limited. Effects indicative of peroxisome proliferation were observed in a repeated-dose study conducted in rats and mice. This could potentially result in the increased incidence of hepatocellular tumours. However, this has been mostly observed at high doses. The

mechanisms of liver carcinogenicity in rodents with peroxisome proliferators have not been fully elucidated. Consequently, relevance in humans remains unclear and cannot be ruled out.

Consideration of the limited available information on genotoxicity indicates that DIHepP is not likely to be genotoxic.

The lowest LOAEL for subchronic and chronic oral exposure was 222–716mg/kg bw/day (NOAEL 50–162 mg/kg bw/day) and 227–750 mg/kg bw/day (NOAEL 50–168 mg/kg bw/day), respectively, based on liver and kidney effects in the 2-generation study (McKee et al. 2006).

Potential exposure to DIHepP for the general population is expected to be from oral dust ingestion. DIHepP use was identified in adhesives and sealants; however, no products used by consumers that would lead to direct subchronic and chronic exposures were identified.

Comparisons of upper-bounding estimates for oral exposure to DIHepP from ingestion of dust for children 0 to 0.5 year of age and adolescents 12 to 19 years of age and above, with the appropriate critical effect levels, result in MOEs ranging from 45 455 to over 1 million, which are considered adequate to address uncertainties in the exposure and health effects databases for DIHepP on an individual substance basis. Further, these MOEs are considered protective of the potential reproductive effects of phthalate toxicity not only in males at older life stages but also in females, in addition to effects in other organ systems (systemic toxicity).

Upper-bounding intakes, sources and respective margins of exposure for the relevant age-specific populations (when points of departure related to the MOA of antiandrogenicity are used) are presented in Table 9-44 below.

Table 9-44. Summary of margins of exposure to DIHepP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for oral NOAEL (mg/kg bw/day)	Margin of exposure (MOE)[b]
Children 0 to 0.5 year of age: dust ingestion, oral	0.096 (1.1)	NOAEL = 50-162 Increased liver and kidney weights with histopathological findings at 222–716 mg/kg bw/day	147 273 (45 455)

Adolescents 12 to 19[a] years of age: dust ingestion, oral	0.0011 (0.013)	NOAEL = 50–168 Significant reduction in AGD and body weight in male F2 pups after *in utero* exposure to DIHepP at the next highest dose tested in rats (309–750 mg/kg bw/day) and liver and kidney effects at the next highest dose (227–750 mg/kg bw/day) in F1 rats	Over 1 million

[a] MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.
[b] Margin of Exposure: central tendancy and (upper bounding)

Based on the information available, there is evidence that DIHepP has effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the MOEs are currently considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to DIHepP and other phthalates exhibiting a similar mode of action.

9.3.7 B79P

Based principally on the weight of evidence from the available information, a critical effect associated with oral exposure to B79P is carcinogenicity.

B79P and the analogue MBzP have not been classified for their potential carcinogenicity by other international agencies, and no chronic/carcinogenicity study was identified for either phthalate. The OEHHA has recently reviewed the evidence of the potential carcinogenicity of the analogue DINP and it has been concluded that DINP has been clearly shown, through scientifically valid testing according to generally accepted principles, to cause cancer and should be listed under Proposition 65 as a carcinogen (OEHHA 2013b). Accordingly, DINP has been listed at the end of 2013 (OEHHA 2013c). DINP has not been classified for its potential carcinogenicity by other international agencies.

DINP has been tested in a number of carcinogenicity studies in rats and mice. Statistically significant increases in many tumour types were observed in animals exposed to high doses of this phthalate, such as an increase in hepatocellular tumours in rats and mice, mononuclear cell leukemia of the spleen in Fischer rats and renal tubular cell carcinomas in rats. Overall, mechanisms of carcinogenicity of DINP in rodents have not been fully elucidated, and formation of tumours following chronic exposure to DINP is of unclear or questionable relevance to humans. Nevertheless, the potential for DINP, and therefore B79P, to be carcinogenic cannot be ruled out.

Consideration of the available information on genotoxicity for B79P and DINP indicates that B79P is not likely to be genotoxic.

For non-cancer effects, the lowest oral LOAEL identified was 152–184 mg/kg bw/day (NOAEL of 15–18 mg/kg bw/day) based on liver effects in both male and female rats exposed to DINP (Lington et al. 1997).

B79P is also associated with developmental effects on the male reproductive system following exposure *in utero*, but at doses higher than those for which B79P is presumed to induce effects on liver and kidneys, based on a review of the health effects of its analogue DINP. Refer to Section 9.2.2.1 of the assessment for DINP (Environment Canada and Health Canada 2015b) for a review of the potential reproductive/developmental effects of DINP for all life-stages. Developmental effects of B79P were reported to include decreased AGD, retained nipples and reproductive tract malformations (cryptorchidism and epispadias). Information from analogues have also reported reproductive effects at later life stages, such as decreased sperm counts and motility as well as reproductive organ weights in adulthood.

Potential exposure to B79P for the general population is expected to be from oral dust ingestion. Additionally, since B79P is a medium-volume chemical (> 100 000 kg, section 71 reporting) and has been notified to be used in textile applications in other jurisdictions dermal exposure from handling plastic articles was assessed for infants (0 to 18 months). The exposure estimates and respective margins of exposure are outlined in Table 8-49.

Comparisons of upper-bounding estimates for dermal exposure to B79P from contact with plastic articles (textiles, upholstery, etc.) for infants 0 to 18 months of age, with a NOAEL of 15–18 mg/kg bw/day for DINP based on liver effects in both male and female rats (Lington et al. 1997), result in an MOE of 694. Comparisons of upper-bounding estimates for oral exposure to B79P from dust ingestion for children 0 to 0.5 year of age and adolescents 12 to 19 years of age, with the same endpoint, result in MOEs ranging from 319 149 to over 1 million. In both cases, MOEs are considered adequate to address uncertainties in the exposure and health effects databases for B79P. See Table 9-45 below.

Table 9-45. Summary of margins of exposure to B79P for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Margin of exposure (MOE)[b] based on an oral NOAEL of 15 mg/kg bw/day from Lington et al. (1997)
Infants (0 to 18 months): exposure to plastic articles, dermal	2.7[a] (21.6)	5556 (694)
Adults (20+): contact with plastic articles, dermal	2.7[a] (8.5)	5556 (1765)

Children 0 to 0.5 year of age: dust ingestion, oral	0.0063 (0.047)	Over 1 million (319 149)
Adolescents 12 to 19[a] years of age: dust ingestion, oral	< 0.001	Over 1 million

[a] Estimated lower-end exposure.
[b] Margin of Exposure: central tendancy and (upper bounding)

Based on the information available, there is evidence that B79P has effects on the developing male reproductive system, indicative of RPS, and may have a common mode of action with other phthalates in the grouping. Although the MOEs are currently considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to B79P and other phthalates exhibiting a similar mode of action.

9.3.8 CHIBP, BCHP and BIOP

An examination of the potential developmental and reproductive toxicity of CHIBP, BCHP and BIOP using appropriate analogues for read-across revealed that these medium-chain phthalates have the potential to have significant effects on the developing male, in addition to systemic effects (liver, kidney).

Based on the information available, it can be concluded that CHIBP, BCHP and BIOP meet the criteria for inclusion in the evaluation of the potential cumulative risk of phthalates on the developing male reproductive system based on evidence of the effects of their analogues; however, as there is no exposure at this time, they will not be included in risk characterization in a cumulative context.

Results from a section 71 industry survey for 2012 suggest that CHIBP, BCHP and BIOP are not currently in use above the specified reporting threshold, and the likelihood of exposure to the general population in Canada is considered to be negligable. Consequently, the risk to human health for these substances is not expected.

9.4 Uncertainties in evaluation of risk to human health

Empirical health effects data for medium-chain phthalates range from robust to very limited and create uncertainty in the evaluation of risk to humans. There is some uncertainty associated with the use of analogues to characterize the human health effects of phthalates with limited or no available toxicological information. This lack of available toxicological information applies to DMCHP, CHIBP, BCHP, DBzP, B84P, BIOP and B79P.

There are no studies by any route of administration on developmental neurotoxicity for any of these phthalates. In the case of DIBP, DMCHP, CHIBP, BCHP, DBzP, B84P, BIOP and B79P, there are no 2-generation studies. The majority of the reproductive and developmental toxicity data for these medium chain phthalates is generally limited to

one species (rat) and to males. There is some uncertainty associated with not only the potential biological significance of effects, but also the sensitivity of effects after exposure to this substance group in both female and male humans.

There is also limited or no information on repeated-dose effects via the inhalation and dermal routes of exposure for the majority of phthalates in this grouping.

There is uncertainty regarding the potential carcinogenicity of some medium-chain phthalates due to the lack of long-term studies (DIBP, DMCHP, CHIBP, BCHP, DBzP, DIHepP, B84P, BIOP and B79P). However, there is available information from carcinogenicity studies for certain analogues (BBP and DINP) to address this endpoint for B84P and B79P, respectively.

There is uncertainty associated with the mode of induction of tumours for BBP and DINP. Postulated mechanisms have been identified for some tumour-types, but the mechanisms have not been fully elucidated.

Studies used for risk characterization for medium-chain phthalates ranged from high-quality OECD Guideline studies to those with limited information. This uncertainty was addressed in the selection of precautionary target MOEs, where required.

Although a rigorous evaluation approach was conducted with the available human epidemiological data, uncertainty still exists as to the relevance of these studies implicating the potential hazard that certain phthalates pose to humans.Thoroughly conducted epidemiologic studies showing robust and consistent associations between an exposure factor and an outcome may provide strong implication for causal inference. However, observational studies in diverse populations pose challenges in both the measure of exposure and the measure of the outcome, and inherently have biases and confounding factors (Lucas and McMichael 2005). The majority of epidemiological studies examined were cross-sectional in which a temporal sequence whereby exposure precedes the outcome cannot be established. In addition, several outcomes associated with phthalate exposure in human epidemiological studies have long latencies (such as cancer, diabetes, obesity, cardiovascular disease) and multifactorial etiologies (geographical location, socioeconomic status, diet, lifestyle factors, genetic propensity, nonchemical stressors) and are chronic in nature, whereas phthalates have short biological half-lives and their measurement therefore reflects a snapshot of recent exposure. Moreover, biomonitoring data showed that exposure to certain phthalates is ubiquitous and therefore cannot be dichotomized as present or absent but is instead a continuous variable, often with a limited range.

While it has been argued that even in the absence of consistent methods, a robust association should yield consistent findings (La Kind et al., 2012), poor reproducibility continues to feature prominently in epidemiological studies involving phthalates. Adding to the lack of clarity is the fact that humans are simultaneously exposed to multiple phthalates from multiple sources via multiple routes, as well as other environmental agents that may share coinciding effect domains, including bisphenol A, certain metals

and organochlorine compounds, such as PCBs, dioxins and various persistent organic pesticides. In its final report in 2014, the US Chronic Hazard Advisory Panel (CHAP) on Phthalates concluded that although there is a growing body of studies reporting associations between phthalate exposure and human health, and many of the reported health effects are consistent with testicular dysgenesis syndrome in humans, there are acknowledged limitations of these studies similar to those described above. These were therefore not used in risk characterization (US CPSC CHAP 2014). Another recent review also found that epidemiological evidence for associations with reproductive and developmental effects from phthalates is minimal to weak in most cases (Kay et al. 2014).

No monitoring data on the presence of BCHP, CHIBP and BIOP in environmental media and food were identified for Canada or elsewhere. Based on information submitted to Environment Canada and known international use patterns, exposure to the general population is not expected.

There are uncertainties associated with estimating intakes of phthalates from environmental media due to minimal monitoring data available for these phthalates in air, drinking water and soil. Confidence is moderate to high that derived intake estimates from household dust are representative of the potential exposure of the general Canadian population, since the exposure estimates are based on a Canadian house dust monitoring study. However, B84P was not monitored in dust, as no standard was available. Moreover, despite the presence of BIOP and DBzP peaks in dust analysis chromatograms, BIOP was assumed not to be present in dust based on a zero kilogram production volume in Canada. Therefore, uncertainty exists in the quantification of dust exposure for these two substances. However, despite these collective uncertainties, there is confidence that assumptions made in estimating exposure are conservative enough to account for these uncertainties (use of higher metric concentrations).

For phthalate presence in food, there is uncertainty in the literature regarding the presentation of LODs and LOQs, as a portion of publications present the LOD of the instrument rather than incorporating the background level of phthalate contamination.

For quantification of food exposure, from DIBP and DCHP presence in food, US and UK surveys were used for analysis. Uncertainty therefore exists, as these intakes are extrapolated for the general Canadian population. There is uncertainty associated with potential intake from food containing DBzP since this substance is present on international databases indicating potential food contact exposure. However, no monitoring data as to its presence in food was identified.

There is also uncertainty associated with exposure estimates calculated from DIBP monoester (MIBP) presence in breast milk. This is related to the quantification of exposure (conversion of metabolite exposure to parent phthalate exposure) and the evaluation of margins of exposure between exposure intakes derived from metabolite

exposure (infants ingesting breast milk containing DIBP), and toxicology studies evaluating effects of parent phthalate exposure.

For DIBP, B84P and B79P, there is uncertainty as to the estimation of dermal exposure from contact with manufactured items containing these phthalates, based on limited substance-specific information with regard to the presence and migration over time of phthalates from these products. Therefore, it is unclear as to how much phthalate is available for transfer to skin from contact. Additional uncertainty is associated with the parameters used (e.g., dermal absorption and migration rate) in estimating exposure from manufactured items; however, there is confidence that the assumptions used were conservative.

A number of assumptions have been made to derive intake estimates from biomonitoring data that represent a source of uncertainty, that is to say, the assumption that spot urine samples are representative of steady state daily concentrations and assumptions around the use of creatinine-corrected concentrations. However, there is confidence that the assumptions used in deriving estimates of intakes are appropriate and conservative. Also, confidence in the biomonitoring database for DIBP is high, as it represents a substantially large number of data points collected recently in Canadian individuals spanning a wide age spectrum, including subpopulations such as pregnant woman.

Due to the lack of or limited health effects data for all relevant routes and durations of exposure, route-to-route extrapolation was required, and/or use of effect levels from studies with a longer or shorter duration of exposure than the exposure scenarios was applied. Conservatism in the derivation of exposure estimates is recognized by the application of conservative dermal absorption values.

Uncertainty is recognized in the potential oral bioavailability of medium-chain phthalates, in particular the estimated internal dose at which effects were observed in animal studies after administration. Information exists that absorption of these phthalates is highly variable (30–95%) and is influenced by rates of metabolism and excretion of an organism and by different routes at any given time of measurement. These limitations do not allow for accurate adjustments in risk characterization for each phthalate; however, estimated MOEs are considered adequate to account for this uncertainty.

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Appendices

Appendix A. Structural identity and physical chemical properties of analogue substances

Table A-1. Substance identities of BBP, DPhP, DBP, DIOP and DEHP

Acronym (CAS RN)	Chemical formula	Molecular weight (g/mol)	SMILES
BBP (85-68-7)	$C_{19}H_{20}O_4$	312.35	O=C(Occ1ccccc1)c2ccccc2(C(=O)OCCCC)
DPhP (84-62-8)	$C_{20}H_{14}O_4$	318.33	O=C(OC1=CC=CC=C1)C1=CC=CC=C1C(=O)OC1=CC=CC=C1
DBP (84-74-2)	$C_{16}H_{22}O_4$	278.34	O=C(OCCCC)c1ccccc1(C(=O)OCCCC)
DIOP (27554-26-3)	$C_{24}H_{38}O_4$	390.56	75% CCCCI(C)COC(C1=CC=CC=C1IC(C)C(C)CCC)=O)=O 25% OIOCCCCCC(C)C)C1=CC=CI1C(OCCCCCC(C)C)=O
DEHP (117-81-7)	$C_{24}H_{38}O_4$	390.56	O=C(OCC(CC)CCCC)c1ccccc1(C(=O)OCC(CC)CCCC)

Table A-2. Physical and chemical properties of BBP, DPhP, DBP, DIOP and DEHP

Acronym (CAS RN)	Physical form*	Melting point (ºC)	Boiling point (ºC)	Vapour pressure (Pa)
BBP (85-68-7)	Liquid	< -35 (exp)[a]	370 (exp)[a]	1.1 (25°C) (exp)[a]
DPhP (84-62-8)	Solid	73 (exp)[b]	255 (exp)[b]	0.082 (exp)[b]
DBP (84-74-2)	Liquid	< -70 (exp)[a]	340 (exp)[a]	9.7× 10-3 (25°C) (exp)[a]
DIOP (27554-26-3)	Liquid	-4[d]	370 (exp)[c]	7.3× 10-4 (25°C) (exp)[c]
DEHP (117-81-7)	Liquid	-50 (exp)[a]	374 (exp)[a]	3.0 × 10-5 (25°C) (exp)[a]

Abbreviations: exp = experimental; mod = modelled
*Based on melting point
[a] [ECHA] 2007–2014a
[b] PhysProp 2006
[c] HSDB 1983–2014
[d] MSDS 2014

Table A-3. Physical and chemical properties of BBP, DPhP, DBP, DIOP and DEHP (continued)

Acronym (CAS RN)	Water solubility (mg/L)	Henry's Law constant ($Pa \cdot m^3/mol$)	Log K_{ow} (unitless)	Log K_{oc} (unitless)	Log K_{oa} (unitless)
BBP (85-68-7)	2.69 (exp)[a]	4.28×10^{-3} (bond estimate)[b]	4.91 (exp)[a]	3.8 (mod)[b]	9.2 (mod)[b]
DPhP (84-62-8)	0.082 (exp)[c]	3.1×10^{-3} (bond estimate)	4.36 (median of modelled values)[d]	4.12	10
DBP (84-74-2)	11.4 13 (exp) [e]	0.124	4.46	3.06	8.6
DIOP (27554-26-3)	0.09 (exp)[f]	1.20 (bond estimate)[b]	75%: 7.52 (median of modelled values)[d] 25%: 7.96 (median of modelled values)[d]	4.9 (mod)[b]	11.3 (mod)[b]
DEHP (117-81-7)	3.0×10^{-3} (20°C) (exp)[a] 0.40 (25°C) P	1.20 (bond estimate)[b]	7.14 (exp)[a]	5.1 (mod)[b]	12 (mod)[b]

Abbreviations: exp = experimental; mod = modelled
[a] [ECHA] c2007–2014a
[b] EPI Suite 2012
[c] PhysProp 2006
[d] Median of modelled values from Epi Suite 2012, [VCCLab] 2005 and ACD/Percepta c1997–2012
[e] Wolfe et al. 1980
[f] HSDB 1983–2014

Appendix B. Physical and chemical properties for the substances in the medium-chain phthalate subgroup

Table B-1. Physical and chemical properties of medium-chain phthalates

CAS RN Acronym	Physical form	Melting point (ºC)	Boiling point (ºC)	Density (kg/m^3)	Vapour pressure (Pa)
84-69-5 DIBP	Liquid[a]	-64† (exp)[b] -52 (exp)[i]	296.5† (exp)[d] 320 (exp)[i]	1049 (exp)[d]	0.01† (exp, 20°C)[i] 6.3×10^{-3} (exp, 25°C)[e] 0.313 (mod, 25°C)[c]
84-64-0 BCHP	Liquid[d]	25† (exp)[f]	~ 205 (exp)[d] 366.48 (mod)[c]	1076 (exp)[d]	6.36×10^{-4}† (4.77×10^{-7} mm Hg; exp, 25°C)[g] 7.13×10^{-3} (mod, 25°C)[c]
5334-09-8 CHIBP	Liquid[j]	No data	359.48 (mod)[c]	No data	1.05×10^{-2}† (mod, 25°C)[c]
84-61-7 DCHP	Solid[i]	63–65 (exp)[a] 65.6 (exp)[i] 66† (exp)[d]	220–230 (exp)[a] 225 (exp)[d] 322 65.6 (exp)[i] 394.85 (mod)[c]	787 (exp)[i]	3.8×10^{-6} (exp, 20°C)[a] 8.8×10^{-6}† (exp, 25°C)[a] 1.16×10^{-4} (8.69×10^{-7} mm Hg; exp, 25°C)[g] 6.1×10^{-4} (mod, 25°C)[c]
27987-25-3 DMCHP	No data	No data	411.33 (mod)[c]	No data	1.98×10^{-4}† (mod, 25°C)[c]

CAS RN Acronym	Physical form	Melting point (ºC)	Boiling point (ºC)	Density (kg/m^3)	Vapour pressure (Pa)
71888-89-6 DIHepP	Liquid[a]	-40[†] (exp)[a]	393.74 (mod)[c]	994 (exp)[a]	< 1 (exp, 20°C)[a] 9.33×10^{-5}[†] (calc, 25°C)[h] 1.08×10^{-3} (mod, 25°C)[c]
523-31-9 DBzP	Solid*	44[†] (exp)[f]	436.79 (mod)[c]	No data	9.34×10^{-5}[†] (mod, 25°C)[c]
16883-83-3 B84P	Liquid[a]	No data	473.87 (mod)[c]	1096 (exp)[i]	8.48×10^{-7}[†] (mod, 25°C)[c]
27215-22-1 BIOP	Liquid[k]	No data	419.87 (mod)[c]	No data	6.68×10^{-5}[†] (mod, 25°C)[c]
68515-40-2 B79P	Liquid[a]	No data	390 (exp)[a] 419.87 (mod)[c]	1059 (exp)[i]	6.25×10^{-4}[†] (mod, 25°C)[c]

Abbreviations: calc = calculated value; exp = experimental value; ext = extrapolated value; mod = modelled value
[†] Indicates selected value for modelling.
*Based on melting point
[a] European Commission 2000
[b] HSDB 1983–
[c] MPBPVPWIN 2010
[d] Haynes and Lide 2010
[e] Daubert and Danner 1989
[f] PhysProp 2006
[g] Werner 1952
[h] Cousins and Mackay 2000
[I] ECHA c2007–2014
[j] MSDS 2012
[k] MSDS 2011

Table B-2. Physical and chemical properties of substances in the medium-chain phthalate subgroup (continued)

CAS RN Acronym	Water solubility (mg/L)	Henry's Law constant (Pa·m^3/mol)	Log K_{ow} (unitless)	Log K_{oc} (unitless)	Log K_{oa} (unitless)
84-69-5 DIBP	20.3[†] (exp, 20°C)[a] 6.2 (exp, 24°C)[b]	0.12 (mod, bond estimate, 25°C)[d]	4.11[†] (exp)[a]	2.99 (average of model predictions)[h]	8.41 (mod)[i]

CAS RN Acronym	Water solubility (mg/L)	Henry's Law constant ($Pa \cdot m^3/mol$)	Log K_{ow} (unitless)	Log K_{oc} (unitless)	Log K_{oa} (unitless)
84-64-0 BCHP	3.67† (median of model predictions)[c]	9.64×10^{-2} (mod, bond estimate, 25°C)[d]	5.22† (Median of model predictions)[g]	3.69 (average of model predictions)	9.82 (mod)[i]
5334-09-8 CHIBP	4.85† (median of model predictions)[c]	9.64×10^{-2} (modelled, bond estimate, 25°C)[d]	5.13† (Median of model predictions)[g]	3.63 (median of model predictions)	9.74 (mod)[i]
84-61-7 DCHP	0.2† (exp, 20°C)[j] 4.0 (exp, 24°C)[b]	7.49×10^{-2} (mod, bond estimate, 25°C)[d]	4.82 (exp)[i] 5.76† (Median of model predictions)[g]	3.79 (Median of model predictions)	10.72 (mod)[i]
27987-25-3 DMCHP	0.275† (Median of model predictions)	0.132 (mod, bond estimate, 25°C)[d]	6.75† (Median of model predictions)[g]	4.61 (Median of model predictions)	11.31 (mod)[i]
71888-89-6 DIHepP	0.017† (exp, 22°C)[k]	33.5 (cal)[f]	6.15[l]	4.69 (median of model predictions)[h]	10.97 (mod)[i]
523-31-9 DBzP	0.51† (median of model predictions)[c]	1.48×10^{-4} (mod, bond estimate, 25°C)[d]	5.09† (Median of model predictions)[g]	4.13 (average of model predictions)[h]	12.30 (mod)[i]
16883-83-3 B84P	0.81† (exp, 22°C)[j]	5.58×10^{-5} (mod, bond estimate, 25°C)[d]	6.76† (Median of model predictions)[g]	5.38 (average of model predictions)[h]	14.65 (mod)[i]
27215-22-1 BIOP	0.22† (median of model predictions)[c]	1.33×10^{-2} (mod, bond estimate, 25°C)[d]	5.87† (Median of model predictions)[g]	4.63 (average of model predictions)[h]	11.93 (mod)[i]

CAS RN Acronym	Water solubility (mg/L)	Henry's Law constant ($Pa \cdot m^3/mol$)	Log K_{ow} (unitless)	Log K_{oc} (unitless)	Log K_{oa} (unitless)
68515-40-2 B79P	0.3† (exp, 25°C)[j]	1-1.76 × 10^{-2} (mod, bond estimate, 25°C)[d]	5.5† (exp)[j]	4.3 (average of model predictions)[h]	11.93 (mod)[i]

Abbreviations: exp = experimental value; log K_{oc} = organic carbon-water partition coefficient; log K_{ow} = octanol water partition coefficient; log K_{oa} = organic carbon-air partition coefficient; mod = modelled value
Note: Values in parentheses represent the original ones as reported by the authors or as estimated by the models.
† Indicates selected value for modelling.
[a] Leyder and Boulanger 1983
[b] Yalkowsky et al. 2010
[c] WSKOWWIN 2010
[d] HENRYWIN 2011
[e] VP/WS estimate derived using modelled values for vapour pressure (MPBPVPWIN 2010) and water solubility (WSKOWWIN (2010).
[f] VP/WS estimate derived using empirical values for vapour pressure and/or water solubility.
[g] KOWWIN 2010
[h] KIIWIN 2010
[i] KOAWIN 2010
[j] European Commission 2000
[k] Letinski et al. 2002
[l] VCCLab 2005

Appendix C. Results of Level III fugacity modelling (EQC 2011) for the medium-chain phthalate esters in the phthalate substance grouping

Table C-1. Percentage of substance partitioning into each environmental compartment

Substance name	100% released into	Air	Water	Soil	Sediment
DIBP	Air	39.56	10.12	50.13	0.2
DIBP	Water	0	98.02	0	1.94
DIBP	Soil	0	0	99.63	0
BCHP	Air	21.09	7.94	70.36	0.6
BCHP	Water	0	92.92	0	7.04
BCHP	Soil	0	0	99.92	0
CHIBP	Air	36.39	9.62	53.35	0.64
CHIBP	Water	0	93.7	0	6.27
CHIBP	Soil	0	0	99.91	0
DCHP	Air	2.65	4.22	91.19	1.92
DCHP	Water	0	68.4	0	31.5
DCHP	Soil	0	0	99.94	0
DMCHP	Air	10.19	5.46	78.98	5.37
DMCHP	Water	0	50.39	0	49.59
DMCHP	Soil	0	0	99.96	0

Substance name	100% released into	Air	Water	Soil	Sediment
DIHepP	Air	21.85	7.44	62.79	7.92
DIHepP	Water	0	48.38	0	51.54
DIHepP	Soil	0	0	99.97	0
DBzP	Air	0.1	4.36	93.68	1.88
DBzP	Water	0	69.9	0	30.1
DBzP	Soil	0	0	99.93	0
B84P	Air	0.03	2.63	84.97	12.37
B84P	Water	0	17.54	0	82.46
B84P	Soil	0	0	99.97	0
BIOP	Air	5.81	4.52	84.63	5.05
BIOP	Water	0	47.2	0	52.77
BIOP	Soil	0	0	99.97	0
B79P	Air	3.69	4.66	88.61	3.03
B79P	Water	0	60.59	0	39.4
B79P	Soil	0	0	99.95	0

Appendix D. Bioaccumulation

Table D-1. Empirical BCF data for analogues of medium-chain phthalate esters

Substance	Test organism	Exposure duration (days)	Exposure concentration (µg/L)	Derivation of BCF calculation	BCF Value	Reference
BBP	Rainbow trout	61	100	Total water concentration	918	Ratzlaff 2004
BBP	Rainbow trout	61	100	Operational freely dissolved	1890	Ratzlaff 2004
BBP	Rainbow trout	61	100	Predicted freely dissolved concentration	11500	Ratzlaff 2004
BBP	Bluegill sunfish	3	34	Intact BBP[1]	9.4 (whole fish)	Carr et al. 1997
BBP	Bluegill sunfish	3	34	Total radioactivity	194 (whole fish)	Carr et al. 1997
BBP	Bluegill sunfish	21	9.7	Total radioactivity	663	Barrows et al.

						1980
BBP	Bluegill sunfish	21	2	Total radioactivity	188	Heidolph and Gledhill 1979
BBP	Bluegill sunfish	Not specified	34	Total radioactivity	449	Carr et al. 1992
DEHP	Fathead minnow	56	1.9 - 62	Total radioactivity	155–886	Mayer 1976
DEHP	Fathead minnow	56	1.9 - 62	GC measured DEHP[2]	91–569	Mayer 1976

[1] The authors refer to intact BBP as the amount of the parent compound measured.
[2] BCF is calculated using the gas-chromatographic value of DEHP in a pooled sample of four fish.

Table D-2. Modelled bioaccumulation data for medium-chain phthalate esters

Substance	Rate constant for 10 g fish (k_M)	BCF[1] (L/kg ww) BCFBAF v3.01	BAF[1,2] (L/kg ww) Arnot and Gobas 2003
DIBP	11.63	34.29[3]	34.7
BCHP	3.424	112.8[3]	114.8
CHIBP	3.852	101.1	102.3
DCHP	1.639	185[3]	234.4
DBzP	3.52[4]	96	112.2
DMCHP	0.5091	237.1	398.1
DIHepP	1.324	121.6[3]	239.9
B79P[5]	12.33–13.02	30.19–31.82[3]	30.2 – 31.6
BIOP	5.871	35.82	61.7
B84P	3.52[4]	45	53.7

[1] Mid-trophic level, including biotransformation rate estimates.
[2] BAF predictions, calculated based on Arnot et al. 2003, used a dietary uptake efficiency of 1%.
[3] Predictions based on user-entered phys-chem properties.
[4] k_M modified according to values in Arnot et al. 2008b.
[5] Ranges are shown for predictions obtained using the C7 and C9 structures.

Table D-3. Empirical bioaccumulation data for medium-chain phthalate esters and the analogues BBP and DEHP

Substance	Test organism	Endpoint	Value	Reference
DIBP	Green algae, *Enteromorpha intestinalis*	BAF, ww[1]	229 L/kg	Mackintosh 2002
DIBP	Pacific staghorn sculpin, *Leptocottus armatus*	BAF, ww[1]	78 L/kg	Mackintosh 2002

DIBP	Spiny dogfish muscle, *Squalus acanthias*	BAF, ww[1]	251 L/kg	Mackintosh 2002
DIBP	Green algae, *Enteromorpha intestinalis*	BSAF, lipid normalized	0.812 kg OC/kg lipid	Mackintosh 2002
DIBP	Pacific staghorn sculpin, *Leptocottus armatus*	BSAF, lipid normalized	1.05 kg OC/kg lipid	Mackintosh 2002
DIBP	Spiny dogfish muscle, *Squalus acanthias*	BSAF, lipid normalized	0.122 kg OC/kg lipid	Mackintosh 2002
DIBP	Beluga whale, *Delphinapterus leucas*	BSAF, lipid normalized	4.19 kg OC/kg lipid	Morin 2003
DIBP	Arctic cod, *Boreogadus saida*	BSAF, lipid normalized	2.75 kg OC/kg lipid	Morin 2003
DIHepP[2]	Green algae, *Enteromorpha intestinalis*	BAF, ww[1]	331 L/kg	Mackintosh 2002
DIHepP[2]	Blue Mussel, *Mytilus edulis*	BAF, ww[1]	426 L/kg	Mackintosh 2002
DIHepP[2]	Pacific staghorn sculpin, *Leptocottus armatus*	BAF, ww[1]	115 L/kg	Mackintosh 2002
DIHepP[2]	Green algae, *Enteromorpha intestinalis*	BSAF, lipid normalized	0.449 kg OC/kg lipid	Mackintosh 2002
DIHepP[2]	Pacific staghorn sculpin, *Leptocottus armatus*	BSAF, lipid normalized	0.526 kg OC/kg lipid	Mackintosh 2002
BBP	Green algae, *Enteromorpha intestinalis*	BAF, ww[1]	2692 L/kg	Mackintosh 2002
BBP	Pacific staghorn sculpin, *Leptocottus armatus*	BAF, ww[1]	631 L/kg	Mackintosh 2002
BBP	Spiny dogfish muscle, *Squalus acanthias*	BAF, ww[1]	912 L/kg	Mackintosh 2002
BBP	Green algae, *Enteromorpha*	BSAF, lipid normalized	0.671 kg OC/kg lipid	Mackintosh 2002

	intestinalis			
BBP	Pacific staghorn sculpin, *Leptocottus armatus*	BSAF, lipid normalized	0.611 kg OC/kg lipid	Mackintosh 2002
BBP	Spiny dogfish muscle, *Squalus acanthias*	BSAF, lipid normalized	0.0353 kg OC/kg lipid	Mackintosh 2002
DEHP	Green algae, *Enteromorpha intestinalis*	BAF, ww[1]	1096 L/kg	Mackintosh 2002
DEHP	Pacific staghorn sculpin, *Leptocottus armatus*	BAF, ww[1]	41 L/kg	Mackintosh 2002
DEHP	Spiny dogfish muscle, *Squalus acanthias*	BAF, ww[1]	37 L/kg	Mackintosh 2002
DEHP	Green algae, *Enteromorpha intestinalis*	BSAF, lipid normalized	0.277 kg OC/kg lipid	Mackintosh 2002
DEHP	Pacific staghorn sculpin, *Leptocottus armatus*	BSAF, lipid normalized	0.0496 kg OC/kg lipid	Mackintosh 2002
DEHP	Spiny dogfish muscle, *Squalus acanthias*	BSAF, lipid normalized	0.0018 kg OC/kg lipid	Mackintosh 2002

[1] BAF calculations are based on total water concentrations (including phthalates bound to large- and small-diameter suspended matter and freely dissolved) and have been converted from their log BAF values reported in the study.
[2] The study identifies the substance as the isomeric mixture di-iso-heptyl.

Table D-4. Empirical biomagnification factors for medium-chain phthalate esters

Substance	Number of trophic levels	Endpoint	Value	Reference
DIBP	2	BMFL	1.52	Morin 2003
DIBP	4	FWMF	0.86	Mackintosh et al. 2004
DIBP	4	FWMF	0.4	McConnell 2007
DIHepP	4	FWMF	0.94	Mackintosh et al. 2004
DIHepP	4	FWMF	0.54	McConnell 2007

Abbreviations: BMF= biomagnification factor; FWMF = food-web magnification factor

Table D-5. Empirical biomagnification factors analogues of medium-chain phthalate esters

Substance	Number of trophic levels	Endpoint	Value	Reference
BBP	2	BMFL	1.07	Morin 2003
BBP	4	FWMF	0.89	Mackintosh et al. 2004
BBP	4	FWMF	0.38	McConnell 2007

Abbreviations: BMF = biomagnification factor; FWMF = food-web magnification factor

Appendix E. Toxicity values

Table E-1. Empirical aquatic toxicity data for medium-chain phthalate esters

Substance	Test organism	Type of test	Endpoint	Value (mg/L)	Reference
DIBP	Medaka, *Oryzias latipes*	Acute (96 h)	LC_{50}	3	ECHA c2007–2014b
DIBP	Medaka, *Oryzias latipes*	Chronic (21 d)	NOEC	0.39	ECHA c2007–2014b
DIBP	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	0.9	ECHA c2007–2014b, Geiger et al. 1985
DIBP	Fathead minnow, *Pimephales promelas*	Acute (96 h)	EC_{50}, behaviour	0.73	ECHA c2007–2014b, Geiger et al. 1985
DIBP	Harpacticoi, *Nitocra spinipes*	Acute (96 h)	LC_{50}	3	ECHA c2007–2014b; Linden et al. 1979
DIBP	Water flea, *Daphnia magna*	Acute (48 h)	EC_{50}, mobility	4.8	ECHA c2007–2014b
DIBP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, reproduction	0.27 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Pseudokirchneriella subcapitata*	Chronic (72 h)	EC_{50}, growth rate	1.8	ECHA c2007–2014b
DIBP	Green alga, *Pseudokirch*	Chronic (72 h)	NOEC, growth rate	0.37	ECHA c2007–

	neriella subcapitata				2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{50}, growth rate	1.7 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	NOEC, growth rate	0.35 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	LOEC, growth rate	0.9 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{50}, biomass	0.56 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	NOEC, biomass	0.35 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	LOEC, biomass	0.9 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{10}, growth rate	0.36 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{20}, growth rate	0.64 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{10}, biomass	0.28 (measured)	ECHA c2007–2014b
DIBP	Green alga, *Desmodesmus subspicatus*	Chronic (72 h)	EC_{20}, biomass	0.36 (measured)	ECHA c2007–2014b
DIBP	Micro-organisms	(14 d)	NOEC, res–iration rate CO_2 - evolution	14.5[a]	ECHA c2007–2014b

DCHP	Medaka, *Oryzias latipes*	Acute (96 h)	LC_{50}	> 2	ECHA c2007–2014c
DCHP	Water flea, *Daphnia magna*	Acute (48 h)	NOEC	> 2	ECHA c2007–2014c
DCHP	Water flea, *Daphnia magna*	Chronic (21 d)	LC_{50}	1.04 (measured)	ECHA c2007–2014c
DCHP	Water flea, *Daphnia magna*	Chronic (21 d)	EC_{50}	0.679 (measured)	ECHA c2007–2014c
DCHP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, mortality	0.181 (measured)	ECHA c2007–2014c
DCHP	Water flea, *Daphnia magna*	Chronic (21 d)	LOEC	0.572 (measured)	ECHA c2007–2014c
DCHP	Green alga, *Pseudokirchnerella subcapitata*	Chronic (72 h)	NOEC	> 2	ECHA c2007–2014c
DIHepP	Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	NOEC, survival	0.2[b]	US EPA 2010
DIHepP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, mortality, growth, reproduction	0.92[b]	US EPA 2010
DIHepP[c]	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, reproduction	1[b]	Brown et al. 1998
B84P	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	> 1000[d]	ECHA c2007–2013
B84P	Fathead minnow, *Pimephales promelas*	Acute (96 h)	NOEC	1000[d]	US EPA 2010
B84P	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	> 5[d]	ECHA c2007–2013
B84P	Fathead	(14 d)	EC_{50}	> 0.3[d]	ECHA

	minnow, *Pimephales promelas*				c2007–2013
B84P	Fathead minnow, *Pimephales promelas*	Chronic (30d)	MATC	> 0.3[d]	ECHA c2007–2013
B84P	Steelhead trout, *Salmo gairdneri*	Acute (96h)	NOEC	1000[d]	US EPA 2010
B84P	Rainbow trout, *Oncorhynchus mykiss*	Acute (96h)	LC_{50}	> 1000[d]	ECHA c2007–2013
B84P	Rainbow trout, *Oncorhynchus mykiss*	Acute (96h)	LC_{50}	> 5[d]	ECHA c2007–2013
B84P	Bluegill, *Lepomis macrochirus*	Acute (96h)	LC_{50}	> 0.3[d]	ECHA c2007–2013
B84P	Water flea, *Daphnia magna*	Acute (48h)	LC_{50}	7.5[d] (nominal)	Study Submission 2014a; ECHA c2007–2014g
B84P	Green alga, *Pseudokirchneriella subcapitata*	Chronic (96 h)	EC_{50}, cell number	> 1000[d]	ECHA c2007–2014g
B84P	Green alga, *Pseudokirchneriella subcapitata*	Chronic (96 h)	LOEC, reduction of cell number, chlorophyll concentration	≥ 360 (nominal)[d]	US EPA 2010
B84P	Green alga, *Pseudokirchneriella subcapitata*	Chronic (96 h)	EC_{50}, biomass	> 5[d]	ECHA c2007–2014g
B79P	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	> 0.3[e]	ECHA c2007–2013
B79P	Fathead	Acute	LC_{50}	> 1000[e]	ECHA

	minnow, *Pimephales promelas*	(96 h)			c2007–2014d
B79P	Fathead minnow, *Pimephales promelas*	Acute (14 d)	EC_{50}	> 0.3[e]	ECHA c2007–2014d
B79P	Fathead minnow, *Pimephales promelas*	Chronic (30 d)	MATC	> 0.3[e]	ECHA c2007–2014d
B79P	Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	LC_{50}	> 1000[e]	ECHA c2007–2014d
B79P	Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	NOEC	1000[e]	US EPA 2010
B79P	Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	LC_{50}	> 0.3[e]	ECHA c2007–2014d
B79P	Bluegill, *Lepomis macrochirus*	Acute (96 h)	LC_{50}	> 0.3[e]	ECHA c2007–2014d
B79P	Water flea, *Daphnia magna*	Acute (48 h)	LC_{50}	4.5[e] (nominal)	Study Submission 2014a
B79P	Water flea, *Daphnia magna*	Acute (48 h)	EC_{50}	0.3[e]	ECHA c2007–2014d
B79P	Water flea, *Daphnia magna*	Acute (48 h)	NOEC	< 1	ECHA c2007–2014d
B79P	Water flea, *Daphnia magna*	Chronic (22 d)	NOEC, reproduction	0.039	ECHA c2007–2014d
B79P	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, reproduction	1[e]	Brown et al. 1998
B79P	Green alga, *Selenastrum capriconutum*	Chronic (96 h)	EC_{50}, cell number	521[e]	ExxonMobil 2006
B79P	Green alga,	Chronic	EC_{50}, *in vivo*	674[e]	ExxonMobil

	Selenastrum capriconutum	(96 h)	chlorophyll a		2006
BIOP	B79P as analogue				

Abbreviations/definitions: EC_{50} = the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50} = the concentration of a substance that is estimated to be lethal to 50% of the test organisms; IC_{50} = the inhibiting concentration for a specified percent effect. A point estimate of the concentration of a test substance that causes a 50% reduction in a quantitative biological measurement such as growth rate; NOEC(L) = the no observed effect concentration/level is the highest concentration/level in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC(L) = the lowest observed effect concentration/level is the lowest concentration/level in a toxicity test that caused a statistically significant effect in comparison to the controls; MATC = the maximum allowable toxicant concentration, generally presented as the range between the NOEC(L) and LOEC(L) or as the geometric mean of the two measures.

* These references did not specify a CAS RN, so phthalate identity was assumed based on chemical name.

[a] This concentration value exceeds solubility limit of DIBP (CAS 84-69-5), reported by HSDB (2013) as 6.2 mg/L.

[b] This concentration value exceeds solubility limit of DIHepP (CAS 71888-89-6), reported by US EPA EPI Suite (2012) as 0.002446 mg/L.

[c] Reported as di-iso-heptyl phthalate in the study.

[d] This concentration value exceeds solubility limit of B84P (CAS 16883-83-3), reported by US EPA (2010) as 0.00147 mg/L.

[e] This concentration value exceeds solubility limit of B79P (CAS 68515-40-2), reported by US EPA EPI Suite (2012) as 0.0864 mg/L.

Table E-2. Empirical data for the aquatic toxicity of analogues used in the ecological assessment

Substance	Test organism	Type of test	Endpoint	Value (mg/L)	Reference
BBP	Rainbow trout, *Salmo mykiss*	Acute (96 h)	LC_{50}	0.82	Adams et al. 1995
BBP	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	1.5	Adams et al. 1995
BBP	Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h)	LC_{50}	1.7	Adams et al. 1995
BBP	Zebrafish embryo, *Danio rerio*	Acute (72 h)	LC_{50}	0.72	Chen et al. 2014
BBP	Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h)	LC_{50}	48	Buccafusco et al. 1981
BBP	Bluegill sunfish, *Lepomis macrochirus*	Acute (48 h)	LC_{50}	1.7	Gledhill et al. 1980

BBP	English sole, *Parophrys vetulus*	Acute (96 h)	LC_{50}	0.55	Randall et al. 1983
BBP	Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	LC_{50}	> 0.68	Adams et al. 1995
BBP	Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	LC_{50}	3	Gledhill et al. 1980
BBP	Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	NOEC	360	Heitmuller et al. 1981
BBP	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	2.1	Gledhill et al. 1980
BBP	Fathead minnow, *Pimephales promelas*	Chronic (30 d)	NOEC	0.14	Leblanc, 1980
BBP	Fathead minnow, *Pimephales promelas*	Chronic (21 d)	NOEC (fecundity, fertility and hatchability)	> 0.0646	Study Submission 2014d; ECHA c2007–2014e
BBP	Fathead minnow, *Pimephales promelas*	Chronic (126 d)	NOEC (fry survival, length and weight)	> 0.0675	Study Submission 2014d; ECHA c2007–2014e
BBP	Japanese medaka, *Oryzias latipes*	Chronic (42 d)	NOEC	0.15	NITE 2010
BBP	Water flea, *Daphnia magna*	Acute (48 h)	EC_{50}	> 0.96	Adams et al. 1995
BBP	Water flea, *Daphnia*	Acute (48 h)	EC_{50}	1.6	Barera and Adams

	magna				
BBP	Water flea, *Daphnia magna*	Acute (96 h)	EC_{50}	3.7	Gledhill et al. 1980
BBP	Water flea, *Daphnia magna*	Acute (48 h)	LC_{50}	92	Leblanc 1980
BBP	Mysid shrimp, *Mysidopsis bahia*	Acute (48 h)	LC_{50}	> 0.9	Adams et al. 1995
BBP	Mysid shrimp, *Americamysis bahia*	Acute (96 h)	LC_{50}	0.9	Gledhill et al. 1980
BBP	Mysid shrimp, *Mysidopsis bahia*	Chronic (28 d)	NOEC	0.075	Study Submission 2014c
BBP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC	0.52	NITE 2010
BBP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC	0.28	Rhodes et al. 1995
BBP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC	0.26	Adams and Heidolph, 1984
BBP	*Hyalella azteca*	Chronic (10 d)	LC_{50}	0.46	Call et al. 2001
BBP	*Lumbriculus variegatus*	Chronic (10 d)	LC_{50}	1.23	Call et al. 2001
BBP	*Chironomus tentans*	Chronic (10 d)	NOEC	0.64	Call et al. 2001
BBP	Green algae, *Selenastrum capricornutum*	Chronic (96 h)	EC_{50}	0.21	Adams et al. 1995
BBP	Green algae, *Selenastrum capricornutum*	Chronic (96 h)	NOEC	< 0.10	Adams et al. 1995

BBP	Green algae, *Pseudokirchneriella subcapitata*	Chronic (96 h)	EC_{50}	0.6	Gledhill et al. 1980
BBP	Diatom, *Skeletonema costatum*	Chronic (96 h)	EC_{50}	0.4	Gledhill et al. 1980
BBP	Diatom, *Navicula pelliculosa*	Chronic (96 h)	EC_{50}	0.6	Gledhill et al. 1980
DPhP	Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC_{50}	0.08	Geiger et al. 1985
DIOP	Fathead minnow, *Pimphales promelas*	Acute (96 h)	LC_{50}	> 0.14	Adams et al. 1995
DIOP	Fathead minnow, *Pimphales promelas*	Acute (96 h)	LC_{50}	> 0.29	Adams et al. 1995
DIOP	Rainbow trout, *Salmo mykiss*	Acute (96 h)	LC_{50}	> 0.23	Adams et al. 1995
DIOP	Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	LC_{50}	> 0.48	Adams et al. 1995
DIOP	Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h)	LC_{50}	> 0.13	Adams et al. 1995
DIOP	Water flea, *Daphnia magna*	Chronic (21 d)	NOEC, mortality and reproduction	0.062	Rhodes et al. 1995
DIOP	Water flea, *Daphnia magna*	Chronic (21 d)	LOEC, mortality and reproduction	0.14	Rhodes et al. 1995
DIOP	Water flea, *Daphnia magna*	Acute (48 h)	EC_{50}	> 0.16	Adams et al. 1995

DIOP	Midge, *Paratanytarsus parthenogeneticus*	Chronic (96 h)	EC_{50}	> 0.12	Adams et al. 1995
DIOP	Green algae, *Selenastrum capricornutum*	Chronic (96 h)	EC_{50}	> 0.13	Adams et al. 1995
DIOP	Mysid shrimp, *Mysidopsis bahia*	Chronic (96 h)	EC_{50}	> 0.55	Adams et al. 1995

Table E-3. Modelled aquatic toxicity values for medium-chain phthalates

Name	Fish 96-hr LC_{50} (mg/L)	Daphnid 48-hr LC_{50} (mg/L)	Algae EC_{50} or LC_{50}* (mg/L)	Model
DIBP[1]	1.479	2.212	0.724	ECOSAR v1.00
BCHP[1]	0.467	0.619	0.183	ECOSAR v1.00
CHIBP	0.515[2]	0.688	0.205[2]	ECOSAR v1.00
DCHP[1]	0.178	0.213[2]	0.058	ECOSAR v1.00
DBzP[1, 3]	0.818	1.130	0.346	ECOSAR v1.00
DMCHP	0.064[2]	0.069[2]	0.017[2]	ECOSAR v1.00
DIHepP[1, 3]	0.040	0.041	0.010[2]	ECOSAR v1.00
B79P[1, 4]	0.049–0.164	0.050–0.193	0.012–0.052	ECOSAR v1.00
B79P	0.0045	N/A	N/A	TOPKAT v6.1
B79P[1, 4]	0.22	1.74 – 1.77[3]	0.21 – 0.23	CPOPs 2008
B79P[4]	0.697 – 0.763[3]	29.82 – 31.11[3]	1.29 – 1.36[3]	AIEPS v2.05
BIOP	0.108[2]	0.122[2]	0.032[2]	ECOSAR v1.00
BIOP[1]	0.14	1.18[3]	0.11	CPOPs 2008
BIOP	0.504[3]	13.89[3]	1.75[3]	AIEPS v2.05
B84P[1]	0.086	0.092	0.023	ECOSAR v1.00

Abbreviations: N/A, not available

*ECOSAR v1.00 provides a predicted 96-hr EC_{50}, AIEPS provides a predicted 72-hr EC_{50} and CPOPs provides a predicted LC_{50} for algae.

[1] Prediction based on user-entered phys-chem properties.

[2] Flag from ECOSAR that chemical may not be soluble.
[3] Prediction exceeds water solubility.
[4] Range shown for predictions obtained using the C7 and C9 structures.

Table E-4. Secondary endpoints for BBP and DEHP in aquatic organisms

Substance	Test organism	Duration of test (days)	Endpoint(s) observed	Effect concentration (mg/L) or dose (mg/kg)	Reference
BBP	Fathead minnow	126	VTG induction	> 0.0675 mg/L	Study Submission 2014d; ECHA c2007–2014e
BBP	Fathead minnow	21	Fecundity GSI VTG induction Male secondary sex characteristics	> 0.071 mg/L	Harries et al. 2000
BBP	Rainbow trout	18	VTG induction	500 mg/kg	Christiansen et al. 2000
BBP	Rainbow trout	7	Abundance of hepatic estrogen receptors Zona radiata protein induction	> 50 mg/kg	Knudsen et al. 1998
BBP	Transgenic medaka, *Oryzias melastigma*, eleuthero embryos	1	Green fluorescence signal	1.5 mg/L	Chen et al. 2014
BBP	Rainbow trout, liver estrogen receptor	N/A, *in vitro* test	Reduced binding of E2 by	0.3 mg/L (reported as	Jobling et al. 1995

			approximately 40%	10^{-6} M)	
BBP	Rainbow trout, *Oncorhynchus mykiss*, liver estrogen receptor	N/A, *in vitro* test	Produced 10–25% displacement of specifically bound E2	51.5 mg/L (reported as 165 µM)	Knudsen and Pottinger 1999
BBP	Rainbow trout, *Oncorhynchus mykiss*, plasma sex steroid-binding protein	N/A, *in vitro* test	Inhibition of 50% of E2 binding to sex steroid-binding protein	1124 mg/L (reported as 3.6×10^{-3} M)	Tollefsen 2002
BBP	African clawed frog, *Xenopus laevis*, estrogen receptor	N/A, *in vitro* test	Inhibition of 50% of E2 binding to ERα	7.4 mg/L (reported as 1.9×10^{-5} M)	Suzuki et al. 2004
BBP	*Xenopus laevis*	N/A, *in vitro* test	VTG induction	> 31 mg/L (reported as 1×10^{-4} M)	Norman et al. 2006
BBP	*Xenopus laevis*	N/A, *in vitro* test	50% inhibition of T_3-dependent luciferase activity	12.5 mg/L (reported as 40 µM)	Sugiyama et al. 2005
BBP	*Xenopus laevis*	N/A, *in vitro* test	> 50% inhibition of TRβ transcript	1.25 mg/L (reported as 4 µM)	Sugiyama et al. 2005
BBP	*Xenopus laevis* tadpoles	5	48% inhibition of TRβ transcript	1.25 mg/L (reported as 4 µM)	Sugiyama et al. 2005
DEHP	Japanese medaka, *Oryzias latipes*	5	VTG induction	> 0.1 mg/L	Kim et al. 2002[1]
DEHP	Japanese medaka, *Oryzias latipes*	3 months	VTG induction	> 0.05 mg/L (males)[2] 0.001 mg/L (females)[2]	Kim et al. 2002
DEHP	Japanese medaka,	3 months	GSI	0.01 mg/L	Kim et al. 2002

	Oryzias latipes			(females) > 0.05 mg/L (males)	
DEHP	Japanese medaka, *Oryzias latipes*	3 months	Histological analysis – oocytes Histological analysis – testes	0.001 mg/L > 0.05 mg/L	Kim et al. 2002
DEHP	Fathead minnow, *Pimephales promelas* (female)	472	VTG induction	0.005 mg/L in water and 125 mg/kg in food	ECHA c2007–2014f
DEHP	Fathead minnow, *Pimephales promelas* (male)	472	VTG induction	Not statistically significant	ECHA c2007–2014f
DEHP	Zebrafish, *Danio rerio* (female)	21	VTG induction	2×10^{-5} mg/L	Carnevali et al. 2010
DEHP	Zebrafish, *Danio rerio* (female)	21	Increase in GSI	Not statistically significant	Carnevali et al. 2010
DEHP	Chinese rare minnow, *Gobiocypris rarus*	21	VTG induction	LOEC 0.0128 mg/L (female) LOEC 0.0394 mg/L (male)	Wang et al. 2013[1]
DEHP	Chinese rare minnow, *Gobiocypris rarus*	21	GSI increase	0.117 mg/L (male and female)	Wang et al. 2013[1]
DEHP	Chinese rare minnow, *Gobiocypris rarus*	21	Increase in T/E2 ratio (female) and decrease in T/E2 ratio (male)	0.0394 mg/L	Wang et al. 2013[1]
DEHP	Marine medaka, *Oryzias*	6 months	VTG induction	0.1 mg/L	Ye et al. 2014[1]

	melastigma		(male) Decrease in T/E2 ratio (male) Histological changes (male and female)		
DEHP	Atlantic salmon, *Salmo salar*	4 months (28 days of exposure)	HSI Increased incidence of intersex fish	> 1500 mg/kg 1500 mg/kg	Norman et al. 2007
DEHP	Atlantic salmon, *Salmo salar* (IP injection)	17	VTG induction	> 160 mg/kg bw	Norrgren et al. 1999
DEHP	Zebrafish, *Danio rerio* (IP injection)	10	HSI VTG induction	5000 mg/kg	Uren-Webster et al. 2010
DEHP	*Xenopus laevis*	N/A, *in vitro* test	50% inhibition of T_3-dependent luciferase activity	> 19.53 mg/L (reported as > 50 µM)	Sugiyama et al. 2005
DEHP	*Xenopus laevis*	N/A, *in vitro* test	29% inhibition of TRβ transcript	19.53 mg/L (reported as 50 µM)	Sugiyama et al. 2005
DCHP	*Xenopus laevis*	N/A, *in vitro* test	50% inhibition of T_3-dependent luciferase activity	0.43 mg/L (reported as 11 µM)	Sugiyama et al. 2005
DCHP	*Xenopus laevis*	N/A, *in vitro* test	42% inhibition of TRβ transcript	6.6 mg/L (reported as 20 µM)	Sugiyama et al. 2005

Abbreviation: N/A = not applicable (duration not applicable in *in vitro* tests)

Appendix F-1. Estimates of daily intake

Table F-1a: Central tendency and (upper-bounding) estimates of daily intake of DIBP by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Ambient air[i]	< 0.001	< 0.001	< 0.001	< 0.001 (0.0014)	< 0.001 (0.0011)	< 0.001	< 0.001	< 0.001
Indoor air[j]	0.032 (0.42)	0.032 (0.42)	0.032 (0.42)	0.068 (0.89)	0.053 (0.70)	0.030 (0.40)	0.026 (0.34)	0.023 (0.30)
Drinking water[k]	-	-	-	-	-	-	-	-
Food and beverages[l]	1.5 (5.4)	F (0.12)	F (0.12)	0.024 (0.065)	0.018 (0.048)	0.011 (0.034)	0.004 (0.017)	0.0033 (0.012)
Soil[m]	-	-	-	-	-	-	-	-
Dust[n]	0.026 (0.081)	0.026 (0.081)	0.026 (0.081)	0.018 (0.057)	0.0087 (0.027)	< 0.001	< 0.001	< 0.001
Total oral intake	**1.6 (5.9)**	**0.058 (0.62)**	**0.058 (0.62)**	**0.11 (1.0)**	**0.080 (0.78)**	**0.041 (0.43)**	**0.03 (0.36)**	**0.026 (0.31)**

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the < 6 months age group, as presented in Table F1b, were used to represent dietary intake for this age group (applicable to formula- and non-formula-fed group).

[b] Infants 0-6 months assumed to ingest 0.742 litre breast milk/day (USEPA, 2011). Fromme et al. (2011) reported both the concentration of the parent compound (DIBP) and its metabolite (MIBP) in breast milk in Germany. These data were used as an analogue here. The median (11.8 µg/L) and maximum (43.8 µg/L) values for MIBP were used for exposure characterization. In this case, the metabolite (MIBP) concentration was used with a correction factor (ratio of parent MW/metabolite MW). Health Canada detected DIBP in 8% of 305 breast milk samples (personal communication FD to ESRAB November 2014). These data were not used to quantify intakes as it is thought that a majority of DIBP will metabolize to the MIBP quickly; thus, MIBP is expected to be found at greater quantities (and higher detection frequency) than DIBP in breast milk (Koch et al. 2012). MIBP was not analyzed in the MIREC samples.

[c] Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Formula concentrations obtained from Bradley et al. 2013b – DIBP were detected in 1 out of 16 formula samples: concentration of 13 µg/kg.

[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the 1–3-year age group, as presented in Table F1b, were used to represent dietary intake for this age group.

[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the 4–8-year age group, as presented in Table F1b, were used to represent dietary intake for this age group.

[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 9–13-year age group, as presented in Table F1b, were used to represent dietary intake for this age group.

[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 19–30-year age group, as presented in Table F1b, were used to represent dietary intake for this age group.

[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 51–70-year age group, as presented in Table F1b, were used to represent dietary intake for this age group.

[i] No Canadian data measuring DIBP in ambient air were identified. Rudel et al. 2010 measured DIBP in outdoor samples (40 homes) in N. California. Concentrations used in exposure characterization – median: 0.0036µg/m3, maximum: 0.018 µg/m3.

[j] No Canadian data measuring DIBP in indoor air were identified. Rudel et al. 2010 measured DIBP in (40 homes) in N. California. Median (0.13 µg/m3) and maximum (1.7 µg/m3) concentrations were used in exposure characterization.

[k] No data were identified regarding phthalate concentrations in drinking water. DIBP levels in a Canadian bottled water survey (Cao 2008) were used for semi-quantitative exposure characterization; the range of the highest exposure group is presented in the text.

[l] Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix F-2 (see Table F-1a). Note gender and age groups do not fully match; therefore, the highest intake from within an age group was input into the table: e.g., male intakes (51–70 years) were input into the 60+ (unisex) column because this age group had the highest intake of all the groups in the 51–71-year range. F, notates significant variation; therefore, estimates not presented.

[m] No data on the levels of DIBP in soil were identified in Canada or elsewhere.

[n] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DIBP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (5.17 µg/g) and 95th percentile (16.2 µg/g) of DIBP in indoor dust, was used for exposure characterization (Kubwabo et al. 2013).

Table F-1b – Probabilistic estimates of daily intake of DIBP from food (µg/kg/day)

DRI group	Median	90th percentile
< 6 months	F	0.12[a]
6 months–1 yr	0.021	0.076 [a]
1–3 yrs	0.024	0.065
4–8 yrs	0.018	0.048
M: 9–13 yrs	0.011	0.034
F: 9–13 yrs	0.0093	0.029
M: 14–18 yrs	0.0067	0.026
F: 14–18 yrs	0.0050	0.018
M: 19–30 yrs	0.0040	0.017
F: 19–30 yrs	0.0042	0.016
M: 31–50 yrs	0.0039	0.015
F: 31–50 yrs	0.0034	0.013
M: 51–70 yrs	0.0033	0.012
F: 51–70 yrs	0.0027	0.011
M: > 71 yrs	0.0030	0.0011
F: > 71 yrs	0.0031	0.0011

[a] These values should be interpreted with caution, cumulative variation > 16%.
F these values have been suppressed, cumulative variation > 33%.

Table F-2. Central tendency and (upper-bounding) estimates of daily intake of DCHP by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula- fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Indoor air[k]	< 0.001 (0.069)	< 0.0010(0.069)	< 0.001 (0.069)	0.0018-0.15	0.0014 (0.12)	< 0.001 (0.065)	< 0.001 (0.056)	< 0.001 (0.049)
Dust[o]	0.0010 (0.0051)	0.0010 (0.0051)	0.0010 (0.0051)	< 0.001 (0.0035)	< 0.001 (0.0017)	< 0.001	< 0.001	< 0.001
Total oral intake	**0.0010 (0.074)**	**0.0010 (0.074)**	**0.0010 (0.074)**	**0.0018 (0.15)**	**0.0014 (0.12)**	**< 0.001 (0.065)**	**< 0.001 (0.056)**	**< 0.001 (0.049)**

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] P4 study data indicate that MCHP (metabolite of DCHP) was not detected in any breast milk samples (n = 56) (unpublished data, personal communication in Sept 2013).
[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[i] No data, Canadian or otherwise measuring DCHP in ambient air was identified. Therefore, due to lack of data, intakes were not generated (marked as "-").
[j] Scientific notation is included in parentheses for values that were not true zeros or were rounded.
[k] DCHP was measured in 102 samples in Cape Cod and was detected at a frequency of 21% (DL: 2 ng/m3, range: ND–280 ng/m3).
[l] No data on the levels of DCHP in drinking water were identified in Canada or elsewhere. Therefore, due to lack of data, intakes were not generated (marked as "-").
[m] Estimates of exposure from probabilistic analyses show that intake from food, for DCHP, is negligible. Therefore, not presented and marked as " - ".
[n] No data, Canadian or otherwise, measuring DCHP in soil were identified. Therefore, due to lack of data, intakes were not generated (marked as "-").
[o] The amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (0.21 µg/g) and 95th percentile (3.4 µg/g) concentrations of DCHP were used for exposure characterization (Kubwabo et al. 2013).

Table F-3. Central tendency and (upper-bounding) estimates of daily intake of DMCHP by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Dust[i]	0.0027 (0.054)	0.0027 (0.054)	0.0027 (0.054)	0.0018 (0.038)	< 0.001 (0.018)	< 0.001	< 0.001	< 0.001

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] No data were identified for DMCHP or its metabolites in breast milk
[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[i] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DMCHP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (0.53 µg/g) and 95th percentile (10.7 µg/g) were used for exposure characterization (Kubwabo et al. 2013).

Table F-4. Central tendency and (upper-bounding) estimates of daily intake of DBzP by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Dust[i]	0.016 (0.097)	0.016 (0.097)	0.016 (0.097)	0.011 (0.068)	0.0051 (0.032)	< 0.001 (0.0011)	< 0.001 (0.0011)	< 0.001 (0.0011)

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] No data were identified for DBzP or its metabolites in breast milk.
[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

[i] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DBzP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (3.09 µg/g) and 95th percentile (19.1 µg/g) were used for exposure characterization (Kubwabo et al. 2013).

Table F-5. Central tendency and (upper-bounding) estimates of daily intake of B84P using B79P as an analogue by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breastfed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Dust[i]	0.0063 (0.047)	0.0063 (0.047)	0.0063 (0.047)	0.0044 (0.033)	0.0020 (0.015)	< 0.001	< 0.001	< 0.001

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] No data were identified for B84P or its metabolites in breast milk
[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[i] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (1.2 µg/g) and 95th percentile (9.2 µg/g) were used for exposure characterization (Kubwabo et al. 2013).

Table F-6. Central tendency and (upper-bounding) estimates of daily intake of DIHepP by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Dust[i]	0.096 (1.1)	0.096 (1.1)	0.096 (1.1)	0.067 (0.79)	0.032 (0.37)	0.0011 (0.013)	0.0011 (0.013)	0.0011 (0.012)

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] No data were identified for DIHepP or its metabolites in breast milk [c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[i] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DIHepP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (18.9 µg/g) and 95th percentile (222.5 µg/g) were used for exposure characterization (Kubwabo et al. 2013).

Table F-7. Central tendency and (upper-bounding) estimates of daily intake of B79P by various age groups (µg/kg-bw per day)

Route of exposure	0–0.5 year[a] Breast fed[b]	0–0.5 year[a] Formula-fed[c]	0–0.5 year[a] Not formula-fed	0.5–4 years[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
Dust[i]	0.0063 (0.047)	0.0063 (0.047)	0.0063 (0.047)	0.0044 (0.033)	0.0020 (0.015)	< 0.001	< 0.001	< 0.001

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[b] No data were identified for B79P or its metabolites in breast milk
[c] Formula-fed infants are assumed to have an intake rate of 0.75 kg of formula per day.
[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
[i] The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (1.2 µg/g) and 95th percentile (9.2 µg/g) were used for exposure characterization (Kubwabo et al. 2013).

Appendix F-2: Derivation of dietary intakes

Occurrence data – DIBP and DCHP

Occurrence data for DIBP and DCHP were obtained from an American total diet study (Schecter et al. 2013), and any data gaps were filled using data from a British total diet study (Bradley et al. 2013b). Occurrence data for these two phthalates, in food, that was reported as less than the analytical LOD were assigned values of ½ LOD. However, a value of 0 (zero) was assigned to all samples within a broad food category when no phthalates were detected above the LOD in any sample in that category.

Food consumption data and matching to occurrence data

The phthalate concentrations in individual foods were matched to consumption figures for these foods from the Canadian Community Health Survey (CCHS) B Cycle 2.2 on Nutrition (Statistics Canada 2004) to generate distributions of phthalate exposure for various age-sex groups. The CCHS included 24-hour dietary recall information for over 35 000 respondents of all ages across Canada.

If a food line item belonged to a recipe that was matched to a set of the assayed foods, then the associated phthalate levels matched to the recipe were assigned to the ingredient. Otherwise, if the food line item itself matched to a set of the assayed foods then the phthalate levels matched to the food line item were assigned. For DIBP and DCHP, 989 foods and 23 recipes were matched with assayed foods.

Body weight information

For the purpose of determining per kilogram body weight exposure estimates, infant body weights were set to the mean body weights, as derived from the body weight data from the United States Department of Agriculture Continuing Survey of Food Intakes by Individuals (CSFII; 1994–96, 1998). For all age groups, body weights reported in the CCHS, whether measured or self-reported, were used and, where missing, were imputed using the median for the corresponding age-sex group and quintile of energy intake.

Probabilistic exposure assessment

For each food consumed by a respondent in the CCHS survey, phthalate concentrations were randomly selected from the matching list of assayed values. For each individual respondent, exposure estimates from each food were summed, generating a distribution of exposure for all respondents. This was repeated 500 times (500 iterations) to model the variability of the distribution of exposures due to the variability of the phthalates levels. For each age-sex group, the median and 90th percentile exposures were derived from the empirical distribution generated by the 500 iterations.

Appendix G. Derivation of daily intakes for DIBP based on biomonitoring

P4 pregnant women and MIREC CD+ infants:

$$\text{DIBP daily intake}\left(^{\mu g}/_{\text{kg bw. day}}\right) = \frac{C_{SUM}\left(\frac{\text{moles}}{\text{g Cr}}\right) \times \text{CER} \times \text{MW of DIBP}}{FUE_{Sum} \times BW}$$

Where, $C_{SUM}\left(\frac{\text{moles}}{\text{g Cr}}\right)$ = Sum of molar concentrations of metabolites, CER: 24 hour creatinine excretion rate (estimated using the Mage Equation), FUE_{Sum}: Sum of FUE of the metabolites = 0.91, MW of DIBP= 278

Step 1: Conversion of concentrations

$$C_{metabolite}\left(\frac{moles}{g\ Cr}\right) = \frac{C_{metabolite}\ (^{\mu g}/_{g\ Cr})}{MW_{metabolite}}$$

$$C_{MIBP}\left(\frac{moles}{g\ Cr}\right) = \frac{C_{MIBP}\ (^{\mu g}/_{g\ Cr})}{222\ g/mol}$$

$$C_{2OH-MIBP}\left(\frac{moles}{g\ Cr}\right) = \frac{C_{2OH-MIBP}\ (^{\mu g}/_{g\ Cr})}{239\ g/mol}$$

Step 2: Sum the concentrations from Step 1

$$C_{SUM}\left(\frac{moles}{g\ Cr}\right) = \Sigma\ C_{MIBP} + C_{2OH-MIBP}$$

Step 3: Sum FUEs
FUEs for MIBP and 2OH - MIBP are 0.71 and 0.195, respectively. Therefore, the sum would be 0.91.

Step 4: Compute DI for DIBP using Equation 1.

CHMS

Statistical analysis: The data were analyzed with SAS 9.2 (SAS Institute Inc., USA) and SUDAAN 10.0.1 software (RTI International, USA). Variance estimates were produced using bootstrap weights, taking into account the 11 degrees of freedom for cycle 1 and 13 degrees of freedom for cycle 2, as suggested in the CHMS data user guide. All analyses were weighted using the CHMS cycle 1 survey weights (phthalate subsample) and CHMS cycle 2 survey weights (environmental urine subsample) in order to be representative of the Canadian population. Phthalate concentrations that were below LOD were assigned a value of LOD/2.

Estimation of creatinine excretion rate (CER): For each study, the participant creatinine excretion rate was calculated using the Mage equations (Huber et al. 2010). The adiposity adjustment (discussed in the supplemental information [Huber et al. 2010]) was applied for all participants, and the body surface area adjustment was applied for children under the age of 18. Median BMIs by age for the adiposity adjustment were computed using the entire CHMS sample. The CHMS phthalate subsample dataset had 174 children who exceeded height limits in the Mage equations (186 cm for males and 172 cm for females). The Mage equations were applied directly to the observed heights in order to extrapolate creatinine excretion rates for these participants. The predicted excretion rates for these individuals appeared to be reasonable despite the extrapolation.

Daily intake estimation: The daily intake of DIBP, based on urinary concentrations of the monoester MIBP, was estimated for each participant using the following equation (David et al. 2000; Koch et al. 2007):

Equation 1

$$\text{Daily intake } (\mu g/kg\ BW/day) = \frac{UC_{Cr}\left(\frac{\mu g}{g\ Cr}\right) \times CER\left(\frac{g}{day}\right)}{BW\ (kg) \times FUE} \times \frac{MW_D}{MW_M}$$

The fractional urinary excretion (FUE) is defined as the fraction of the diester exposure dose excreted as metabolites in urine, calculated on a mole basis. For the calculation, an FUE of 0.71 for MIBP was used (Koch et al. 2012). MW_D and MW_M are the molecular weights of the diester (DIBP: 278 g/mol) and the monoester (MIBP: 222 g/mol), respectively.

Arithmetic and geometric means, and selected percentiles along with their 95% confidence intervals of daily intake, were produced for the Canadian population by age group, sex and fasting status. Descriptive statistics were computed using SUDAAN proc DESCRIPT and SAS proc SURVEYREG.

Appendix H. Summary of toxicokinetics of medium-chain phthalates (MCPs)

A review of the available literature indicates that almost all *in vivo* studies on the toxicokinetics of medium-chain phthalates (MCPs) have been conducted via oral and dermal routes (only one inhalation study was found). Several *in vitro* studies were found, mainly investigating dermal absorption (cell diffusion), intestinal absorption (everted gut) and metabolism (microsomal preparations, tissue homogenates from liver, kidney, intestines, testes, plasma and purified enzymes). Most studies have been conducted with Di-(2-ethylhexyl) phthalate (DEHP) in rats, but some studies have examined the toxicokinetics of medium-chain phthalates in other rodents and non-rodent species.

Oral route

There is evidence that phthalates, regardless of chain length, are absorbed from the gastrointestinal (GI) tract after oral exposure. However, several studies have shown that the extent of absorption of phthalates in the GI tract of rats was not linear with increasing dose, likely due to saturation of the mechanism of uptake or of the diester hydrolysis, particularly for the phthalates with long carbon chains on the ester linkage. Similarities and differences are seen across the phthalates with respect to metabolism and chain length. The smaller phthalates undergo hydrolysis to their respective monoester in the GI tract and are excreted without further metabolism. Larger

phthalates, such as medium-chain phthalates, undergo hydrolysis in the GI tract to their respective monoester but can also undergo further oxidative metabolism to other metabolites and be excreted as such or as conjugates.

Absorption

Three human studies regarding oral absorption of DEHP were found. There is variability in the rates of absorption reported in these low-dose studies (≥ 70% over 44 hours at 0.005–0.65 mg/kg [Koch et al. 2005], 70–89% over 36 hours at 3 mg/person [Kurata et al. 2012a] and 11–25% over 24–58 hours at < 0.5 mg/kg [Schmid and Schlatter 1985]). All of the studies in animals were conducted at higher doses (2.90–2800 mg/kg) and, due to possible saturation at high doses, may not be directly comparable. However, at low doses (2.9 mg/kg in rat; Daniel and Bratt 1974) and at relatively low doses in other animals (50–100 mg/kg in monkeys, marmosets, rats, dogs and pigs), the absorption rates (56–66% and 30–50%, respectively, in urine) were in the same range as those reported in humans at very low doses (Short et al. 1987; Ikeda et al. 1980; Rhodes et al. 1986; Lhuguenot et al. 1985). Consequently, the data available do not provide evidence of strong differences between the absorption of DEHP in the GI tract of humans and of other mammals. See Table 1 for a summary of the absorption rates of DEHP in animals and humans.

Similar to DEHP, human studies for other phthalates (DBP, BBP and DIBP) were conducted at very low doses (< 1.3 mg/kg), while animal studies were usually conducted at doses higher than 50 mg/kg, with the exception of one study with BBP (Eigenberg et al. 1986a). BBP is the only phthalate with data at low doses in both humans and animals, and a comparison of their absorption rates indicates that absorption is similar in both species (67–84% over 24 hours in humans vs. 70–80% over 96 hours in rats) (Anderson et al. 2001; Eigenberg et al. 1986a). For DBP, the values obtained in humans (69–92% over 8–48 hours at 0.255–5 mg/kg) were also comparable to those obtained in rats at the lowest tested doses (77–96% over 24–48 hours at 100 mg/kg) (Williams and Blanchfield 1975; Fennell et al. 2004; Seckin et al. 2009; Anderson et al. 2001; Koch et al. 2012). A more recent study by Koch et al. (2012) using one male volunteer determined that approximately 92% of the orally administered dose of DBP was excreted within the first 24 hours, while only < 1% of the dose was excreted in urine after 48 hours. See Table E-1 for a summary of the absorption rates of other phthalates studied in animals and humans.

Several studies have shown that the absorption of phthalates in the GI tract of rats and marmosets was not linear with increasing dose. This might be due to saturation of the mechanism of uptake or of the diester hydrolysis. At environmental levels, DBP is most likely absorbed as MBP in the GI tract of rats due to the high lipase enzyme activity *in situ*. At relatively high doses (100–250 mg/kg), however, direct absorption of the unhydrolyzed phthalate most likely occurs due to enzymatic saturation (Silva et al. 2007a). Saillenfait et al. (1998) also showed that at a dose of 500 mg/kg of DBP, 60% of DBP was absorbed, whereas only 48% was absorbed at a dose of 1500 mg/kg (based on urinary excretion over 48 hours). An even greater discrepancy was reported by

Eigenberg et al. (1986a), with 70–80% absorption at 2–200 mg/kg and only 22% at 2000 mg/kg (based on urinary excretion over 96 hours) for BBP.

Similar observations were done with DEHP administered to marmosets, with a 2-fold increase in absorption for a 20-fold increase in dose (Rhodes et al. 1986). More recently, Kurata et al. (2012a) observed a ~3.5-fold drop in absorption of DEHP with a 25-fold increase in dose in marmosets based on plasma concentrations (AUC_{all}). With BBP administered to rats, saturation seemed to occur between 475 and 780 mg/kg, since absorption rates were 58, 54, 43 and 30% (based on urinary excretion over 24 hours) at 150, 475, 780 and 1500 mg/kg of BBP, respectively (Nativelle et al. 1999).

Absorption also seems to differ with respect to the age of the animal. Plasmatic MEHP levels were measured after repeated exposure to DEHP (1000 mg/kg/day) in rats of different ages (25, 40 and 60 days old) for 14 days. The mean plasmatic AUC of MEHP in the youngest age group was reported to be twice as high as in the two older groups (Sjoberg et al. 1986). It was suggested by Sjoberg et al. (1985a) that absorption is greater in young rats when DEHP is orally administered. The authors proposed that this may be related to the higher relative proportion of intestinal tissue to body weight and to the higher blood flow through the intestinal tissue in young rats compared to older rats. This may occur in humans since blood flow decreases with age, but experimental evidence on age differences in absorption is non-existent. However, recent work by Kurata et al. (2012a) examining the toxicokinetics of DEHP in 3-month-old and 18-month-old marmosets did not detect any age-related differences in absorption as measured by plasma concentrations.

Table H-1. Summary of oral absorption percentages for medium-chain phthalates

Substance	Species	Dose[a]	Basis	Absorption (% of dose)	Reference
DEHP	Cynomolgus monkey	100 mg/kg	Urine	At least 30% over 24 h	Short et al. 1987
DEHP	Cynomolgus monkey	100 mg/kg (after daily pre-treatment at 100 mg/kg for 21 days)	Urine	About 40% over 4 days	Short et al. 1987
DEHP	Cynomolgus monkey	500 mg/kg (daily pre-treatment at 500 mg/kg for 21 days)	Urine	About 10% over 4 days	Short et al. 1987
DEHP	Dog	50 mg/kg (after daily pre-treatment at 50 mg/kg for 21–28 days)	Urine + bile	30% over 4 days	Ikeda et al. 1980
DEHP	Human	0.0047/0.0287/ 0.65 mg/kg	Urine	At least 70% in 44 h	Koch et al. 2005

Substance	Species	Dose[a]	Basis	Absorption (% of dose)	Reference
DEHP	Human	30 mg (< 0.5 mg/kg)	Urine	At least 11–25% over 24–58 h	Schmid and Schlatter 1985
DEHP	Human	0.31 and 2.8 mg	Urine	47.1 +/- 8.5% in 48h	Anderson et al. 2011
DEHP	Human	3 mg/person	Urine	69-86% (male) and 80–89% (female) in 36 h	Kurata et al. 2012b
DEHP	Marmoset	100 mg/kg	Urine Urine + bile	17% over 8 h 30% over 3 days, 45% over 7 days	Rhodes et al. 1986
DEHP	Marmoset	2000 mg/kg	Urine	4% over 7 days	Rhodes et al. 1986
DEHP	Marmoset	Daily 2000 mg/kg on days 5 and 14	Urine	2% over 24 h following days 5 and 14	Rhodes et al. 1986
DEHP	Marmoset	100 and 2500 mg/kg	Urine	18.3% and 9.9% over 7 days	Kurata et al. 2012a
DEHP	Pig	50 mg/kg (after daily pre-treatment at 50 mg/kg for 21–28 days)	Urine	37% over 24 h, 75% over 4 days	Ikeda et al. 1980
DEHP	Rat	100 mg/kg	Urine	58% over 24 h	Kurata et al. 2012a
DEHP	Rat	0.001% diet 0.1% diet 0.2% diet	Urine	95% over 15 days 95% over 15 days 91.92% over 15 days	Williams and Blanchfield 1974
DEHP	Rat	1.36 µCi	Urine	33% over 24 h, 47.3% over 3 days	Tanaka et al. 1975
DEHP	Rat	100 mg/kg	Urine	30% over 24 h	Short et al. 1987
DEHP	Rat	1000 mg/kg	Urine	50–65% over 24 h, 53–70%	Williams and

Substance	Species	Dose[a]	Basis	Absorption (% of dose)	Reference
				over 8 days	Blanchfield 1974
DEHP	Rat	1000 mg/kg	Urine	44% (25-day-old rats) over 3 days 26% (60-day-old rats) over 3 days	Sjoberg et al. 1985a
DEHP	Rat	1000/6000/ 12 000 ppm	Urine	At least 50–70% over 4 days	Short et al. 1987
DEHP	Rat	2.9 mg/kg 2.9 mg/kg (after 7 days, pre-treatment with 1000 ppm DEHP in diet)	Urine + bile	56% over 7 days 66% over 7 days	Daniel and Bratt 1974
DEHP	Rat	200 mg/kg	Urine	34% over 24 h	Schulz and Rubin 1973
DEHP	Rat	2800 mg/kg	Urine	At least 20% over 72 h	Teirlynck and Belpaire 1985
DEHP	Rat	50 mg/kg (after daily 50 mg/kg for 21–28 days)	Urine	27% over 24 h	Ikeda et al. 1980
DEHP	Rat	50 mg/kg/day for 3 days	Urine	49% over 4 days	Lhuguenot et al. 1985
DEHP	Rat	500 mg/kg/day for 3 days	Urine	63% over 4 days	Lhuguenot et al. 1985
DEHP	Rat	800 mg/kg	Urine	49–79% over 8 days	Williams and Blanchfield 1974
DEHP	Rat	Daily 2000 mg/kg for 14 days	Urine	50% over 24 h following days 5 and 14	Rhodes et al. 1986
BBP	Human	253 µg (< 0.05 m/kg) 506 µg (< 0.01 m/kg)	Urine	67% over 24 h 84% over 24 h	Anderson et al. 2001

Substance	Species	Dose[a]	Basis	Absorption (% of dose)	Reference
BBP	Rat	2, 20, 200 mg/kg 2000 mg/kg	Urine	70–80% over 96 h 22% over 96 h	Eigenberg et al. 1986a
BBP	Rat	150 mg/kg 475 mg/kg 780 mg/kg 1500 mg/kg	Urine	58% over 24 h 54% over 24 h 43% over 24 h 30% over 24 h	Nativelle et al. 1999
DBP	Hamster	270– 2310 mg/kg	Urine	93.5% over 48 h	Williams and Blanchfield 1975
DBP	Human	3600 µg (< 0.18 mg/kg)	Urine	64% over 8 h	Seckin et al. 2009
DBP	Human	250 µg (< 0.05 mg/kg) 510 µg (< 0.01 mg/kg)	Urine Urine	64% over 24 h 73% over 24 h	Anderson et al. 2001
DBP	Human	5 mg total (0.06 mg/kg)	Urine	92.2% over 24 h	Koch et al. 2012
DBP	Rat	Twice 0.2 ml (85% radioactive; at 24 h interval)	Urine	24.6% over 48 h	Albro and Moore 1974
DBP	Rat	200 mg/kg	Urine	63% over 24 h	Foster et al. 1983
DBP	Rat	100–130 mg/kg	Urine	96% over 48 h	Williams and Blanchfield 1975
DBP	Rat	100 mg/kg	Urine	77% over 24 h	Fennell et al. 2004
DBP	Rat	500 mg/kg 1500 mg/kg	Urine	60% over 48 h 48% over 48 h	Saillenfait et al. 1998
DIHepP	Rat	250 mg/kg	Urine + bile	75% over 4 days bile and 7 day urine	Sato et al. 1984
DIBP	Human	5.38 mg (0.06 mg/kg)	Urine	90.3% over 24 h	Koch et al. 2012

[a] For human subjects, doses provided were converted into mg/kg to allow comparison with other species. The body weight used (not provided in the studies) was arbitrarily set to 50 kg.

Distribution

Distribution of medium-chain phthalate compounds after oral absorption was studied *in vivo* in several rodent (rat and mice) and non-rodent (dog, pig, marmoset, cynomolgus monkey and human) species mainly for two phthalates: DBP and DEHP. Overall, it appears as though adipose tissues, absorptive organs and excretory organs are the major initial repositories for the dialkyl esters, with distribution through the body at varying levels according to the phthalate administered, the dose and the species used. Several studies have also examined the distribution of phthalates in pregnant animals and fetuses. Most human studies refer to biomonitoring of phthalates in serum, amniotic fluid or breast milk within the general population (environmental exposure).

A dietary study conducted in rats (1000 ppm labelled DBP in diet) showed particularly high radioactivity in the liver but also in kidney and adipose tissue. The radioactivity persisted after 96 hours in the adipose tissue, while it disappeared rapidly from the other tissues after termination of exposure. Data also suggested an accumulation, after four weeks of exposure (compared to one day) in testes (1.6 vs. 0.3 µg/g) and in adipose tissue (11.2 vs. 8.35 µg/g) in rats (Williams and Blanchfield 1975). More recent work using rats has shown that DBP is rapidly distributed (distribution half-life of 5.77 min) after administration (30 mg/kg, *i.v.*) and undetectable in the plasma with low cumulative fecal excretion after oral administration (100 mg/kg, oral gavage) after 48 hours (Chang et al. 2013).

In studies conducted in animals that were exposed repeatedly, there was no evidence of accumulation of the monoester of DEHP in plasma. Phokha et al. (2002) reported no cumulative effect on the area under the curve (AUC) of the monoester MEHP in rats after repeated oral administrations of DEHP (500 mg/kg/day, in aqueous emulsion). In a study by Clewell et al. (2009), peak MBP concentrations in maternal and fetal plasma from rats exposed to DBP (0, 50, 100 and 500 mg/kg, in corn oil) on GD12–19 were 67 and 55% lower than those after a single dose (0 or 500 mg/kg, in corn oil).

Tissue distribution of DEHP may be governed by its lipophilicity since higher concentrations occurred in adipose tissue compared to liver in rats administered DEHP (0 or 5000 ppm in diet) for 13 weeks (Poon et al. 1997). At the end of the study, the levels in adipose tissue were 23 ppm (males) and 31 ppm (females), compared to a barely detectable level (3 ppm) in the liver for both sexes.

Although most studies have shown that the liver and kidneys are initially the most common retention repositories in rats (Williams and Blanchfield 1974, 1975), radioactivity accumulation in muscles was also documented. Tanaka et al. (1975) showed that after a single oral administration of 500 mg/kg of radiolabelled DEHP, the distribution of radioactivity was in the following order after 3 hours: intestine (C_{max} = 51%) > muscle (4.86%) > liver (2.75%) > other organs. Excretion of DEHP appeared to be delayed in adipose tissue.

In a species comparison study, a single oral dose of labelled DEHP (50 mg/kg) administered to rats, dogs and miniature pigs showed that distribution of radioactivity in pigs and rats was similar (high radioactivity in the liver and the adipose tissues at 4 hours, with a steady decline thereafter). Dogs showed a different pattern, with radioactivity initially high in the liver and muscles, whereas radioactivity in the adipose tissue was very low (Ikeda et al. 1980). In another study, oral exposure of rats to ^{14}C-DEHP labelled in the phenyl ring (2000 mg/kg/day) for 14 days demonstrated the magnitude of tissue distribution in the following order: liver (205 µg/g of DEHP equivalent) > kidney (105 µg/g) > blood (60 µg/g) > testes (40 µg/g) (Rhodes et al. 1986).

Distribution appeared different in monkeys exposed under the same conditions as described above; their tissue concentrations were lower (10–15% of the amounts in rats) and the levels of DEHP equivalent were as follows: testes (3.75 µg/g) > kidney (3 µg/g) > liver (2.5 µg/g) > blood (1 µg/g) (Short et al. 1987). In juvenile and adult marmosets, the highest radioactivity of orally administered ^{14}C-DEHP was found in the kidney 2 hours after dosing and was attributed to be the result of urine excretion (Kurata et al. 2012a). There was no abnormal distribution of radioactivity in the testis or other male reproductive organs.

Potential distribution to the fetus and infant

Daily oral administration of DEHP (750 mg/kg bw, in corn oil) in rats showed that the parent compound and its metabolites cross the placental barrier and reach the fetal gonads (Stroheker et al. 2006). However, fetal livers contained a major part of radioactivity (20–31%) and gonad levels were low (2–5%). More recently, Hayashi et al. (2012) measured hepatic MEHP levels in pregnant mice and their offspring and found that concentrations of this metabolite were 1.5 times higher in the liver of pregnant dams than those of postpartum mice. Further, MEHP concentrations in foetuses were 1.7 times higher than in pups at the same dose levels of DEHP (0.05%).

Fennell et al. (2004) showed the presence, in female rats, of MBP and its glucuronide levels in maternal plasma, foetal plasma and amniotic fluid. MBP concentrations were two- to four-fold higher in maternal plasma than in foetal plasma. In amniotic fluid, MBP is initially the major metabolite, but 24 hours after oral administration, MBP glucuronide became the major metabolite. The half-life reported was very different between free MBP (6–11 hours) and MBP glucuronide (up to 64 hours) (Fennell et al. 2004). A non-linear increase in MBP was observed in both maternal plasma (by ten-fold) and fetal plasma (by eight-fold), while the dose increased by only five-fold in rats administered DBP (100 or 250 mg/kg/day) on GD12–18 (Fennell et al. 2004). That MEHP and MBP are primarily unconjugated the day after the last dosing (while in maternal urine, both free and conjugated monoesters are important) was confirmed by Calafat et al. (2006a).

Since many studies indicate that DBP and its metabolites are rapidly cleared from the body, it was previously suggested that it was unlikely that DBP would be stored in

maternal tissues and released during pregnancy and lactation (Foster et al. 1982; Tanaka et al. 1978; Williams and Blanchfield 1975). Indeed, Saillenfait et al. (1998) showed that the amount of radioactivity in the embryo peaked at 0.12% of the total administered dose at 6 hours post-dosing and rapidly declined to undetectable levels thereafter, following a single oral dose of 1500 mg/kg [^{14}C]-DBP to pregnant rats on GD14.

The effect of repeated doses on the distribution of DBP metabolites in maternal tissues and amniotic fluid was studied by Clewell et al. (2009). Pregnant rats were exposed to DBP (0, 50, 100 and 500 mg/kg, in corn oil) on GD12–19. MBP concentrations in the amniotic fluid were reduced with repeated doses of DBP (at 500 mg/kg). MBP-glucuronide, however, was not decreased. In fact, the MBP-glucuronide concentrations in amniotic fluid were consistently higher in the repeated-dose study than in the single-dose study. Maternal liver MBP levels were also reduced after multiple exposures (the C_{max} for MBP after multiple doses was 72% of the value at single dose). Maternal liver MBP-glucuronide concentrations were not significantly different in the single- and repeated-dose groups.

The effect of dose on distribution of radioactivity from ^{14}C-DBP was also studied by Saillenfait et al. (1998). Rats were administrated a single oral dose of ^{14}C-DBP (500 or 1500 mg/kg, in mineral oil). In all tissues studied (maternal kidneys, liver, ovaries, stomach, intestine and uterus), C_{max} and AUC for MBP were higher at 1500 mg/kg than at 500 mg/kg. However, an increase of AUC was disproportionate in embryo and amniotic fluid, with an eight-fold increase in $AUC_{0-\infty}$ (interestingly, the high dose was embryotoxic), suggesting a more pronounced embryonic exposure to MBP at high doses. This was confirmed in a study by Calafat et al. (2006a). In this study, oral administration of DBP (0, 11, 33, 100 and 300 mg/kg/day) to pregnant rats showed that increasing doses resulted in increased concentration of metabolites in the amniotic fluid. There was also an exponential relationship between MEHP levels in amniotic fluid and maternal urine. A strong correlation between MEHP levels in amniotic fluid and maternal DEHP dose was reported when dams were administered DEHP (0, 11, 33, 100 or 300 mg/kg, in corn oil); pups were likely to receive some intact DEHP (Calafat et al. 2006a).

Silva et al. (2007b) showed a linear dose-related increase of serum concentrations of MBP and its oxidative metabolites (mono-n-hydroxybutyl phthalate [MHBP] and mono-(3-carboxypropyl) phthalate [MCPP]). There was a non-linear dose-related increase of MBP concentration in fetal amniotic fluid, the concentration in amniotic fluid being increased by approximately 10-fold (mean 1.4 µg/mL and 13.4 µg/mL, respectively), while the dose administered (100 and 250 mg/kg/day) differed by only 2.5-fold. However, the detection of MBP in amniotic fluid does not provide definitive evidence of MBP crossing the placenta (or of DBP metabolism in the fetus). According to Fennell et al. (2004), the rapid appearance of MBP and the delay in appearance of its glucuronide could indicate fetal metabolism of MBP at a much slower rate than by the mother, if in fact MBP glucuronide does not cross the placenta. Alternatively, it could be an indication that the MBP glucuronide does cross the placenta, but at a much slower rate than MBP.

When considering potential distribution of medium-chain phthalates during lactation, the increasing fat solubility of longer-chain phthalates may facilitate their higher segregation into maternal milk, since lipophilic chemicals readily partition into high fat materials (Main et al. 2006; Kluwe 1982). In a study where female rats received three daily administrations of DEHP (2000 mg/kg) on days 15–17 of lactation, DEHP was not detected in dam's plasma, whereas milk concentrations of DEHP were very high (216 µg/mL). This may be explained by the association of DEHP with lipoproteins in the plasma and with lipids in rat milk, or by uptake of lipoproteins by the mammary gland for milk synthesis (Dostal et al. 1987).

Species differences in distribution of phthalates during pregnancy have been examined in a study conducted in rats and marmosets. This work suggested that MEHP tissue burden may be smaller in marmoset fetuses than in those of rats, since at a similar daily dose (500 mg/kg), C_{max} and normalized AUC of MEHP in marmoset blood were up to 7.5- and 16-fold lower, respectively, than in rats (Kessler, et al. 2004).

Humans

In the general population, monoesters of phthalates were found in serum with a glucuronide distribution pattern similar to that in urine (Silva et al. 2003). This is in line with the results obtained in an experimental study conducted in one man administered a single oral dose of DEHP (Koch et al. 2005). However, a recent study by Kessler et al. (2012) found surprisingly high concentrations of the parent DEHP in the blood of male volunteers compared with animal data, and MEHP was detected almost immediately (15 min) after ingestion.

Several monoesters (MEP, MBP and MEHP) were found in human amniotic fluid at 2- to 3-fold lower levels than in serum (Silva et al. 2004a). These results were in accordance with those reported in experimental studies (Fennell et al. 2004).

Calafat et al. (2004) suggested that phthalate metabolites may be present in breast milk and, therefore, can be transferred to the nursing child. Indeed, several phthalate diesters have been found to be present in samples of human milk. The most commonly detected compounds were DEHP, DBP, DIBP, BBP and DEP (as well as their monoesters) (Latini et al. 2009; review by Fromme et al. 2011; Guerranti et al. 2012). In the study conducted by Fromme et al. (2011), DCHP was also detected in 17% of milk samples. Oxidative metabolites of DEHP and DINP were not detected (Latini et al. 2009; Fromme et al. 2011; Guerranti et al. 2012).

Metabolism

The metabolism of DEHP has been extensively studied. There appears to be a consensus that the metabolism of other phthalate compounds is qualitatively similar. Briefly, the diester is first hydrolyzed into a monoester (before, during and/or after absorption). The monoester can then either be i) hydrolyzed into phthalic acid, ii) conjugated to be further excreted, or iii) metabolized into primary and secondary

hydroxyl products that can further be oxidized to yield diacids. Thus, the metabolites of phthalate diesters are monoesters, phthalic acid and products of the oxidative metabolism. These metabolites may be conjugated before excretion or be excreted under their free form (see Table H-2 for summary). Some studies have shown that metabolic pathways may saturate at high doses.

Metabolic pathways

Although metabolism is not exactly the same for all phthalate diesters, a metabolic pathway for the most common plasticizers, those having saturated alkyl groups, has been postulated based on the identification of metabolites produced *in vivo* and excreted in urine (Albro 1986). The obligatory first step is the hydrolysis of the parent to its monoesters by a non-specific lipase (esterase) found in several organs and tissues, particularly in the pancreas, intestinal mucosa, liver, skin and lung (Albro and Lavenhar 1989). Enzymes capable of hydrolyzing phthalate diesters have been found in human saliva (Silva et al. 2005b), breast milk (Calafat et al. 2004) and serum (Kato et al. 2003).

Hydrolysis of the phthalate diester to the monoester may occur in many tissues (e.g., small intestine, skin, pulmonary tract, liver and kidney), but more extensive metabolism may be limited to some tissues, especially the liver (Kluwe 1982). In most cases, especially with large molecules, a rapid hydrolysis of phthalate diesters to their respective monoesters takes place before absorption, and the phthalic moiety is further distributed into the body (Ono et al. 2004). Studies conducted in rats with DEHP indicate that a large proportion of diester administered orally was hydrolyzed to monoester in the intestine (Phokha et al. 2002). However, a study with DEHP, DnOP and DCHP reported a faster rate of hydrolysis in the presence of small intestine contents than with caecal contents, suggesting that such diesters are hydrolyzed by esterases of both bacterial and mammalian origin (Rowland et al. 1977).

During the second phase of metabolism, the monoester can either be i) hydrolyzed into phthalic acid by microsomal esterase, ii) conjugated by UDP-glucuronyltransferase, or iii) metabolized into primary and secondary hydroxyl products by microsomal monooxygenase (analogous to the cytochrome P450 associated fatty acid ω- and ω-1 hydroxylase). The primary and secondary hydroxyl products resulting from the latter pathway are subject to oxidation by the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), respectively, leading to diacids or ketoacids. Finally, the diacids are subject to α- and β-oxidation to yield shorter diacids (Albro et al. 1973a,b; Albro 1986; Albro and Lavenhar 1989). See Figure H-1 below for a postulated metabolic pathway for DEHP as an example.

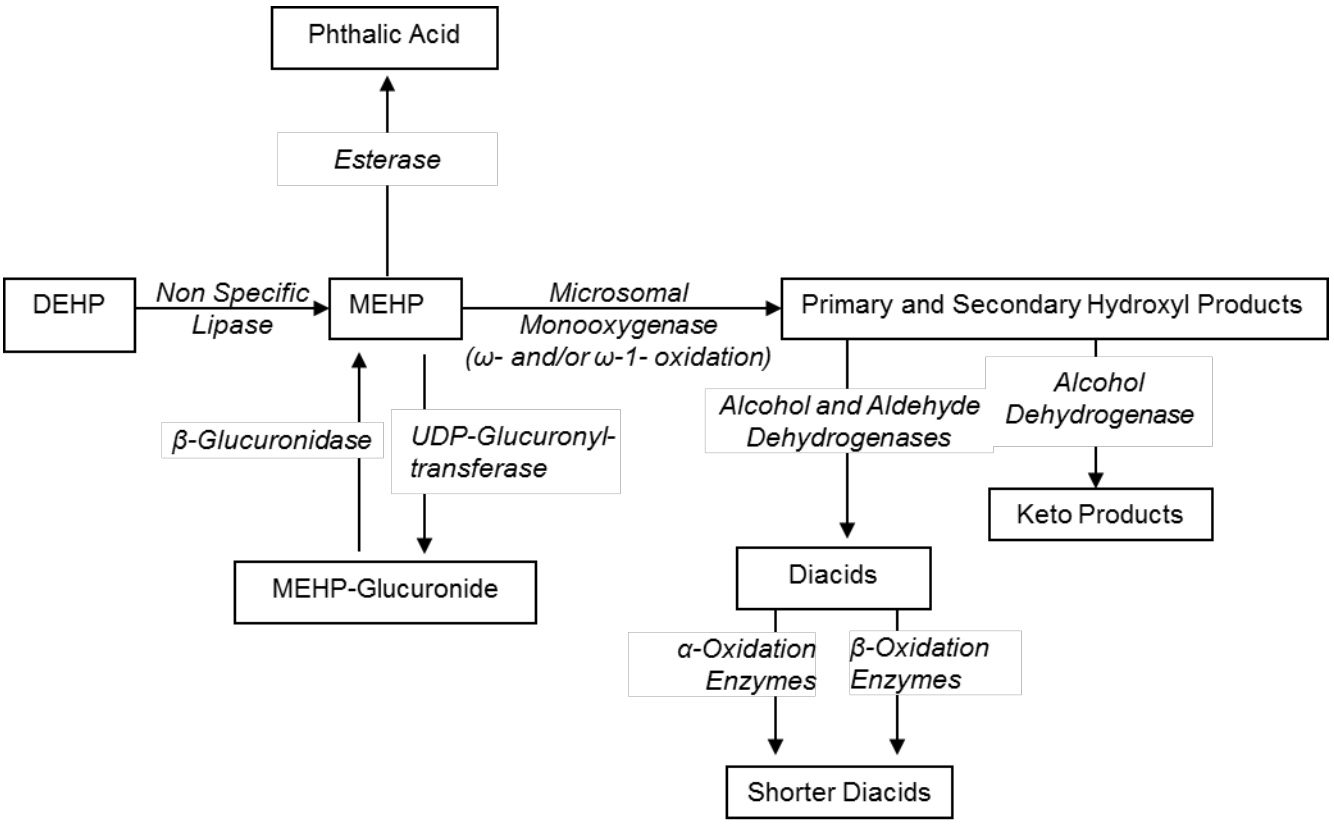

Figure H-1. Figure showing postulated pathways for metabolism of DEHP in mammals (adapted from Albro 1986).

DEHP is by far the most studied phthalate diester (Koch et al. 2005; Kessler et al. 2012; Anderson et al. 2012; Kurata et al. 2012a). Other diesters have similar metabolic steps, but the involvement of each pathway may differ from one substance to another. It is considered that, after oral ingestion, DEHP is hydrolyzed by acid lipases in the stomach, followed by immediate resorption of the monoester (Kessler et al. 2012). The peak plasma level of the parent DEHP lagging one hour after ingestion is attributed to its structural similarity with lipids. Lipid resorption does not start before gastric emptying and the formation of an emulsion with bile. MEHP is assumed to be resorbed into the portal blood as it binds preferentially to serum albumin. Hayashi et al. (2012) measured hepatic MEHP levels in pregnant mice and their offspring along with enzyme activities of lipase and uridine 5'-diphosphate-glucuronosyltransferase (UGT). UGT activity appeared to be 1.5-fold higher in the liver of pregnant dams than postpartum ones. This was potentially reflective of the higher MEHP levels measured in pregnant dams compared to postpartum mice, based on the hypothesis that some MEHP is conjugated with uridine 5'diphosphate (UDP)-glucuronide by the catalytic action of UGT and is excreted in the urine (Albro and Lavenhar 1989). The remaining MEHP is also excreted directly in the urine or is oxidized by cytochrome P450A (CYP4A) (Hayashi et al. 2012).

Kessler et al. (2012) also found that there was significant variability in time between the four volunteers tested and that individual blood burdens of DEHP and MEHP can be estimated from the DEHP dose. Further, the mean AUC/D of DEHP was 50 and 100 times higher than in rats and marmosets, respectively (Kessler et al. 2004). This can be explained by the species differences in intestinal resorption and hydrolysis [see Figure H-2, and DEHP and other medium-chain phthalates in Table H-2].

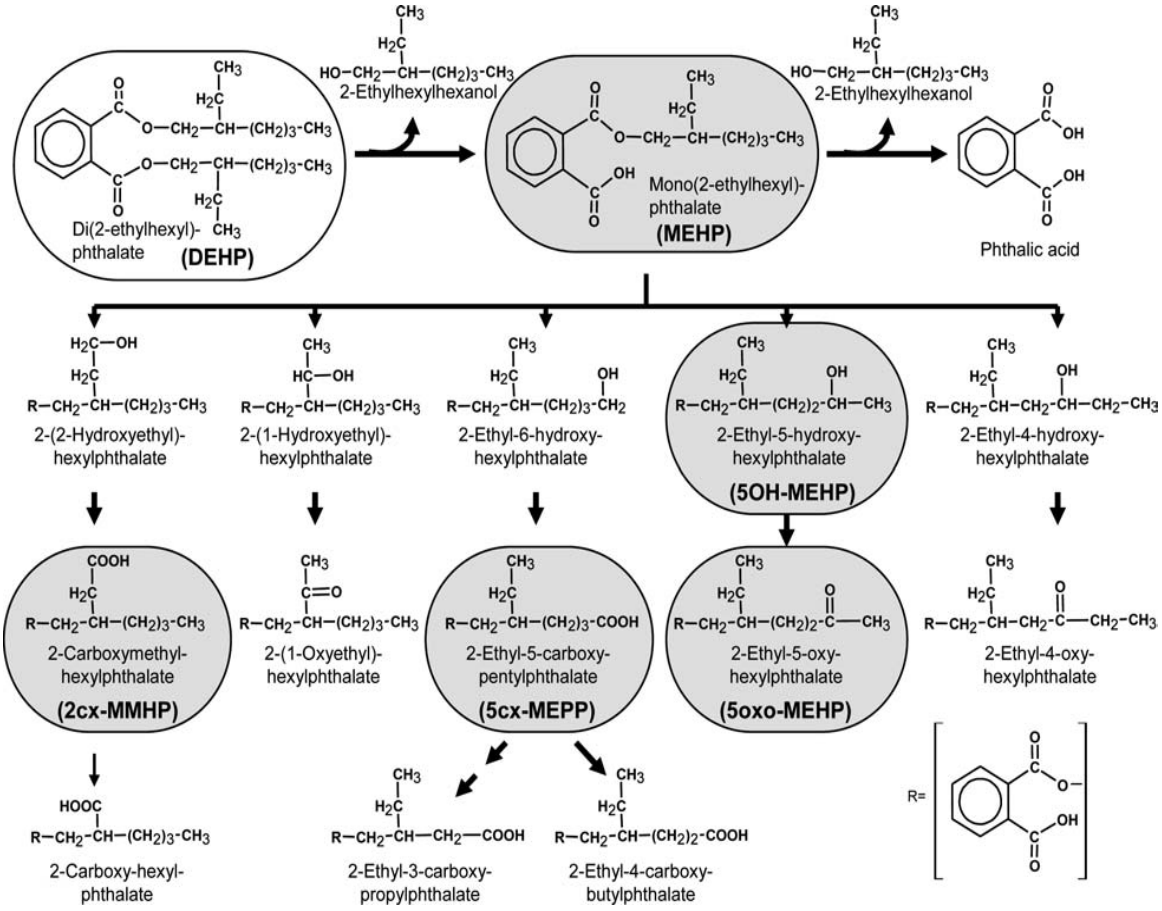

Figure H-2. The metabolism of DEHP is illustrated in this figure (adapted from Koch et al. 2005). DEHP is rapidly metabolized to its monoester, MEHP, which is further extensively modified by various side-chain hydroxylation and oxidation reactions. The major metabolites of DEHP are bolded.

Recent studies by Kurata et al. (2012a,b) determined that there are significant species differences between humans, marmosets and rats in the ratio of excreted conjugated and non-conjugated forms (G/F ratio) of the secondary metabolites of DEHP in urine. The G/F ratios for humans and marmosets were similar (77.6–84.2% and 87.7%, respectively) for the glucuronidated form of metabolites in urine after 24 hours, compared to only 11.2% G/F ratio in rats (Kurata et al. 2012b). For rats, the majority of the secondary metabolites were in their free form (87.4% G/F ratio).

Information on the metabolism of other medium-chain phthalates is not as detailed, but the pathways are qualitatively similar to the one described for DEHP. The toxicokinetics of DIBP was recently evaluated by Koch et al. (2012) using one human male volunteer. It appears as though mono-iso-butylphthalate (MIBP) is the major urinary metabolite of DIBP (about 70% of the administered dose), followed by 2OH-mono-iso-butylphthalate (2OH-MIBP) (19%) and 3OH-mono-iso-butylphthalate (3OH-MIBP) (0.69%) after 24 hours. Therefore, the oxidized metabolites account for about 20% of the overall dose.

BBP is an asymmetric diester that can potentially form equal amounts of monobutylphthalate (MBP) and monobenzylphthalate (MBeP). However, a higher proportion of MBP (29–34%) compared to MBzP (7–12%) was reported in rats after repeated oral administrations of BBP; in this study, the major metabolite was hippuric acid (51–56%) and there was no glucuronide (Nativelle et al. 1999). The metabolic pathways of BBP in rats proposed by these authors are illustrated in Figure 5. In contrast, in humans administered BBP orally (253 and 506 µg, single dose), there was a preferential cleavage of the butyl ester link (leading to more MBzP) and there was little further metabolism of MBzP; MBzP was thus the major urinary metabolite in humans (Anderson et al. 2001). In a more recent study, the species differences in BBP hydrolysis by liver microsomes were investigated among humans, monkeys, dogs, rats and mice. It was found that the hydrolysis activities of BBP to MBP in monkey, rat and mouse liver microsomes were 28-, 22- and 44-fold higher than that in human liver microsomes, although the activity of dog liver microsomes was comparable to that in human liver microsomes. In contrast, the hydrolysis activities of BBP to MBzP in monkey, rat and mouse liver microsomes were 34, 9.3 and 12% of that in human liver microsomes, respectively, whereas the activity in dog liver microsomes was 1.6-fold higher than that in human liver microsomes. The authors proposed that the hydrolysis of BBP to monoester phthalates in mammalian liver microsomes could be classified into two types: MBzP>MBP type for humans and dogs, and MBP>MBzP type for monkeys, rats and mice. Since the formation profile of MBP and MBzP in liver microsomes of dogs highly paralleled that of human liver microsomes, it was also suggested that the properties of carboxylesterase isoform(s) of dogs involved in BBP hydrolysis could be much more similar to those of humans than other animal species (Takahara et al. 2014).

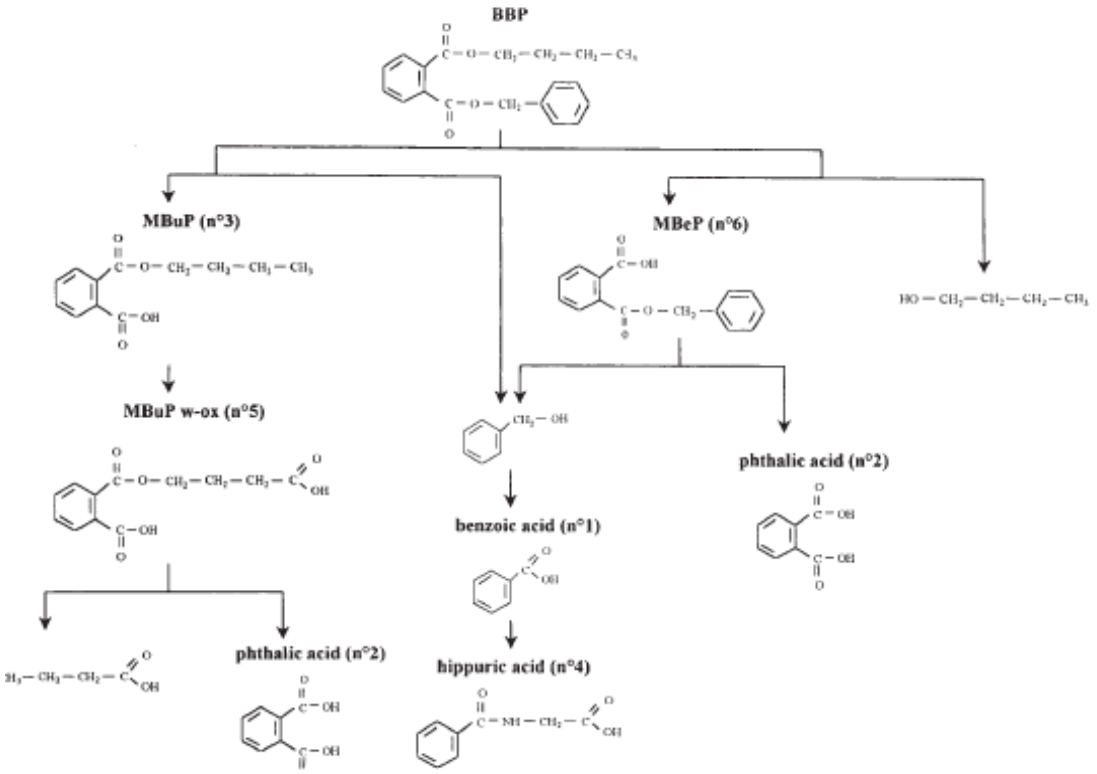

Figure H-3. Proposed routes of BBP metabolism in female Wistar rats (adapted from Nativelle et al. 1999). The six metabolites of BBP (n°1 to 6) recovered in urines are reported in this figure.

Induction and saturation of metabolic pathways

Several studies documented an induction of metabolic pathway after repeated exposure to phthalate diesters. For example, DnOP and DCHP were shown to induce the hepatic activity of monoxygenases involved in their own metabolism after oral absorption (Lake et al. 1982; Poon et al. 1997). In rats, MEHP blood levels were lower and their half-life was shorter after repeated oral administrations of DEHP (1055 mg/kg bw/day) than after a single administration (Sjoberg et al. 1986), suggesting an induction of MEHP hydrolysis. Daniel and Bratt (1974) suggested that the DEHP/MEHP ratio (reflecting hydrolysis of DEHP) in the GI tract may be altered by induction or inhibition of pancreatic lipase. Induction of metabolic pathway appears to be consistent during pregnancy as well. After repeated oral exposure of pregnant rats to DBP, maternal and fetal plasma MBP levels were consistently lower compared to single doses, suggesting induced MBP metabolism (Clewell et al. 2009).

This effect is not limited to rodents. In Cynomolgus monkeys, hydrolysis and ω-oxidation were induced by repeated oral doses of DEHP, as reflected by increased urinary levels of mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MCPP) and decreased levels of mono(2-ethyl-3-carboxypropyl) phthalate (MECPrP) (Short et al. 1987).

β-oxidation was increased after repeated dietary administrations of DEHP in the same study using rats, as reflected by a decreased urinary level of 5cx-MCPP. However, there was an increased level of MECPrP (Shor et al. 1987).

Conversely, the metabolism of phthalate diesters also appears to be saturable at several steps. Metabolism can be saturated at hydrolysis of the diester as seen in a study showing that after oral administration of a high dose of DEHP (2800 mg/kg), unchanged DEHP was recovered in blood. Saturation was suggested to occur before (in the gut content) or after absorption through the GI tract (Teirlynck and Belpaire 1985).

Metabolism of the monoester was also suggested to become saturated after oral administration of a single dose of DEHP. Kinetics of MEHP metabolism was slower at 1000 mg/kg compared to 30 mg/kg (AUC in blood was only twice as high at 1000 mg/kg; delayed time point for maximal blood levels) in female Sprague–Dawley rats (Kessler et al. 2004). In pregnant rats, the metabolism of MEHP also appeared to be lower at 500 mg/kg compared to 30 mg/kg (the blood AUCs for DEHP were comparable, while the normalized blood AUC for MEHP was higher at the highest dose) (Kessler et al. 2004).Further along metabolism, during the oxidation of downstream products, it was shown that β-oxidation (5cx-MEPP to MECPrP) appeared to be saturated in rats administered DEHP through their diet (≥ 6000 ppm in diet) (Short et al. 1987).

Saturation was also seen in other phthalates. Metabolism appeared to be saturated at 780 and 1500 mg/kg/day in female rats administered BBP orally for three days. At these doses, urinary elimination of metabolites (hippuric acid, MBP, MBeP, phthalic acid) as the percentage of the administered dose (43 and 30% at 780 and 1500 mg/kg, respectively) was lower than at the low dose (54–58% at 150 and 475 mg/kg/day) (Nativelle et al. 1999).

In pregnant rats administered DBP (single dose: 50, 100 or 250 mg/kg), glucuronidation of MBP appeared saturated at 250 mg/kg since the time to reach maximal plasma concentration of MBP and MBP-glucuronide was longer than at 50 or 100 mg/kg (MBP: 2 hours vs. 0.5 hour, MBP-glucuronide: 2 hours vs. 1 hour). There was a non-linear increase of AUC for MBP (disproportionate increase: by 10-fold vs. at 50 mg/kg) and the maternal and fetal plasmatic concentrations exhibited two peaks, one at 0.5 hour (followed by a decrease at 1 hour) and an absolute peak at 2 hours (maternal plasma) or 4 hours (fetal plasma) (Fennell et al. 2004).

Metabolic differences related to species, age and inter-individual variation

Some studies have shown that there are some species differences in the metabolism of phthalates. For example, lipase, which transforms DEHP into MEHP, may play a predominant role in interspecies variability of DEHP metabolism. Enzymatic activities involved in the metabolism of DEHP differ between primates (marmosets) and rodents (rats and mice) (Ito et al. 2005). It was shown that lipase activity in various tissues (liver, small intestine, kidney and lung) was lower in marmosets than in rats or mice by at least

one order of magnitude. Lipase activity was found to be higher in the small intestine than in the liver of both rats (by 1.7-fold) and mice (by 4.3-fold). In contrast, lipase activity was 1.6-fold higher in the liver of marmosets compared to the small intestine. Similarly, the ratio V_{max}/K_m for lipase activity in the liver of marmosets (1.38) was dramatically lower than in rats (227) or mice (333). Hepatic UGT activity was also lower (2- to 3-fold) in marmosets compared to rodents. However, ADH and ALDH activities were generally similar or higher in marmosets, suggesting that ω- or ω-1 oxidized metabolites of MEHP (by CYP4A) are more difficult to further metabolize in rats and mice compared to marmosets (Ito et al. 2005). Overall, the activity of marmoset lipases appears to be much less than that of the rat and this may explain the different metabolite patterns between these two species during urinary excretion (Rhodes et al. 1986; Kurata et al. 2012a). Kurata et al. (2012a) postulated that the secondary metabolites of DEHP appeared to be promptly conjugated and excreted in marmosets (as observed in humans) and, therefore, this species would be a good analogue to measure toxicity of phthalates in humans because conjugation may potentially reduce the bioactivity of the metabolites by reducing their bioavailability.

In Ito et al. (2014), the activities of the same four DEHP-metabolizing enzymes were measured in the livers of 38 human subjects of various ages and in eight 129/Sv male mice. Microsomal lipase activity was significantly lower in humans than in mice regardless of sex, age or race differences. The V_{max}/K_m value in humans was one-seventh of that in mice. Microsomal UGT activity in humans was a sixth of that in mice, and cytosolic ALDH activity for 2-ethylhexanal in humans was one-half of that in mice. In contrast, ADH activity for 2-ethylhexanol was two-fold higher in humans than in mice. The total amount of DEHP urinary metabolites and the concentration of MEHP were much higher in mice than in the U.S. general population based on data reported in the 2003–2004 U.S. National Health and Nutrition Examination Survey, regardless of the similar estimated DEHP intake between these mice and the human reference population. However, mono(2-ethyl-5-oxo-hexyl)phthalate (5oxo-MEHP) and mono(2-ethyl-5 carboxypentyl)phthalate (5cx- MEPP) levels in urine were higher in humans than in mice (Ito et al. 2014).

In vitro hepatic studies (for DMP, DEP, DBP, DnOP, DEHP and DCHP) have also revealed quantitative species differences in the phthalate diester hydrolase activity, with higher alkaline esterase activities in non-human primates (baboons) than in rats, and higher activity in rats than in ferrets. Similar studies conducted with intestinal mucosal cell preparations also indicated a higher activity in baboons than in rats, and higher activity in rats than in ferrets. However, these values were not strictly comparable on an interspecies basis because the intestinal sections used (30–40 cm) may refer to different intestinal regions in rats, baboons and ferrets (Lake et al. 1977a).

The enzymatic activities of esterase and β-glucuronidase in the liver, intestinal mucosa and testes were also examined and compared between rats and hamsters for DBP metabolism (Foster et al. 1983). It was shown that esterase activity (which transforms MBP into phthalic acid) in the liver and intestinal mucosa was 2- and 1.3-fold higher,

respectively, in hamsters than in rats. In contrast, the β-glucuronidase activity in the testes of rats was higher (by 2.2- to 6.5-fold) than in hamsters.

To facilitate excretion, metabolites may be conjugated. The rates of conjugation were found to vary between species (Lake et al. 1976; Albro et al. 1982; Egestad et al. 1996). It is noticeable that rats present the particularity of not conjugating the metabolites of DEHP. To compensate, three to six oxidative steps occur to produce metabolites with carboxyl groups on the side chain (Albro et al. 1982).

Glucuronidation of phthalate metabolites may also be affected by life stage. Rat fetuses do not have a functional glucuronidation pathway at GD17 (Calafat et al. 2006a). A slower fetal metabolism of MBP compared to maternal glucuronidation was suggested by the results obtained by Fennell et al. (2004). After oral administration of DBP (50 or 100 mg/kg) to pregnant rats on GD20, MBP appeared rapidly in both maternal and fetal plasma (maximal concentration reached 0.5 and 1 hour after administration, respectively), but there was a delay in the appearance of MBP-glucuronide in fetal plasma (time to reach maximal concentration: 4 hours vs. 1 hour in maternal plasma). These results could indicate either a slower fetal metabolism of MBP (vs. maternal glucuronidation) if MBP-glucuronide does not cross the placenta, or that MBP-glucuronide crosses placenta at a much slower rate than MBP (Fennell et al. 2004). This might have significant impact on the level of toxicity caused by phthalates during fetal development.

In relation to gender differences in metabolism in humans, a recent study by Anderson et al. (2012) measuring low- and high-dose administrations of DEHP to ten male and ten female volunteers showed that there was no statistically significant difference in the excretion kinetics or the metabolite composition between males and females, but there was a considerable amount of inter-individual variability. Ito et al. 2014 has proposed that the inter-individual variation in the metabolism of DEHP in humans may be greater that the inter-species differences between mice and humans based on the variability in the measurement of four enzymes involved in DEHP metabolism in the livers of human subjects and male mice (10- to 26-fold for inter-individual variation vs. 2- to 7-fold for inter-species variation).

Chemical-specific factors affecting metabolism

Significant work has been done investigating whether there is a relationship between the molecular weight, chain length, chemical structure and/or lipophilic characteristics of phthalates and their metabolism in rodents (*in vivo* and *in vitro*), primates (*in vitro*) and humans (*in vitro*).

In vitro studies conducted with rat liver and kidney homogenates have shown that there is a direct relationship between the molecular weight of phthalate diesters (DMP, DBP, DnOP and DEHP) and their metabolic rates in these organs. In both the liver and kidney, hydrolysis to the monoester was faster for the diesters for a lower-molecular-weight phthalate (metabolic rate ranking: DMP>DBP>>DnOP>DEHP) than the larger

phthalate (Kaneshima et al. 1978a). Similarly, the metabolism of phthalate diesters by intestinal mucosal preparations was shown to be inversely related to the alkyl side chain length of phthalates (DMP>DEP>DBP>DnOP). This relationship was observed with rat and baboon intestinal mucosa cell preparations, and with human duodenum and jejunum preparations (Lake et al. (1977a).

In vivo studies examining the second phase of metabolism were conducted on rats administered phthalate diesters orally. Results have shown that hydrolytic monoesters are more likely to be the ultimate metabolites of the small phthalate diesters (e.g., DBP) than of the comparatively larger C8+ phthalates (Albro and Lavenhar 1989; Albro and Moore 1974; Albro et al. 1973; Calafat et al. 2006b; McKee et al. 2002). *In vitro* metabolism studies conducted with rat liver and kidney homogenates also suggested a possible relationship between the molecular structure of phthalate diesters and their metabolic rates in these organs. It was shown that hydrolysis of DNOP, an n-alkyl C8 phthalate diester, was faster than hydrolysis of DEHP, a branched C8 diester (Kaneshima et al. 1978a).

The lipophilicity of a phthalate appears to also play a role in its metabolism. The affinity of phthalate diesters for purified rat liver carboxylesterases (pI 5.6 and pI 6.2/6.4) has been shown to increase (i.e., decreasing K_m values) with increasing lipophilicity (K_{ow}) diester compounds (K_m values ranking: DMP>DEP>DBP>DIBP). For the reaction rates (V_{max}), a similar relationship was observed for esterase pI 5.6; however, for esterase pI 6.2/6.4, there was no evident link between V_{max} and log K_{ow} (Mentlein and Butte 1989).

Table H-2. Summary of medium-chain phthalate diesters and their metabolites found in urine after oral administration

Substance	Metabolite found in urine after oral administration	Abbreviation	Reference (species)
DIBP	Monoisobutyl phthalate	MIBP	Koch et al. 2012 (human)
DIBP	2OH-mono-iso-butylphthalate	2OH-MIBP	Koch et al. 2012 (human)
DIBP	3OH-mono-iso-butylphthalate	3OH-MIBP	Koch et al. 2012 (human)
DEHP	Mono(2-ethyl hexyl)phthalate	MEHP	Anderson et al. 2011 (human) Koch et al.2005 (human) Ikeda et al. 1980 (pig) Rhodes et al. 1985 (marmoset) Kurata et al. 2012a (marmoset) Short et al. 1987 (monkey)

Substance	Metabolite found in urine after oral administration	Abbreviation	Reference (species)
			Calafat et al. 2006a,b (rat) Daniel and Bratt 1974 (rat) Sjoberg et al. 1985b (rat) Koo and Lee 2007 (rat) Albro et al. 1982 (rat, guinea pig, mouse) Albro et al. 1983 (rat) Lake et al. 1976 (ferret)
DEHP	Mono(2-ethyl-5-oxohexyl) phthalate	MEOHP [5oxo-MEHP]	Anderson et al. 2011 (human) Koch et al. 2005 (human) Kurata et al. 2012a (marmoset) Albro et al. 1982 (hamster, mouse) Daniel and Bratt 1974 (rat) Lhuguenot et al. 1985 (rat)
DEHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP [5OH-MEHP]	Anderson et al. 2011 (human) Koch et al. 2005 (human) Kurata et al. 2012a (marmoset) Albro et al. 1982 (rat, hamster, mouse) Daniel and Bratt 1974 (rat) Lhuguenot et al. 1985 (rat)
DEHP	Mono(2-ethyl-5-carboxypentyl) phthalate	MECPP [5cx-MEPP]	Anderson et al. 2011 (human) Kurata et al. 2012a (marmoset) Koch et al. 2005 Albro et al. 1982 (rat, guinea pig, hamster)

Substance	Metabolite found in urine after oral administration	Abbreviation	Reference (species)
			Lhuguenot et al. 1985 (rat)
DEHP	Mono[2-(carboxymethyl)hexyl] phthalate	MCMHP [2cx-MMHP]	Koch et al. 2005 Daniel and Bratt 1974 (rat)
DEHP	Mono-(3-carboxypropyl) phthalate	MCPP	Calafat et al. 2006b (rat)
DEHP	Monooctylphthalate	MOP	Anderson et al. 2001 (human)
DEHP	Phthalic acid	PA	Albro et al. 1982 (rat, guinea pig, hamster, mouse); Albro et al. 1983 (rat) Ikeda et al. 1980 (pig) Short et al. 1987 (monkey) Daniel and Bratt 1974 (rat) Short et al. 1987 (rat) Lake et al. 1976 (rat)
DEHP	Glucuronidated secondary metabolites	COOH-MEHP-Gluc OH-MEHP-Gluc Oxo-MEHP Gluc MEHP-Gluc	Kurata et al. 2012a (rat, marmoset) Kurata et al. 2012b (human)
DBP	Mono-n-butyl phthalate (urine in rats also contained the glucuronidated form of MBP)	MBP	Koch et al. 2012 (human) Anderson et al. 2001 (human) Seckin et al. 2009 (human) Silva et al. 2007? (human, rat) Struve et al. 2009 (rat) Tanaka et al. 1978 (guinea pig, hamster, rat) Foster et al. 1983 (hamster) Albro and Moore 1974 (rat) Calafat et al. 2006a,b

Substance	Metabolite found in urine after oral administration	Abbreviation	Reference (species)
			(rat) Fennell et al. 2004 (rat) Foster et al. 1983 (rat) Kaneshima et al. 1978b (rat) Saillenfait et al. 1998 (rat) Williams and Blanchfield 1975a (rat) Coldham et al. 1998 (cow)
DBP	Mono-3-hydroxy-n-butyl phthalate	3OH-MBP	Koch et al. 2012 (human) Silva et al. 2007 (human, rat) Williams and Blanchfield 1975a (rat)
DBP	Mono-4-hydroxy-n-butyl phthalate	4OH-MBP	Koch et al. 2012 (human) Williams and Blanchfield 1975a (rat)
DBP	Mono-2-hydroxy-n-butyl phthalate	2OH-MBP	Koch et al. 2012 (human)
DBP	Mono-n-hydroxybutylphthalate (urine in rats also contained the glucuronidated form)	OH-MBP	Fennell et al. 2004 (rat) Coldham et al. 1998 (cow)
DBP	Mono(3-carboxypropyl) phthalate	MCPP	Koch et al. 2012 (human) Silva et al. 2007a (human, rat)
DBP	Phthalic acid (urine in rats also contained the glucuronidated form of PA)	PA	Tanaka et al. 1978 (guinea pig, hamster, rat) Foster et al. 1983 (hamster) Albro and Moore 1974 (rat) Fennell et al. 2004 (rat) Foster et al. 1983 (rat) Williams and Blanchfield 1975a (rat)

Substance	Metabolite found in urine after oral administration	Abbreviation	Reference (species)
			Coldham et al. 1998 (cow)
DBP	Monobutanoicphthalic acid (urine in rats also contained the glucuronidated form)	MBPA	Fennell et al. 2004 (rat)
DBP	Mono(3-carboxypropyl) phthalate	MCPP	Calafat et al. 2006b (rat)
DBP	Monoethylphthalate	MEP	Coldham et al. 1998 (cow)
BBP	Monobenzyl phthalate	MBzP	Anderson et al. 2001 (human) Clewell et al. 2009a (rat) Eigenberg et al. 1986a (rat) Nativelle et al. 1999 (rat)
BBP	Monobutyl phthalate	MBP	Anderson et al. 2001 (human) Clewell et al. 2009a (rat) Eigenberg et al. 1986a (rat) Nativelle et al. 1999 (rat)
BBP	Hippuric acid	HA	Nativelle et al. 1999 (rat)
BBP	Phthalic acid	PA	Nativelle et al. 1999 (rat)
DIHepP	5-hydroxy-5-methylhexyl phthalate		Sato et al. 1984 (rat)
DIHepP	6-hydroxy-5-methylhexyl phthalate		Sato et al. 1984 (rat)
DIHepP	5-carboxyhexyl phthalate		Sato et al. 1984 (rat)
DIHepP	3-carboxypropyl phthalate		Sato et al. 1984 (rat)
DIOP	mono-(3-carboxypropyl) phthalate	MCPP	Calafat et al. 2006 (rat)
DIOP	mono-*n*-octyl phthalate	MnOP	Calafat et al. 2006 (rat)
DIOP	monoisononyl phthalate	MINP	Calafat et al. 2006 (rat)

*Measurements of metabolites in humans are from an epidemiological study measuring phthalate metabolites in urine, not after specific administration, but shows that these metabolites are found in humans as well.

Excretion

Urine is the major route of elimination for medium-chain phthalate diesters and their metabolites. In all species and for all phthalate compounds for which data were available, the metabolites present in urine are both free and glucuronidated, except for DEHP in rats (metabolites only present under the free form). The pattern of urinary excretion of DEHP in humans can be illustrated by the results of Dirven et al. (1993b), who reported that 26% of the metabolites quantified were MEHP, 52% were products of a (ω-1)-hydroxylation of MEHP and 22% were the product of a ω-hydroxylation.

As urine is the most important route of excretion for most phthalates, it is largely used to conduct human biomonitoring in order to estimate exposure to phthalates. Generally, the metabolites allow for the identification of the parent compound, but some metabolites are common to several compounds and are thus poor biomarkers of exposure to their precursor phthalate diester. For instance, mono(3-carboxypropyl) phthalate (MCPP), a major metabolite of DnOP, is also recovered at varying levels in the urine of rats administered DIOP, DINP, DIDP, DEHP and DBP (Calafat et al. 2006b). These authors also suggested that the hydrolytic monoesters of the larger (C8+) phthalates are poor biomarkers of exposure in rats and, although there may be differences in metabolism among species, the lower molar ratios of the hydrolytic monoesters of these phthalates compared to those of the oxidative metabolites may explain the relatively low frequency of detection of the hydrolytic metabolites in humans.

Fecal excretion represents both the part of the compound not absorbed by the GI tract and the part of the compound excreted in the bile and not further reabsorbed. Fecal excretion may be an important route of excretion, depending on the parent compounds, the dose (higher fecal excretion when metabolism is saturated) and the route of administration. For instance, for DEHP, the feces contained relatively high concentrations of unoxidized MEHP, while the more polar metabolites (e.g., diacids and hydroxyl acids) were in much higher relative abundance in the urine in rodents and monkeys (Albro and Lavenhar 1989). At doses not associated with metabolic saturation, fecal excretion is generally less important than urinary excretion for most phthalates.

Biliary excretion was shown to occur for a limited number of phthalate compounds, i.e. DMHP, DEHP, DIDP and DBP (Sato et al. 1984; Ikeda et al. 1980; Daniel and Bratt 1974; General Motors Research Laboratories 1983; Tanaka et al. 1978). Generally, bile contains the monoester (free or glucuronidated), which can be reabsorbed in the intestine. Biliary elimination of phthalates was demonstrated using bile-cannulated animals. In rats, Daniel and Bratt (1974) reported that after an oral dose of 2.6 mg/kg of labelled DEHP, 14% of the administered dose was recovered in bile after four days. In dogs, biliary excretion was detected one day post-dosing at 10% of administered dose after repeated oral administration (50 mg/kg/day) of DEHP (Ikeda et al. 1980).

Kluwe (1982) suggested that hepato-biliary excretion may saturate at high doses or that it may happen only at a given period of time after absorption. These hypotheses were based on results by Tanaka et al. (1978) and Daniel and Bratt (1974) for DBP and

DEHP, respectively. The suggestion of delayed biliary excretion is based on the finding that only 10% of an intravenous dose of 50 mg/kg DBP was recovered in bile in 5 hours, in comparison to 44% of an oral dose of 60 mg/kg in 24 hours. Biliary excretion may be followed by further reabsorption in the intestine (and finally, urinary excretion of the reabsorbed part). Enterohepatic recirculation of DEHP is suggested by the observation that only 8% of an oral dose (gavage) of 1.0 g/kg DEHP was isolated from feces as DEHP metabolites (another explanation, less likely, would be that biliary excretion is not a major route of elimination in this dose range) (Kluwe 1982).

Differences in excretion related to species and age

Most toxicokinetic studies are conducted in male rats, but there is some information acquired on other rodents or primate species. There appears to be similarities among species for the metabolic pathways, resulting in the excretion of similar metabolites. However, there may be species-related differences in the importance of each metabolic route.

The studies allowing for interspecies comparisons were essentially conducted with DEHP. The metabolic pathways extensively described in the rat (hydrolysis to MEHP and further oxidative metabolism (ω-, (ω-1)- and β-oxidations) were also found to occur in other species (Albro et al. 1981; Albro et al. 1982; Lake et al. 1976; Rhodes et al. 1986; Short et al. 1987), including humans (Silva et al. 2006). A study conducted in marmoset indicated a urinary metabolite pattern qualitatively similar to that in the rat, but quantitatively different (marmoset excreted principally conjugated metabolites derived from ω-1 oxidation) (Rhodes et al. 1986).

The major difference in urinary excretion of phthalate metabolites seems to be the level of conjugation. Although conjugation facilitates excretion by increasing its hydrophilicity, the conjugation of DEHP metabolites is negligible in rats, while it is important in other species (Frederiksen et al. 2007). Among the six species (rats, mice, guinea pigs, monkeys, humans and hamsters) studied by Albro et al. (1982), all except rats excreted metabolites under conjugated forms. Monkeys appeared to be the best model for elimination of phthalates from humans since both have a similar pattern of urinary excretion (high excretion of MEHP and mostly conjugated metabolites) (Albro et al. 1982). Egestad et al. (1996) imparts an additional precision on the form excreted in mice. The form is not only combined with glucuronide, but also with β-glucose, a phenomenon that is not observable in guinea pigs and (humans) infants.

The effect of age on urinary excretion of DEHP and metabolites was studied in rats aged 60 and 25 days administered labelled DEHP by gavage (Sjoberg et al. 1985b). The authors observed a decreased rate of excretion in the 60-day-old rats compared to younger rats (26 and 44% of radioactivity in urine within 72 hours, respectively). No unchanged DEHP or MEHP was found in urine.

Inhalation route

There is limited information on medium-chain phthalate absorption via inhalation. In humans, an occupational study demonstrated that DEHP can be absorbed through the lungs (Dirven et al. 1993a). These authors measured DEHP concentrations in the air by personal air sampling of nine workers in a PVC boot factory and found these individuals were exposed to a maximum of 1.2 mg/m^3 DEHP. They were able to demonstrate an increase in the urinary concentrations of all four metabolites of DEHP measured in the workers.

Dermal route

Absorption

A summary of *in vitro* and *in vivo* dermal absorption fluxes, Kp's, and % absorbed for medium-chain phthalates is presented in tables 3 and 4, respectively.

Data obtained from *in vivo* and *in vitro* studies have shown that short-chain phthalates have higher absorption through rat and human skin than longer-chain phthalates (Scott et al. 1987; Elsisi et al. 1989; Mint and Hotchkiss 1993; Mint et al. 1994). Data obtained *in vitro* show a decrease in steady state absorption rates and extent of absorption, as the molecular weight and the lipophilicity of phthalates increase (Mint and Hotchkiss 1993; Mint et al. 1994; Payan et al. 2001). *In vivo* studies, conducted in rats, also observed that the extent of absorption (based on urinary excretion and retention in tissues) increases with increasing molecular weight and lipophilicity, and reaches a maximum with DBP. It then decreases as the molecular weight and lipophilicities increase (Elsisi et al. 1989).

In vivo data obtained in humans by Janjua et al. (2007) and Janjua et al. (2008) have also shown that DBP has a slower rate of absorption than DEP (based on urinary excretion and serum samples), suggesting a possible relationship with molecular weight or side chain length in humans. In this two-week study conducted in humans (26 healthy Caucasian males), subjects received whole-body topical applications of control basic cream formulation (dermal load: 2 mg/cm^2), once per day for five consecutive days, followed by five daily topical applications of the same cream containing 2% (V/V) DEP and 2% (V/V) DBP (as well as 2% butyl paraben). Blood and urine were collected during the study and analyzed for levels of MEP and MBP. Two hours after the first application of the cream containing DEP, serum concentration of MEP peaked at 1001 µg/L (corresponding to 6.9 mg) and decreased to 23 µg/L after 24 hours just before the following application. The total percent of DEP absorbed from blood MEP concentrations is approximately 10%. Maximum dermal absorption for DBP from blood concentration could not be evaluated since concentration of MBP peaked over a longer period of time, and the authors started collecting blood at less frequent times (every 1 hour for 4 hours vs. every 24 hours subsequently). However, over the whole period of data collection (120 hours), serum concentrations of MEP were consistently higher than serum concentrations of MBP, indicating that DBP is probably absorbed though skin at

less than 10%. In urine, the average dermal absorption for DEP and DBP, estimated from daily recovery of MEP and MBP, was 5.8 and 1.82%, respectively. However, significant interindividual and daily variations were observed, with a maximum dermal absorption in volunteers corresponding to approximately 13 and 6% of the applied DEP and DBP dose, respectively (Janjua et al. 2007, 2008; NICNAS 2011).

In vitro experiments conducted with rat and human epidermises have also shown that human skin is less permeable than rat skin to phthalate diesters (Table 3). Therefore, the use of rats as a model for dermal phthalate absorption in humans may overestimate dermal bioavailability.

Distribution

Distribution after dermal exposure to medium-chain phthalates was studied *in vivo* in rats and guinea pigs; retention in the skin was also documented in *in vitro* studies (diffusion cells). These studies show that skin may constitute a reservoir and that, similar to oral administration, phthalates are distributed throughout the body at varying levels according to the compound, the applied dose and the species.

Phthalate diesters (5-8 mg/cm^2; skin not washed after exposure) applied topically to the dorsal side of rats revealed that part of the dose remained at the site of application (i.e., retained in the skin) (Elsisi et al. 1989). For all diesters, distribution in tissues after seven days was generally low (< 1% in each tissue), except for BBP (4.6% in muscle) and DEHP (1.1% in skin other than at the site of application and 1.1% in muscle). The ranking of phthalate diester distribution in tissues was muscle>skin>fat for DIBP, DEHP and BBP, and skin>muscle>fat for DBP.

Dermal retention of DBP was also studied *in vitro* with rat and human skin. The results confirmed that skin may play the role of a reservoir for these diesters, and showed that retention in skin was 3- to 6-fold higher in rats compared to humans. With DBP, half of the applied dose (54%) remained on the surface of human skin, compared to 42% of rat skin. The fraction present in the skin was 4% in human skin and 21% in rat skin, respectively (Mint and Hotchkiss 1993; Mint et al. 1994).

Distribution of DBP, after dermal administration, was well documented by Payan et al. (2001). The authors found that after application of ^{14C}-DBP (10 µL/cm^2) on rat skin, DBP penetrated rapidly and diffused into the stratum corneum and/or epidermis, which constituted a reservoir. From this reservoir, DBP was slowly hydrolyzed by skin esterases before reaching systemic circulation. Less than 2% of unchanged DBP was present in the plasma of male haired rats, while MBP and MBP-glucuronide accounted for 61–88% of plasma radioactivity. Apparent plasma elimination of ^{14}C was slightly lower in male than in female haired rats, and radioactivity in plasma decreased 3-fold faster in hairless male rats than in haired male rats. It is also noteworthy that in hairless male rats, the fraction of the applied dose remaining in the carcass and skin (< 5%) was lower than in haired male rats (14–18%).

An *in vivo* study conducted in female hairless guinea pigs administered DEHP (34 nmol/cm^2; skin washed 24 hours after exposure) indicated that seven days after administration, 5% of the applied dose was present in the dosed area of the skin and 4% was present in other body tissues (Ng et al. 1992). The authors also conducted an *in vitro* study with higher doses (35, 153 and 313 nmol/cm^2) applied on the skin of guinea pigs in a diffusion cell (receptor fluid: HHBSS). They reported higher skin retention (about 41%, 38% and 36%, respectively) 24 hours after application and following skin washing. Use of non-viable skin resulted in a lack of metabolism.

Dermal absorption of medium-chain phthalates for risk assessment

As presented above, medium-chain phthalates are absorbed through the skin of rodents, rabbits and humans, but shorter-chain phthalates have higher rates of absorption through rat and human skin than longer-chain phthalates. Recent *in vivo* and *in vitro* studies have also shown that absorption of medium-chain phthalates, such as DBP and DEHP, through human skin is lower than through animal skin. This difference could be explained by species differences, such as difference in skin permeability as demonstrated in *in vitro* studies, and/or other factors related to the different methodology used in the various studies. Considering the maximum percentage of the applied dose recovered in serum for DEP—a short-chain phthalate that is expected to be more dermally available than other medium-chain phthalates—in a study conducted in humans (Janjua et al. 2008), it is expected that the dermal bioavailability for medium-chain phthalates in humans is not likely to be greater than 10%. Additionally, dermal absorption of many medium-chain phthalates (DBP, DIBP, BBP and DEHP) has also been evaluated by various other agencies (Danish EPA, ECHA, NICNAS). A summary of dermal absorption values assigned and main rationales is presented in Table 5. Overall, dermal absorption for these medium-chain phthalates has been proposed to be 10% or less by these agencies.

Given the lack of available data on dermal absorption for some medium-chain phthalates (B84P, B79P), it is therefore proposed that dermal absorption for these diesters is assumed to be 10%. The assignment of 10%, as a default for B84P and B79P, is based on Janjua et al. (2008), which showed a maximal dermal absorption of approximately 10% for DEP and less than 10% for DBP (a medium-chain phthalate with lower molecular weight and log K_{ow} than B84P and B79P) in humans. This default of 10% is also reinforced by the assignment of a dermal absorption of 10% and less, by other agencies, for other medium-chain length phthalates, such as DIBP, DBP, DEHP and BBP (see above and Table E-5).

For DIBP, rat *in vivo* data shows that this substance may be absorbed at approximately 50%. However, DIBP is an isomer of DBP and, as mentioned above, Janjua et al. (2008) found that dermal absorption is less than 10% for DBP. Additionally, DIBP has been assigned a dermal absorption of 10% by other agencies (see Table E-5). Therefore, given the two considerations above, it is proposed that DIBP is dermally absorbed at a maximum of 10%.

Table H-3. Summary of dermal absorption rates for medium-chain phthalates obtained *in vitro* (diffusion cell systems)

Substance	Species	Skin sample	Dose, exposure duration	Receptor fluid	Absorption (% of dose, absorption rate, and/or permeability constant Kp)	Reference
DBP	Human	Full thickness breast skin	20 mg/cm^2, 72 h	HHBSS	0.6% over 72 h Steady state 1.8 µg/cm^2/h	Mint and Hotchkiss 1993
DBP	Rat	Full thickness dorsal skin	20 mg/cm^2, 72 h	HHBSS	11.3% over 72 h Steady state 40.9 µg/cm^2/h	Mint and Hotchkiss 1993
DBP	Human	Epidermis (abdominal skin)	0.5 ml, 30 h	50% EtOH	Steady state: 0.07 µg/cm^2/h Kp = 0.23 x 10^{-5} cm/h	Scott et al. 1987
DBP	Rat	Epidermis (dorsal skin)	0.5 ml, 8 h	50% EtOH	Steady state: 9.33 µg/cm^2/h Kp = 8.95 x 10^{-5} cm/h	Scott et al. 1987
DBP	Rat	Full thickness dorsal skin	50 mg/cm^2, 24 h	RPMI with 2% BSA	Hairless: 39 µg/cm^2/h Haired: 26 µg/cm^2/h	Payan et al. 2001
DBP	Human	Full thickness (abdominal)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	0.59 ± 0.25 µg/h/cm^2	Beydon et al. 2010
DBP	Rat (hair)	Full thickness (dorsal skin)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	24.0 ± 5.2 µg/h/cm^2	Beydon et al. 2010

Substance	Species	Skin sample	Dose, exposure duration	Receptor fluid	Absorption (% of dose, absorption rate, and/or permeability constant Kp)	Reference
DBP	Rat (no hair)	Full thickness (dorsal skin)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	48.9 ± 17.7 µg/h/cm^2	Beydon et al. 2010
DBP	Guinea pig	Full thickness (dorsal skin)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	5.39 ± 0.88 µg/h/cm^2	Beydon et al. 2010
DBP	Rabbit	Full thickness (dorsal skin)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	14.4 ± 4.6 µg/h/cm^2	Beydon et al. 2010
DBP	Mouse (no hair)	Full thickness (dorsal skin)	50 mg/cm^2, 24 h	RPMI 1640 solution 2% BAS	40.4 ± 8.8 µg/h/cm^2	Beydon et al. 2010
DEHP	Human	Stratum corneum	0.3 ml, 32 h	PBS+Volpo-20	Steady state: 0.10 µg/cm^2 /h Kp = 0.0105 x 10^{-5} cm/h	Barber et al. 1992
DEHP	Rat	Full thickness skin	0.3 ml, 32 h	PBS+Volpo-20	Steady state: 0.42 µg/cm^2 /h Kp = 0.0431 x 10^{-5} cm/h	Barber et al. 1992
DEHP	Human	Epidermis (abdominal skin)	0.5 ml, 72 h	50% EtOH	Steady state: 1.06 µg/cm^2 /h Kp = 0.57 x 10^{-5} cm/h	Scott et al. 1987
DEHP	Rat	Epidermis (dorsal skin)	0.5 ml, 53 h	50% EtOH	Steady state: 2.24 µg/cm^2 /h	Scott et al. 1987

Substance	Species	Skin sample	Dose, exposure duration	Receptor fluid	Absorption (% of dose, absorption rate, and/or permeability constant Kp)	Reference
					Kp = 2.28 x 10^{-5} cm/h	
DEHP	Guinea pig	(Not specified)	35.6 nmol/cm^2 153 nmol/cm^2, 24 h 313 nmol/cm^2	HHBSS+4%BSA	6% over 24 h 2.4% over 24 h 2.5% over 24 h	Ng et al. 1992
DEHP	Rat	Epidermis	(Not specified), 72 h	50%EtOH 0.9% PBS	50.5% over 1 h Kp = 94.6 x 10^{-5} cm/h 1.2% over 1 h Kp = 1.30 x 10^{-5} cm/h	Pelling et al. 1997
DEHP	Rat	Dermis	(Not specified), 72 h	50%EtOH 0.9% PBS	5.6% over 1 h Kp = 9.83 x 10^{-5} cm/h 1.7% over 1 h Kp = 4.76 x 10^{-5} cm/h	Pelling et al. 1997

Table H-4. Summary of dermal absorption percentages for medium-chain phthalates obtained *in vivo*

Substance	Molecular weight	Species	Dose	Basis	Absorption (% of dose and/or absorption rate	Reference
DBP	278	Human	5 x 2 mg/cm^2	Urine	At least 1.82% daily over 5 days	Janjua et al. 2008
DBP	278	Human	5 x 2 mg/cm^2	Blood	12–51 µg/L/h for 4 h and increasing following first application	Janjua et al. 2007
DBP	278	Rat	1 x 30-40 mg/kg	Urine + tissues	63% over 7 days	Elsisi et al. 1989

Substance	Molecular weight	Species	Dose	Basis	Absorption (% of dose and/or absorption rate	Reference
DBP	278	Rat	1 x 10 µl/cm^2	Blood + bile + urine	Over the first 8 h: • 20% entered skin • 43 µg/cm^2/h Within 8-48 h: 156 µg/cm^2/h until 48 h	Payan et al. 2001
DBP	278	Rat	1 x 10 µl/cm^2	Urine	Hairless males: • 72% over 30 h • 237 µg/cm^2/h Haired rats: • 56–61% over 30 h 76–92 µg/cm^2/h	Payan et al. 2001
DIBP	278	Rat	1 x 30–40 mg/kg	Urine + tissues	50% over 7 days	Elsisi et al. 1989
BBP	312	Rat	1 x 30–40 mg/kg	Urine + tissues	35% over 7 days	Elsisi et al. 1989
DEHP	391	Guinea pig	1x 53 µg	Urine Urine + tissues	3% (7% after correction) over 24 h 21% (53% after correction) over 7 days 22% over 7 days	Ng et al. 1992
DEHP	391	Rat	1 x 30–40 mg/kg	Urine + tissues	6% over 7 days	Elsisi et al. 1989
DEHP	391	Rat	1 x 30 mg/kg	Urine + tissues	5% over 5 days	Melnick et al. 1987
DEHP	391	Rat	1 x 400 mg (PVC strip)		0.24 µg/cm^2/h	Deisinger et al. 1998

Table H-5. Dermal absorption of medium-chain phthalates evaluated by other jurisdictions

Substance	Molecular weight	Log K_{ow}	Dermal adsorption evaluation	Jurisdiction	Rationale
DBP	278	4.46	**10%** (Danish EPA/ECHA) **5%** (NICNAS)	Danish EPA, ECHA, NICNAS	**DEPA, ECHA** - The log P_{ow} and the molecular weight do not point to a high dermal absorption rate. - From *in vitro* studies, it is concluded that DBP is absorbed more slowly by human skin than by rat skin. From an *in vivo* study with rats, it is seen that approximately 10% is absorbed per day (72% within 7 days). - Considering the available data, dermal absorption is assumed to be 10% (conservative estimate). **NICNAS** - Dermal absorption of DBP in humans is not likely to exceed 2%. However, significant interindividual and daily variations were observed, with a maximum dermal absorption in volunteers corresponding to approximately 6% of the applied DBP dose (Janjua et al.

Substance	Molecular weight	Log K_{ow}	Dermal adsorption evaluation	Jurisdiction	Rationale
					2007, 2008). Based on all data available for DBP, a 5% bioavailability for DBP is estimated for humans through dermal exposure.
DIBP	278.35	4.11	**10%**	Danish EPA, ECHA (read-across of DBP)	See above
BBP	312	4.91	**5%**	Danish EPA, ECHA	- An *in vitro* study showed that DBP, which is very similar to BBP in some of its properties (MW, log K_{ow}, lipophilicity and length of side chain), was absorbed more slowly by human skin than rat skin. - From an *in vivo* study in rats, it was shown that approx. 5% of BBP was absorbed each day, leading to approx. 30% over 7 days vs. 10% over 7 days for DBP. - Considering the available data, dermal absorption is considered to be 5% as a worst-case estimate.
DEHP	391	7.14	**5%**	Danish EPA, ECHA, NICNAS	**DEPA, ECHA** - Based on *in vivo* studies in animals, the cumulative bioavailability of DEHP is 20%. Based

Substance	Molecular weight	Log K_{ow}	Dermal adsorption evaluation	Jurisdiction	Rationale
					on the *in vivo* data and application of an across-species correction factor of 4, a dermal absorption value of 5% is considered reasonable for potential human percutaneous absorption. **NICNAS** - Considering the *in vivo* data results demonstrating that 9 and 26% of dermal absorption of DEHP in rats and guinea pigs, respectively, together with the comparative *in vitro* studies demonstrating that human skin, is significantly less permeable (4-fold) to DEHP than rat skin, the dermal bioavailability of DEHP in humans is not likely to exceed 5%.

Appendix I. Supporting information of the chronic toxicity and carcinogenicity of BBP

Chronic toxicity and carcinogenicity data available for BBP has been summarized previously in a Priority Substances List (PSL) Assessment Report published by Environment Canada and Health Canada (2000). Detailed information is available below.

A carcinogenicity bioassay was conducted by the NTP (1982) in F344 rats. Fifty rats per sex per group were administered BBP via diet, at levels of 0, 6000 or 12 000 ppm (0, 300 and 600 mg/kg bw/day, respectively, using a dose conversion by Health Canada [1994]). Females were exposed for 103 weeks. Because of poor survival, all males were sacrificed at weeks 29–30; this part of the study was later repeated (NTP 1997a).

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

However, these results were not repeated in the two-year dietary study in F344/N rats recently completed by NTP (1997a). The average daily doses (reported by the authors) were 0, 120, 240 or 500 mg/kg bw/day for males and 0, 300, 600 or 1200 mg/kg bw/day for females. The protocol included periodic hematological evaluation and hormonal assays and a 15-month interim sacrifice.

There were no differences in survival between exposed groups and their controls (NTP 1997a). A mild decrease in triiodothyronine concentration in the high-dose females at 6 and 15 months and at termination was considered to be related to a non-thyroidal disorder. Changes in hematological parameters were sporadic and minor. In this bioassay, there was no increase in the incidence of mononuclear cell leukemias in female rats, as was reported in the earlier bioassay (NTP 1982), although the level of exposure (600 mg/kg bw/day) at which the incidence was observed in the early bioassay was common to both studies.

At the 15-month interim sacrifice, the absolute weight of the right kidney in the females at 600 mg/kg bw/day and the relative kidney weight in all exposed males were significantly greater than in controls. The severity of renal tubular pigmentation in high-dose males and females was greater than in controls, at both 15 months and 2 years. The incidence of mineralization in kidney in low- and high-dose females at 2 years was significantly less than in controls; severity decreased in all groups of exposed females. The incidence of nephropathy was significantly increased in all

groups of exposed females (34/50, 47/50, 43/50 and 45/50 in the control, 300, 600 and 1200 mg/kg bw/day groups, respectively) (see Table 2). The incidence of transitional cell hyperplasia (0/50, 3/50, 7/50 and 4/50 in the control, 300, 600 and 1200 mg/kg bw/day groups, respectively) was significantly increased at 600 mg/kg bw/day (NTP 1997a).

At final necropsy, the incidences of pancreatic acinar cell adenoma (3/50, 2/49, 3/50 and 10/50 in the control, 120, 240 and 500 mg/kg bw/day groups, respectively) and pancreatic acinar cell adenoma or carcinoma (combined) (3/50, 2/49, 3/50 and 11/50 in the control, 120, 240 and 500 mg/kg bw/day groups, respectively) in the high-dose males were significantly greater than in the controls and exceeded those in the ranges of historical controls from NTP two-year feeding studies. One carcinoma was observed in a high-dose male; this neoplasm had never been observed in the historical controls. The incidence of focal hyperplasia of the pancreatic acinar cell in the high-dose males was also significantly greater than in the controls (4/50, 0/49, 9/50 and 12/50 in the control, 120, 240 and 500 mg/kg bw/day groups, respectively). Two pancreatic acinar cell adenomas were observed in the high-dose females (NTP 1997a).

The incidences of transitional epithelial papilloma of the urinary bladder in female rats at two years were 1/50, 0/50, 0/50 and 2/50 in the control, 300, 600 and 1200 mg/kg bw/day groups, respectively (NTP 1997a).

The authors concluded that there was “some evidence of carcinogenic activity” in male rats based on the increased incidences of pancreatic acinar cell adenoma and of acinar cell adenoma or carcinoma (combined). There was “equivocal evidence of carcinogenic activity” in female rats based on the marginally increased incidences of pancreatic acinar cell adenoma and of transitional cell papilloma of the urinary bladder (NTP 1997a).

The NTP (1997b) has released a technical report of a study that compared outcomes when chemicals were evaluated under typical NTP bioassay conditions as well as under protocols employing dietary restriction. The experiments were designed to evaluate the effect of dietary restriction on the sensitivity of bioassays towards chemical-induced chronic toxicity and carcinogenicity, and to evaluate the effect of weight-matched control groups on the sensitivity of the bioassays. BBP was included in the protocol; the results were summarized as follows:

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

Fifty $B6C3F_1$ mice per sex per group were exposed to 0, 6000 or 12 000 ppm BBP (0, 780 and 1560 mg/kg bw/day, respectively, using a dose conversion by Health Canada, 1994) via diet for 103 weeks (NTP 1982). Approximately 35 tissues were examined histopathologically. The only compound-related sign of exposure was a dose-related decrease (statistical significance not specified) in body weight in both sexes. Survival was not affected, and there was no increased incidence of any neoplasm that was compound-related. As well, non-neoplastic changes were all within the normal limits of incidence for $B6C3F_1$ mice. The NTP concluded that, under the conditions of the bioassay, BBP "was not carcinogenic for $B6C3F_1$ mice of either sex."

Appendix J. Description and Application of the Downs and Black Scoring System and Guidance for Level of Evidence of An Association

Evaluation of study quality

A number of systematic approaches for assessing the quality of epidemiologic studies were identified and evaluated. The Downs and Black method was selected based on (1) its applicability to the phthalate database, (2) applicability to multiple study designs, (3) established evidence of its validity and reliability, (4) simplicity, (5) small number of components, and (6) epidemiologic focus. Downs and Black consists of a checklist of 27 questions broken down into the following five dimensions: 1) reporting; 2) external validity; 3) internal validity study bias; 4) internal validity confounding and selection bias; and 5) study power. Overall study quality is based on a numeric scale summed over the five categories. The range of the scale allows for more variability in rating study quality. The 27 questions are applicable to observational study designs including case-control, cohort, cross-sectional, and randomized controlled trials.

Studies retained for assessment were scored for quality using the Downs and Black tool. As previously mentioned, the Downs and Black allows for a range of scores from 27 questions, and each epidemiological study design has a maximum score (the maximum score for cohort studies is 21, case-control studies 18, and cross-sectional studies 17). Studies were divided into quartiles based on the scoring distribution for each study design; the distribution of scores for cohort, case-control and cross-sectional studies appears in Figure J-1. The average scores for cross-sectional and case-control studies were 13.1, whereas cohort studies had higher scores than both other study designs with an average score of 14.4.

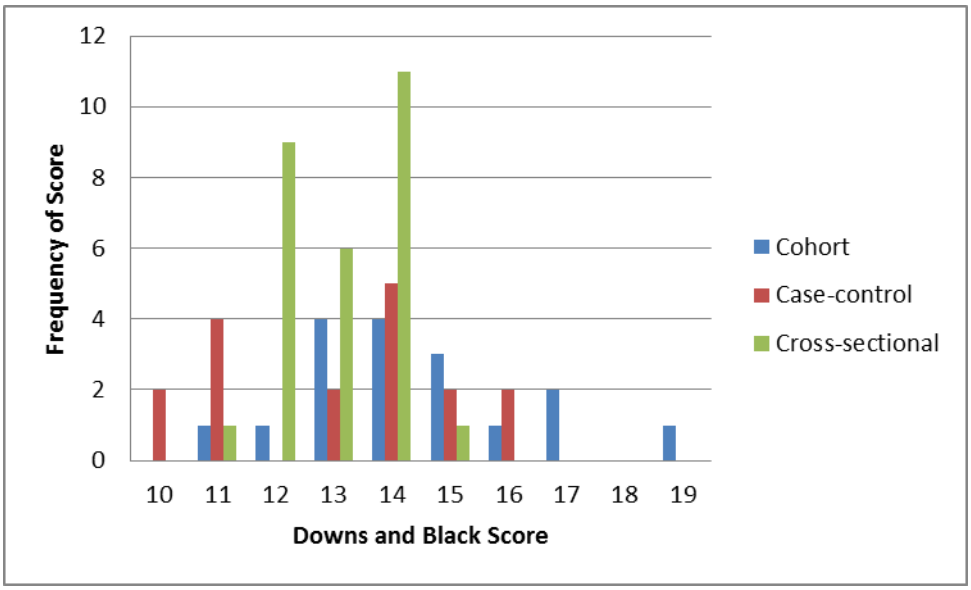

Figure J-1 – Distribution of Downs and Black scores by study design.

Guidance for levels of evidence of an association

The potential for an association between phthalate exposure and each health outcome was assessed based on strength and consistency as well as the quality of the epidemiology studies, as determined by the Downs and Black scores. Descriptions of the levels of evidence of association are as follows:

1. **Sufficient evidence of an association**: Evidence is sufficient to conclude that there is an association. That is, an association between exposure to a phthalate or its metabolite and a health outcome has been observed in which chance, bias and known confounders could be ruled out with reasonable confidence. Determination of a causal association requires a full consideration of the underlying biology/toxicology and is beyond the scope of this document.

2. **Limited evidence of an association**: Evidence is suggestive of an association between exposure to a phthalate or its metabolite and a health outcome; however, chance, bias or confounding could not be ruled out with reasonable confidence.

3. **Inadequate evidence of an association**: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an association.

4. **Evidence suggesting no association**: The available studies are mutually consistent in not showing an association between the phthalate of interest and the health outcome measured.