State of the Science Report

Phthalate Substance Grouping

Short-chain Phthalate Esters

1,2-Benzenedicarboxylic acid, dimethyl ester (Dimethyl phthalate (DMP))

Chemical Abstracts Service Registry Number 131-11-3

Environment Canada
Health Canada

August 2015

Canada

Synopsis

The Ministers of the Environment and the Minister of Health have prepared a state of the science report on 1,2-Benzenedicarboxylic acid, dimethyl ester (DMP) with Chemical Abstracts Service Registry Number (CAS RN[1]) 131-11-3. The purpose of this report is to review the currently available science on DMP 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.

DMP is one of 14 phthalate esters (or phthalates) identified for screening assessment under the Chemicals Management Plan (CMP) Substance Grouping Initiative. 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 discussion on a proposed cumulative risk assessment approach for certain phthalates is provided in an accompanying document (Environment Canada and Health Canada 2015a). DMP belongs to the short-chain phthalate esters subgroup.

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DMP does not occur naturally in the environment. In the calendar year 2012, DMP was imported into Canada in quantities of < 100 000 kg and was reported to have applications in the production of paints, coatings, adhesives and sealants. DMP also has applications as a plasticizer in the production of building materials as well as applications in production of personal care products[2].

Releases of DMP are most likely to occur to air and water. When released into air, DMP is predicted to partition mainly to soil. When released to water or soil, DMP is expected to largely remain in those respective media. Limited environmental concentration data for Canadian media show maximum, but not necessarily representative, concentrations of 5.46 ng/L in surface water, 2 600 ng/L in municipal wastewater treatment plant effluent, and 853 ng/g in sediment. Canadian monitoring data available for DMP in air and soil indicate that concentrations are all below detection limits. DMP is persistent in air, but not in water, soil, or sediment. DMP has very low bioaccumulation potential in aquatic organisms. Acute and chronic experimental data all indicate that DMP is not highly hazardous to aquatic organisms. Exposure scenarios were developed to estimate releases of DMP to air and water from facilities where it is used as a coating additive. Monitoring data were also used to estimate potential exposure concentrations. Risk quotients calculated for both air and water scenarios indicate that harm to aquatic and terrestrial organisms is unlikely.

With regard to human health, the principal source of exposure to DMP, for the general population, is expected to be from breast milk and food, with indoor air and dust also acting as contributors. Dermal and inhalation (aerosol) exposure to cosmetics and personal care products were also evaluated for adults (20 +) and infants (0 to 6 months).The health effects database for short-chain phthalate esters shows no evidence of adverse effects on developmental, reproductive or other organ systems after exposure to DMP. Based on available information, the critical levels selected for risk characterization were mainly related to no-observed-effect levels (NOELs) and a lowest-observed-effect-level based on mild changes in brain weights after chronic dermal exposure.

Comparisons of estimates for exposure to DMP from environmental media, food, and personal care products, as well as biomonitoring levels for all age groups, with the appropriate critical effect levels, results in margins of exposures that are considered adequate to address uncertainties in the exposure and health effects databases.

[2]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 Phthalate 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 2013). 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). Assessing 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. 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 2015), 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 1,2-Benzenedicarboxylic acid, dimethyl ester or DMP (CAS RN[3] 131-11-3). This substance was identified in the categorization of the DSL under subsection 73(1) of CEPA 1999 as priority for assessment. This substance also met the categorization criteria for persistence but not the criteria for inherent toxicity of non-human organisms or bioaccumulation.

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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). 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 a recent document prepared by Health Canada (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 2015).

DMP belongs to the short-chain phthalate esters subgroup (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 October 2014 for the ecological portion and up to August 2014 for the health portion of the assessment. 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 develop a screening assessment in the future.

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. Jack Dempsey (EnRisks), Dr. Michael Jayjock (The Lifeline Group) and Dr. Bernard Gadagbui (Toxicology Excellence for Risk Assessment). 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 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).

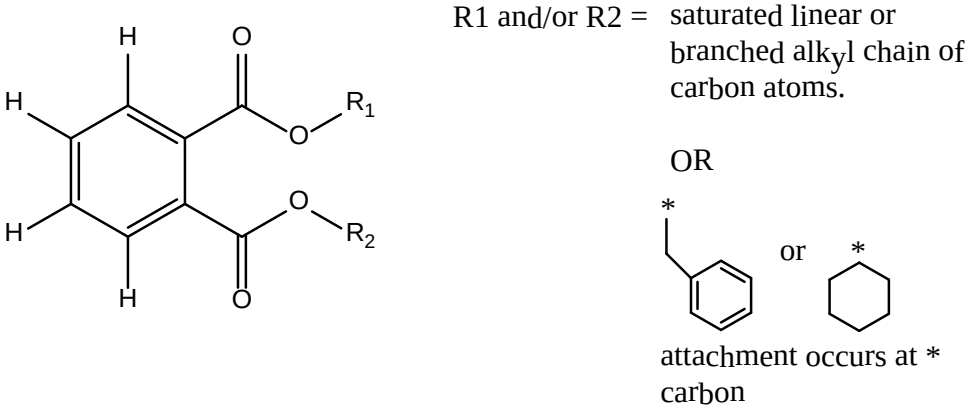
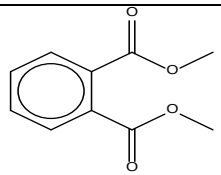


Figure 1.General structure of *ortho*-phthalates.

Dimethyl phthalate (DMP) is one of the 14 phthalate esters in the Phthalate Substance Grouping. Information on the chemical structure and identity of DMP is given in Table 2-1. DMP, having one methyl group in each ester side chain falls into the short-chain subgroup. DMP is a discrete organic substance.

Table 2-1. Substance identity of DMP

CAS RN Acronym	DSL name and common name	Chemical structure and molecular formula	Molecular weight (g/mol)

CAS RN Acronym	DSL name and common name	Chemical structure and molecular formula	Molecular weight (g/mol)
131-11-3 DMP	1,2-Benzenedicarboxylic acid, dimethyl ester Dimethyl phthalate	 C10H10O4	194.19

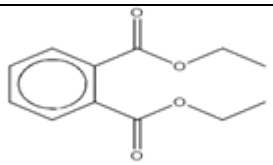
Abbreviations: CAS RN, Chemical Abstract Service Registry Number; DSL, Domestic Substances List.

2.1 Selection of Analogues for Ecological Assessment

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, have been used to inform the ecological and human health assessments.

For the ecological assessment, an analogue was selected that is structurally similar and/or functionally similar to the substance in this subgroup (e.g., based on physical-chemical properties, toxicokinetics), and that had relevant empirical data that could be used to read-across to fill data gaps. The analogue selected, diethyl phthalate (DEP), was specifically chosen to fill data gaps for toxicity to soil and sediment-dwelling organisms, as well as toxicity to terrestrial organisms by inhalation. This choice of analogue is justifiable because the physical-chemical property values for DEP are comparable to those for DMP (e.g., log K_{ow} values are 1.47 for DMP and 2.51 for DEP, respectively), and the two substances share the same nonspecific (narcotic) mode of action (MOA). Further information on the ecological rationale for selecting this analogue is provided in an appendix to the draft approach for considering cumulative risks of phthalates (Environment Canada and Health Canada 2015). The substance identity of DEP is shown below.

Table 2-2. Substance identity of DEP

CAS RN Acronym	DSL name and common name	Chemical structure and molecular formula	Molecular weight (g/mol)
84-66-2 DEP	1,2-Benzenedicarboxylic acid, diethyl ester Diethyl phthalate	 $C_{12}H_{14}O_4$	222.24

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

The applicability of (Q)SAR models was determined on a case-by-case basis.

For the human health effects assessment, the same analogue DEP was selected for read-across. Information on the selection of this analogue is provided in Health Canada (2015a).

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.

A summary of physical and chemical properties for DMP is presented in Table 3-1. When experimental information was limited or not available for a property, data from (Q)SAR models were used to generate predicted values for the substance. Key experimental studies were critically reviewed for validity and these reviews (Robust Study Summaries) are available in Environment Canada (2015).

Table 3-1. Experimental and predicted physical and chemical properties for DMP

Property	Value or range[a]	Type of data	Key reference
Physical state	Liquid (oily, at room temp.)	Experimental	European Commission 2000
Melting point (°C)	5.5[†]	Experimental	Haynes and Lide 2010
Boiling point (°C)	283.7 (at 1013 hPa)	Experimental	Haynes and Lide 2010
Density (kg/m^3)	1190	Experimental	Haynes and Lide 2010
Vapour pressure (Pa)	0.22 (1.65 x 10^{-3} mmHg)	Experimental	Howard et al. 1985
Vapour pressure (Pa)	0.24 (1.8 x 10^{-3} mmHg)	Experimental	Stephenson and Malanowski 1987
Vapour pressure (Pa)	0.72 (5.4 x 10^{-3} mmHg)	Experimental	Cowen and Baynes 1980
Vapour pressure (Pa)	0.411[†]	Experimental	Daubert and Danner 1989
Water solubility (mg/L)	4290[d]	Experimental	Leyder and Boulanger 1983
Water solubility (mg/L)	4000[†]	Experimental	Yalkowsky et al. 2010
Henry's Law constant (Pa·m^3/mol)	2.27 × 10^{-2}	Modelled	HENRYWIN 2011 Bond estimate
Henry's Law constant (Pa·m^3/mol)	6.23 × 10^{-3}	Modelled	HENRYWIN 2011 Group estimate

Property	Value or range[a]	Type of data	Key reference
Henry's Law constant ($Pa \cdot m^3/mol$)	5.94×10^{-2}	Modelled	HENRYWIN 2011 VP/WS estimate[b]
Henry's Law constant ($Pa \cdot m^3/mol$)	1.99×10^{-2}	Modelled	HENRYWIN 2011 VP/WS estimate[c]
log K_{ow} (dimensionless)	1.60	Experimental	Ellington and Floyd 1996
Log K_{ow} (dimensionless)	1.47	Experimental	Howard et al. 1985
Log K_{ow} (dimensionless)	1.61[†]	Experimental	Renberg et al. 1985
Log K_{ow} (dimensionless)	1.80 [e]	Experimental	Macintosh et al. 2006
Log K_{ow} (dimensionless)	1.53	Experimental	Leyder and Boulanger 1983
Log K_{oc} (dimensionless)	1.90 – 2.56	Experimental	Banerjee et al. 1985
Log K_{oc} (dimensionless)	1.68	Modelled	KOCWIN 2010 (K_{ow} estimate)
Log K_{oa}(dimensionless)	6.69	Modelled	KOAWIN 2010
Log K_{oa} (dimensionless)	7.01	Modelled	Cousins and Mackay 2000

Abbreviations: K_{ow}, octanol-water partition coefficient; K_{oc}, organic carbon-water partition coefficient; K_{oa}, octanol-air partition coefficient
[†]Indicates value selected for fate modelling.
[a] All values are for measurements and calculations at 25°C unless otherwise stated.
[b]VP/WS estimate derived using modelled values for vapour pressure (MPBPVPWIN 2010) and water solubility (WSKOWWIN (2010).
[c]VP/WS estimate derived using empirical values of 0.411 Pa and 4000 mg/L for vapour pressure and water solubility, respectively.
[d] At 20°C.
[e]Octanol-seawater

Models based on quantitative structure-activity relationships (QSARs) were used to generate data for some of the physical and chemical properties of DMP, such as the Henry's Law constant. These models are mainly based on fragment addition methods, i.e., they sum the contributions of sub-structural fragments of a molecule to make predictions for a property or endpoint. Most of these models rely on the neutral form of a chemical as input and this approach is appropriate for the phthalates as they occur as neutral (non-ionized) substances in the environment.

Based on experimental and modelled physicochemical property values, DMP is an oily liquid at room temperature and has high water solubility, moderate vapour pressure, a low octanol-water partition coefficient (K_{ow}) value, and a low organic carbon–water partition coefficient (K_{oc}) value.

4. Sources

DMP does not occur naturally in the environment. Under certain conditions, higher molecular weight phthalates, when metabolized or biodegraded, may be a source of DMP in the environment. Hashizume et al. (2002) examined the biodegradation of phthalates in river water, and by microbes isolated from river water and observed that, as DEP and DEHP degraded, DMP was produced. DMP was also produced from DBP in the crude enzyme solution that the authors used. However, it is generally thought that demethylation of the alkyl chains to degrade longer-chain phthalates to shorter-chain phthalates is not a significant degradation pathway in the natural 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). Results of the section 71 industry survey for the year 2012 indicated that DMP was imported into Canada in quantities of 10 000 – 100 000 kg in 2012 (Environment Canada 2014). Due to the targeted nature of the survey, reported use quantities may not fully reflect all uses in Canada.

In the United States, national aggregated production volumes of DMP were reported through Inventory Update Reporting (IUR) between 1986 and 2002 (US EPA 2014ab). Based on non-confidential reporting information, DMP use ranged between > 4536 – 22 680 tonnes in 2002; in 2006, the reported range was also reported to be between 4536 – < 22 680 tonnes (US EPA 2014ab).

Production/use volumes of 10 000 to 100 000 tonnes per year have been reported by registrants under the European Union's REACH Initiative (ECHA 2014). Furthermore, DMP has been identified as a high production volume chemical in Europe (ESIS 2014).

5. Uses

Based on results of an industry survey issued pursuant to section 71 of CEPA 1999, DMP has applications in the production of paints, coatings, adhesives and sealants (Environment Canada 2014a). It also has applications as a plasticizer in the production of building materials (Environment Canada 2014a). According to submissions in response to the Section 71 survey, less than 1000 kg of DMP was used in Canada in 2012.

DMP may be used as a solvent and plasticizer for nitrocellulose, cellulose acetate, and cellulose acetate-butyrate compositions (NICNAS 2008). It is also a plasticizer for coatings and cellulose moulding compounds, and has been reported for use as an auxiliary plasticizer for surface coatings (Valspar 2011). It may also have applications as an inhibiting and stabilizing agent in peroxide (Cheminfo 2013; ECHA 2014). It may have use in explosives and may also be used as a laboratory chemical (Cheminfo 2013, NICNAS 2008, and ECHA 2014).

DMP is listed in the Compilation of Ingredients Used in Cosmetics in the United States, and is known to have uses as a solvent, plasticizer, and fragrance ingredient in cosmetics (Cheminfo 2013; Bailey 2011). Specifically, DMP may be used in creams, perfumes, nail polishes, deodorants, face powders and foundations, bath soaps and detergents, aftershave lotions, hair sprays and shampoos (Versar and SRC 2011; Ash and Ash 2003; Cheminfo 2013). Hair care products containing DMP include hair sprays (aerosol fixatives), hair preparations, and aerosol hair colour sprays, as well as hair conditioners, tonics, dressings, wave sets, personal/hair care products and colouring rinses (CIR Expert Panel 2003; Liebert 1985; ECHA 2014). DMP may also be used as a fragrance base for household cleaning products (NICNAS 2008, SCCP 2007).

DMP may be used in paints and coatings, thinners, paint remover fillers, putties, plasters, modelling clay, finger paints, sealants, polishes and wax blends, varnishes, and adhesives (NICNAS 2008; Versar and SRC 2011; Ash and Ash 2003, ECHA 2014). DMP is also found in paints and coatings, which are not intended for use in children's products (US EPA IUR 2014).

In terms of manufactured articles, DMP may be used to produce foam plastic products/articles, rubber and plastic products (stated to be intended for children), paper articles, wood articles, electrical batteries, accumulators, mechanical appliances and electrical/electronic articles (US EPA IUR 2014; ECHA 2014). DMP also has uses in fabrics, textiles and apparel (ECHA 2014). Additionally, DMP has been detected in headsets and children's toys and products produced from foam plastic (Danish EPA 2006e, 2008d).

In the food industry, DMP is a solvent for adjuvants in food-contact cross-linked polyesters, a food-packaging adhesive, and is found in acrylic food packaging (Ash and Ash 2003). Additionally, DMP may have applications in the production of pharmaceutical products (ECHA 2014).

DMP also may have applications in insecticides and pesticides (NICNAS 2008; Ash and Ash 2003; Versar and SRC 2011). DMP is registered as a formulant in pest control products registered in Canada (January 2015 email from PMRA, Health Canada to Existing Substances Risk Assessment Bureau (ESRAB), Health Canada, unreferenced).

Finally DMP may be used as an excipient in pharmaceuticals and is listed on the U.S. Food and Drug Administration (FDA) Inactive Ingredient Database (FDA 2014). DMP is not 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 a medicinal or non-medicinal ingredient 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).

DMP is 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 2011). Based on notifications submitted under the Cosmetic Regulations to Health Canada, DMP was notified to be present in 3 products however the submissions were all made prior to 2008 (September 2014 email from the Consumer Product Safety Directorate (CPSD), Health Canada to ESRAB, Health Canada).

Finally DMP has been identified to be used in food packaging applications where it is a plasticizer in the manufacture of fibreglass reservoirs to hold water for washing and cleaning purposes in food plants (September 2014 e-mail from the Food Directorate, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced).

6. Releases

In response to the section 71 survey for 2012, one company in the paint and coatings sector reported DMP releases of 2 kg to air (Environment Canada 2014). Manufacturing and use of industrial coatings and sealants could result in releases to water, and potentially to air in the case of spray applications of coatings. Many section 71 submissions indicate no releases, releases unknown, or transport of wastes to off-site facilities for disposal. However, the majority of companies do not appear to measure releases, so releases from industrial facilities are not well quantified. Releases to water may be treated at on-site or off-site wastewater treatment systems.[4] Under the National Pollutant Release Inventory (NPRI) program, one company in Toronto, a user of paints and coatings products, located in Toronto, reported DMP releases of 1 300 kg to air in 2013 (NPRI 1995-).

Based on the uses of DMP identified above, other releases are possible. For example, the use of DMP in personal care products and cosmetics will likely result in releases to municipal wastewater treatment systems from down-the-drain disposal.

Releases of DMP could occur in effluents from both on-site and off-site wastewater treatment systems. During treatment of phthalate-containing wastewater, adsorption and biotransformation are key processes in the removal/degradation responsible for the

[4] 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”.

reduction of phthalates in wastewater system effluent. The importance of adsorption and therefore the removal pathway via sludge increases with increasing molecular weight and with increasing lipophilic character of the substance (Clara et al. 2010). DMP has a low log K_{ow}, and, consequently, we would expect limited adsorption and removal by sludge. In fact, in one wastewater treatment system examined (Clara et al. 2010) adsorption amounted to only 3.4%. The key removal process of DMP, during wastewater treatment is biotransformation. Studies show high removal rates (biotransformation) of DMP during wastewater treatment. For example, in a study of removal efficiencies at wastewater treatment plants (WWTPs) in the EU, Deblonde et al. (2011) found that the mean influent concentration of DMP was 1.51 µg/L, the mean effluent concentration was 0.038 µg/L, and the removal rate was 97.5%. Therefore, based on these studies, releases of DMP to the receiving water body from wastewater effluent are expected to be low.

Other potential releases of DMP could occur from the reconditioning of transport containers and trucks, the migration from plastic products, and washing of phthalate-containing floors and wall-coverings. Leaching of DMP from plastic products in landfills could also occur but that scenario is not evaluated in this report.

7. Environmental Fate and Behaviour

7.1 Environmental Distribution

A summary of the Level III fugacity modelling, i.e., the mass-fraction distribution of DMP based on individual steady-state emissions to air, water and soil, is given in Table 7-1 below. The results in Table 7-1 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 overall results of Level III fugacity modelling suggest that DMP can be expected to distribute mainly into water, soil and air, depending upon the compartment of release (Table 7 1). The substance is not predicted to distribute appreciably into sediment.

Table 7-1. Summary of the Level III fugacity modelling (EQC 2003) for DMP, showing percent partitioning into each medium for three release scenarios

Substance released to:	Air (%)	Water (%)	Soil (%)	Sediment (%)
Air (100%)	13.6	16.7	69.7	negligible
Water (100%)	negligible	99.8	negligible	0.2
Soil (100%)	0.2	11.1	88.7	negligible

When released into air, DMP is predicted to be deposited to soil (69.7%) mainly as wet deposition, with lesser proportions residing in water (16.7%) and air (13.6%). The relatively long half-life of DMP in air (9.32 days) indicates that DMP released to air could potentially be subject to long-range transport (see below, subsection 7.1.1) in the gaseous phase.

7.1.1 Long-range transport potential

The predicted half-life of DMP in air is 9.32 days (see Environmental Persistence Section 7.2). This relatively long half-life, together with some partitioning to air when released into this compartment (Table 7-1), suggests that DMP might have long-range atmospheric transport potential (LRATP) to regions remote from its source of release.

The Transport and Persistence Level III Model (TaPL3 2000) was used to estimate the Characteristic Travel Distance (CTD) of DMP, defined as the maximum distance traveled in air by 63% of the substance. Beyer et al. (2000) have proposed CTDs of >2000 km as representing high LRATP, 700–2000 km as moderate LRATP, and <700 km as low LRATP. Based on the CTD estimate of 668 km, the LRATP of DMP is considered to be low, bordering on moderate. This means that DMP is not expected to be transported through the atmosphere to great distances from its emission sources.

The OECD POPs Screening Model can also be used to help identify chemicals with high persistence and long-range transport potential (Scheringer et al. 2006). The OECD model is a global model that compartmentalizes the Earth into air, water and soil. This model is “transport-oriented” rather than “target-oriented” as it simply identifies the CTD without indicating specifically where a substance may be transported to (Fenner et al. 2005). Klasmeier et al. (2006) have suggested that a threshold of 5098 km, based on the model’s CTD estimate for PCB-180, can be used to identify substances with high long-range-transport potential. PCB-180 is empirically known to be found in remote regions. The CTD calculated for DMP using the OECD model is 1670 km indicating that DMP has some potential for transport in air, but this is below the boundary suggested for global pollutants by Klasmeier et al. (2006). The OECD POPs Screening Model also calculates the transfer efficiency (TE), which is the percentage of emission flux to air that is deposited to the surface (water and soil) in a remote region (TE % = D/E x 100, where E is the emission flux to air and D = the deposition flux to surface media in a target region). The TE for DMP was calculated to be 4.75%, which is above the boundary of 2.248% (PCB-28) established based on the model’s reference substances empirically known to be deposited. The higher TE means that DMP has the potential to be deposited from air to water and soil in regions remote from the source of release. This result is consistent with that obtained through Level III fugacity modelling (EQC 2003) which predicts that about 86% of DMP released into air will further distribute into water and soil (see Table 7-1).

In addition, the modelled log K_{oa} and log K_{aw} values for DMP, 6.69 (KOAWIN 2010) and -5.1 (based on HENRYWIN 2011), respectively, suggest that DMP may have Arctic contamination potential (ACP) when examined using chemical partitioning space plots as described by Wania (2003, 2006).

Measured concentrations of DMP in biota in Hudson’s Bay (Morin 2003), as well as in air and water of the Norwegian Arctic, suggest that there is some potential for long-range transport of DMP (see below, subsection 9.1).

7.2 Environmental Persistence

DMP is persistent in air, but not persistent in water, soil, or sediment. DMP has moderate vapour pressure and equilibrium partitioning (EP) indicates that a significant percentage of DMP released will partition to air. DMP has relatively high water solubility, compared to medium and long-chain phthalates, and EP indicates that DMP released to water will largely remain there.

A couple of biodegradation pathways for phthalates have been proposed, including de-esterification and de-methylation. Pathways appear to depend on the specific organism involved. For example, Babu and Wu (2010) found that the degradation pathways in cyanobacteria are different from those in soil microbes. A detailed discussion of biodegradation pathways for phthalates is found in Environment Canada (2015a).

7.2.1 Abiotic degradation

DMP is persistent in air, according to modelled results, with a predicted half-life of 9.32 days for atmospheric oxidation (AOPWIN 2010).

The half-life in the environment for the hydrolysis of DMP is 2.8 years (HYDROWIN 2008) at pH 7. It can be concluded that hydrolysis in the environment is unlikely to be an important fate process for DMP under typical environmental conditions. It should be noted, however, that DMP is rapidly hydrolyzed within organisms (Lake et al. 1977; Rowland et al. 1977; White et al. 1980).

7.2.2 Biodegradation

Empirical data for the biodegradation of DMP are presented in Appendix A. Studies have reported that phthalates are biodegraded by bacteria, fungi, and algae (Zeng et al. 2004).

The ready biodegradability of DMP was determined using a test similar to the static-culture, flask-screening procedure of Bunch and Chambers (1967), utilizing biochemical oxygen demand (BOD) dilution water as the synthetic medium. In this study (Tabak et al. 1981), the authors used gas chromatography (GC) as well as dissolved organic carbon (DOC) and total organic carbon (TOC) analytical procedures for determining the extent of biodegradation. They found 100% biodegradation of DMP after 7 days in all three subcultures and for both concentrations of DMP tested (5 and 10 mg/L).

Results for the biodegradation of DMP in river water are mixed. Furtmann (1994) reported that DMP in samples of Rhine 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. Addition of sodium azide (bacteriostatic poison of cytochrome oxidase in mitochondria) stopped the degradation processes. Hashizume et al. (2002), however, found somewhat different results in a study of the biodegradation of phthalates, including DMP, in surface waters from rivers located in urban Japan. They

found that DMP was degraded by 49.3% and 100% after 7 days in samples of Tempaku river water from two different locations and that isolates from river water did not degrade DMP at all in 7 days. Biodegradation in surface waters can be variable between different water bodies for the same substance, in part due to different concentrations of suspended matter (Banerjee et al. 1984). It could also be due to differences in strength of the inocula. Differences in the concentration of suspended matter are unlikely to have an effect on the biodegradation of DMP in surface water because DMP has a low K_{oc} and is not expected to partition from water to suspended matter to any significant degree.

Relatively short half-lives (1.9 days to 2.5 days) have been reported for DMP with acclimated sediment/water organisms (Kickham et al. 2012; Sugatt et al. 1984), but somewhat longer periods for degradation of DMP have been reported for marine sediments (11.8 days) (Peng and Li 2012).

Biodegradation data for DMP in soil under aerobic conditions showed a clear effect, by the bacteria Pseudomonas fluoresences FS1, on biodegradation rates; the half-life of DMP ranges from 6 hours to 10 hours (Zeng et al. 2004). Wang et al. (2004) found that DMP was rapidly degraded in soil bioaugmented with acclimated activated sludge, with a half-life of 2.29 days and 100% removal in less than 15 days. Although not specified in these studies, the half-lives and removal rate are likely for primary degradation.

Wang et al. (1996) found that the use of acclimated activated sewage sludge resulted in the rapid removal of DMP, with a half-life of 21 hours. In an activated shake flask CO_2 evolution test, Sugatt et al. (1984) found 86% biodegradation after 28 days, indicating that DMP is readily biodegradable. The authors also found primary biodegradation greater than 99% and a half-life of 1.9 days. The extrapolation of results of such a screening test to natural water systems requires the consideration of factors such as the effect of environmental conditions on the acclimation process.

Babu and Wu (2010) found that some phthalates, including DMP, enhance the growth of the cyanobacteria Anabaena flos-aquae.The authors indicate that, when compared with green algae studied by Hai and Yun-zia (1998), the cyanobacteria evaluated in their study exhibited much higher biodegradation rates for DMP.

The biodegradation kinetics of DMP were investigated using the bacterium Pseudomonas fluorescens FS1 and activated sludge at a petrochemical factory (Zeng et al. 2004). The authors found that biodegradation followed first-order kinetics and the biodegradation half-life was 6.38 hours at an initial concentration of 100 mg/L and a temperature between 20°C and 35°C. They also found that the biodegradation rate was significantly retarded at lower temperatures (e.g. 10°C) and temperatures above 35°C. Battersby and Wilson (1989) studied the ultimate degradation potential of 77 organic chemicals, including DMP, with an anaerobic digesting sludge from the UK. Degradation was assessed in terms of net gas production (NGP) (CH_4 plus CO_2) produced, expressed as a percentage of the theoretical gas production (ThGP). A NGP measurement is a screening test for assessing anaerobic biodegradation potential

under methanogenic conditions. The authors found that, after a lag (adaption) period of 16 days, the NGP for DMP was 41 ± 8.3 % of ThGP, which means that DMP will most likely be degraded in an anaerobic digester. Wang et al. (2000) also studied the biodegradation of DMP under anaerobic conditions and found DMP was degraded quickly (greater than 90% removal in less than 4 days).

While there is evidence for rapid biodegradation of DMP, questions remain about the complete mineralization of certain dialkyl phthalate esters (DPEs) in environmental settings primarily because investigations have often been limited to reduction of initial chemical concentration, not to complete mineralization of DPEs.

The empirical biodegradation data, from ready-biodegradation and other tests, show that the biodegradation of DMP ranges from 0% to 100% over a period of hours. The empirical data are summarized in Appendix A. The weight of experimental and modelled evidence indicates that DMP is readily degradable.

7.2.3 Metabolites

McConnell (2007) investigated the presence, distribution, and bioaccumulation potential of monoalkyl phthalate esters (MPEs) in organisms of an aquatic food. A field study was conducted in False Creek, Vancouver; sediment, seawater, and seven marine organisms were collected. The highest MPE concentrations (200 µg/kg) were observed for mono-n-butyl phthalate (M*n*BP) in mussels. MPEs were not found to biomagnify in the food web. This seems to indicate that MPEs are relatively quickly eliminated, possibly through gill water exchange and/or metabolic transformation. The McConnell (2007) study further suggests that the primary source of MPEs to the aquatic environment is via dietary DPE uptake and subsequent metabolism in biota, although this is less likely to occur with DMP given the lower dietary exposure for this substance compared to phthalates with higher log K_{ow}s.

7.3 Potential for Bioaccumulation

Measured BCFs and BAFs for DMP are similar and are generally in the low end of the bioaccumulation range for discrete organic substances. DMP has a low log K_{ow}, which indicates that significant accumulation in tissues is unlikely. However, bioconcentration factors in fish are lower than expected (when considering log K_{ow}), which is likely related to a comparably high ability of these species to metabolize DMP (van Wezel et al. 2000). The low log K_{ow} also means that DMP has low potential to partition from water into the lipid tissues (e.g. liver) of aquatic organisms.

7.3.1 Bioconcentration factor (BCF)

There are few data for the bioconcentration of DMP. In Barrows et al. 1980, a BCF of 57 was reported for bluegill sunfish. Although the exposure period was 28 days, equilibrium was obtained after 7 days.

There are reliability issues with some BCF studies. For example, Wofford et al. (1981) report a BCF of 6.0 for Sheepshead minnow, but the exposure period was only 24 hours and the tissue for bioaccumulation was not reported.

A maximum BCF of 162 L/kg was reached for the alga Chlorella pyrenoidosa in 24 hours (Yan et al. 1995). Algae were grown in 100-mL flasks containing 25 mL of a medium-phthalate solution at 24°C, and the test concentration of DMP was 100 mg/L. Bioconcentration rates were affected by biodegradation of DMP, which was affected by both the density of algal cells and cell growth rate. This study was not considered reliable, as no source or purity was given for the DMP tested.

The data regarding the bioconcentration of DMP in aquatic organisms are documented in Environment Canada (2015a).

7.3.2 Bioaccumulation factor (BAF)

Experimental BAF data indicate that DMP has very low potential to bioaccumulate. In a study by Ge et al. (2011), tilapia (*Oreochromis* spp.) were given a single dose of 20 mg/kg body weight DMP orally, to evaluate the uptake and tissue residues at two different water temperatures (18ºC and 28ºC). The concentrations of DMP in various tissues were reported. Bioaccumulation factors (BAFs) were calculated (Intrinsik 2013) by dividing tissue concentrations by the dose given (20 mg/kg). In the study, concentrations were measured at different time intervals but for the purpose of BAF calculations, concentrations at the last time interval sampled (360 h) were used. Calculated BAFs for each of several tissue types were all less than 1, suggesting limited potential for accumulation in this study.

DMP has greater bioaccumulation potential, based on field studies, than indicated by its log K_{ow}. For example, the predicted lipid equivalent BAF for sculpins, using the log K_{ow} of 1.78, is 70.4, and the observed lipid equivalent BAF is 19 000 (Gobas et al. 2003). A possible explanation for the high BAF for DMP is the large disequilibrium between sediments and overlying water; contact of organisms with the sediments (e.g., sculpins burying in sediments) may elevate the body burden of DMP in organisms over that absorbed from the overlying water. Additionally, uptake via the gill might be greater than that predicted by the model and/or there might be significant differences in metabolism rate and lipid weight compared with that used in the model.

7.3.3 Biota-sediment accumulation factors (BSAFs) and Biota-air accumulation factors (BAAFs)

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 being in biota compared to the sediment (Morin 2003). Alternatively, ASTM (1997) recommends a “cut-off” value

of 1.7 to represent equilibrium conditions. BSAFs which exceed approximately 1.7 to 3 (on a normalized basis) suggest that biomagnification is increasing and organism chemical concentrations are above equilibrium conditions (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 epibenthic organisms that inhabit the epilimnion. Mackintosh (2004) calculated BSAF values of phthalate esters in 8 organisms in the marine food web by dividing the mean lipid normalized biota concentration by the mean organic carbon normalized sediment concentration. The calculated BSAF for DMP was 0.77.

In a study on the distribution of phthalate esters (including DMP) in mammals, fish, sediment and air in eastern Hudson's Bay, Morin (2003) calculated BSAF values of phthalate esters in beluga whale (Delphinapterus leucas) and arctic cod (Boreogadus saida). Sediment is considered a source of dietary exposure for the beluga, as they use suction while scavenging for benthic organisms and could ingest sediment (Morin 2003). The BSAF values are lipid normalized, and corrected for organic carbon, and reported as 1.37 kg organic carbon/kg lipid in arctic cod and 2.29 kg organic carbon/kg lipid in beluga whale. The value for beluga indicates that DMP has some ability to bioaccumulate. However, since the BSAF for arctic cod is close to unity, it indicates that dietary exposure may not contribute significantly to trophic transfer of DMP and food web accumulation in the environment.

BSAFs were calculated from concentrations in fish and sediment samples taken in 17 rivers in Taiwan. BSAFs for DMP were presented graphically, and ranged from 0.05 to 1.2 in four fish species (Huang et al. 2008), similarly indicating a low level of accumulation.

The BCFBAF model (EPI Suite 2000-2008) predicts, for the mid-trophic level with biotransformation, a BCF and BAF of 2.065 for fish.

No empirical data were available for uptake of DMP from air, water, or soil into plants or other terrestrial organisms. However, Morin (2003) found a lipid-equivalent biota air bioaccumulation factor (BAAF) for beluga whales of 7.66, indicating that air exposure is more significant than dietary exposure in contributing to the bioaccumulation of DMP.

7.3.4 Biomagnification

There are few studies where the measured biomagnification of DMP is reported.

In aquatic systems (eastern Hudson's Bay), Morin (2003) found a wet-weight biomagnification factor (BMF_w) for DMP of 12.3 for beluga whales and lipid-equivalent

biomagnification factor (BMF_l) of 1.67. The BMFl result, however, was not found to be statistically different from 1.0, indicating that DMP has low potential to biomagnify in beluga whales. Explanations for this include: the similarity of trophic positions for the prey (cod: 3.6) and predator (beluga: 3.9), metabolic transformation, and the dietary makeup of the belugas sampled.

No measured data were available on the biomagnification of phthalates in terrestrial ecosystems. All available information indicates that food-web bioaccumulation, i.e., biomagnification, of phthalates does not occur (Gobas et al. 2003).

Summary of Environmental Fate and Behaviour

DMP could be released during industrial activities and, possibly, through consumer use, with releases occurring primarily to air and to pre-treatment wastewaters. Phthalates such as DMP are not chemically bound to polymer matrices, so they can migrate slowly to the surface of the product, and then, possibly enter the environment. DMP entering air will be deposited to soil and, to a lesser extent, remain in air and be deposited to water. DMP released into pre-treatment wastewaters will likely undergo wastewater treatment at on-site or off-site treatment facilities. DMP will biodegrade rapidly and is not expected to be recalcitrant in the environment. Degradation may be slightly slower under anaerobic conditions which will increase the length during which organisms might be exposed. As well, moderate use quantities of DMP, including use in consumer products, indicate that releases to the environment, and therefore exposure, may be continuous. Based on information about releases and the predicted distribution in the environment, soil-dwelling and aquatic organisms will have the highest potential for exposure to DMP. The rapid biodegradation rate of DMP indicates that exposure will be greatest for organisms inhabiting areas close to release sites; concentrations are expected to decrease with increasing distance from points of discharge into the environment although there is some potential for long-range transport. The high water solubility of DMP indicates that exposure will be primarily through direct contact via the surrounding medium rather than through the diet. Empirical and modelled evidence indicate that DMP has low bioaccumulation and biomagnification potential, largely because of high biotransformation capacity.

8. Potential to Cause Ecological Harm

8.1 Ecological Effects

Empirical aquatic toxicity data for DMP are summarized in Appendix B. DMP has low toxicity to aquatic organisms, which is consistent with its low bioaccumulation potential. Fish are more sensitive than algae, while invertebrates span a greater range of toxicological response. In many cases, no Lowest-observed-effect-concentration (LOEC) data were available, due to lack of toxicity at the highest doses tested. Acute toxicity data for fish, invertebrates and plants indicate that DMP has low toxicity to aquatic and terrestrial organisms (LC_{50} or EC_{50} ≥1 mg/L or ≥ 500 mg/kg bw, respectively). Chronic toxicity data for fish and plants, and aquatic invertebrates also indicate that DMP has relatively low toxicity (NOEC ≥0.1 mg/L).

Toxicity of DMP is low partly because equilibrium partitioning and metabolism means that critical body residue (CBR) levels cannot be reached. Also, a comparison of species-dependent QSARs supports the hypothesis that biotransformation is important in explaining observed toxicity differences between species. A study from 1995 (Jaworska et al.) indicates that there is a strong positive correlation between excess toxicity and hydrolysis rate; this explains why fish, with higher *in vivo* hydrolysis rates than algae, are more sensitive to DMP than algae.

Oehlmann et al. (2009) suggest that the low molecular weight phthalates (e.g. DMP) likely act through non-polar narcosis, based on the positive correlation of toxicity data to the K_{ow} values. However, Adams et al. (1995) suggest that low molecular weight phthalates, such as DMP, appear to have higher toxicity relative to neutral organic non-specific narcotics. This indicates that they would be classified as either polar narcotics or compounds having an "unspecified reactivity" mode of action (MoA) such as the "ester MoA", both of which are slightly above the non-polar baseline but overlap it as well. As well, Parkerton and Konkel (2000) indicate that the principal mode of action for phthalates, including DMP, has been reported as polar narcosis. The authors also state that estimated critical body residues (CBRs) for the parent and metabolites were in the range reported for nonpolar narcotics (i.e. baseline toxicity), indicating a possible putative role of phthalate ester metabolites in the toxic response (Parkerton and Konkel 2000). When the metabolites formed consist of a phenol and an acid, the former contributes to a polar MoA, while the later contributes to a non-polar MoA.

8.1.1 Water

DMP has low toxicity to green algae (*Desmodesmus subspicatus* and *Pseudokirchneriella subcapitata)*, with a 72-hr EC_{50} (growth rate) for *Desmodesmus subspicatus* reported at 260 mg/L (ECHA c2007-2013). The low toxicity of DMP to algae is also apparent in other species: a 96-hour EC_{50} (cell count decrease) of 142 mg/L was reported for *Pseudokirchneriella subcapitata* (Adams et al.1996), and a 96-hour EC_{50} (growth) of 313 mg/L was reported for *Chlorella pyrenoidosa* (Yan et al. 1995).

One of the more comprehensive testing programs for the acute toxicity of phthalates was conducted by Adams et al. (1995). These researchers conducted static toxicity studies in which water flea (Daphnia magna), midge (*Paratanytarsus parthenogenetica*) and mysid shrimp (*Americamysis bahia*) were exposed to 14 commercial phthalate esters, including DMP. Although this study was ranked by the European Chemicals Agency (ECHA) as reliable without restrictions, it should be noted that the tests were static and DMP has high biodegradation potential in water. Calculated EC_{50} or LC_{50} values were determined for DMP in various invertebrate species, ranging from a 48-hour EC_{50} for immobilization of 45.9 mg/L (D. magna) to 96-hour LC_{50}s of 68.6 mg/L (mysid shrimp) and 377 mg/L (midge) (Adams et al. 1995). NOEC values reported for immobilization for these three species were <23.5 mg/L, 22.2 mg/L, and <100 mg/L, respectively, suggesting a reasonably low level of toxicity associated with this compound in all species tested (LOEC values not reported due to insufficient toxicity). With respect to chronic studies, Rhodes et al. (1995) exposed *D. magna* in a 21-day

flow-through test to a variety of phthalates to examine potential survival and reproductive effects. The 21-day NOEC and LOEC for the survival of *D. magna* were 9.6 mg/L and 23 mg/L, respectively. Other chronic invertebrate studies were conducted with DMP. For example, Call et al. (2001) reported a 10-day LC_{50} of 246 mg/L DMP for *Lumbriculus variegatus*, a 10-day LC50 of 68.2 mg/L DMP for *Chironomus tentans*, and a 10-day LC_{50} of 28.1 mg/L DMP for *Hyalella azteca*. LOECs of 1.94 mg/L for decreased fertilization and 0.0194 mg/L for chromosome separation in oocytes at anaphase were given for the polychaete worm *Pomatoceros lamarckii* exposed to DMP (Dixon et al. 1999; Wilson et al. 2002).

In addition to standard toxicity tests, a few studies examined the effects of DMP on the development of a marine univalve, abalone (*Haliotis diversicolor supertexta*). Liu et al. (2009) investigated the toxicity of DMP to embryogenesis and larval development of this species by means of a two-stage embryo toxicity test. At the blastula stage, the 9-h EC_{50} value for reduced blastula development was 55.71 mg/L. At 96-h, the NOEC (reduced larval metamorphosis) was 0.020 mg/L (LOEC not reported). Yang et al. (2009) studied toxicity effects of DMP and three other phthalates on embryogenesis and larval development in the same species as Liu et al. (2009), and reported EC_{50}s of 40 mg/L (larval abnormalities) and 0.05 mg/L (larval settlement). Zhou et al. (2011) studied the effect of DMP on fertilization and embryogenesis of abalone. They found that DMP-treated sperm exhibited dose-dependent decreases in fertilization efficiency, morphogenesis and hatchability.

The data reported by Call et al. (2001), Dixon et al. (1999), Wilson et al. (2002), Liu et al. (2009) and Yang et al. (2009) generally support the conclusion that DMP has low potential to harm aquatic organisms on the basis of standard toxicity tests.

A few studies reported 96-hour LC_{50} values for DMP for fathead minnow (29 mg/L, Adams et al. 1995), bluegill sunfish (38 mg/L, ECHA c2007-2013), rainbow trout (56 mg/L, Adams et al. 1995), and sheepshead minnow (56 mg/L, Adams et al. 1995).) A 96-hour LC50 of 121 mg/L was also reported in Adams et al. (1995) for the static test performed on the fathead minnow; however, the 96-hour LC_{50} for the flow-through test on the same species was 39 mg/L. Flow-through tests are considered more reliable for assessing toxicity. The LC_{50} value of 39 mg/L is in general agreement with that reported by US EPA (2010) for fathead minnow of 56 mg/L, following a 96-h exposure period. It also indicates that the chemical activity of DMP is within the range of that for narcosis. NOECs (96-hour; survival) for DMP exposure to these species of 3.2 mg/L (sheepshead minnow) to 38 mg/L (rainbow trout) were also reported by this author (Adams et al. 1995; LOECs not provided). Other studies (Heitmuller et al. 1981; Linden et al. 1979) support the assertion that DMP has low toxicity to aquatic organisms (LC_{50} or $EC_{50} \geq 1$ mg/L).

Available chronic toxicity data were more limited for fish. One study assessed chronic effects to DMP (Rhodes et al. 1995). LOEC and NOEC (survival, growth, and hatchability) values of 24 and 11 mg/L, respectively, were reported for DMP following 102 days of exposure.

For further perspective, Staples et al. (2000) calculated a predicted no effect concentration (PNEC) for DMP using two methods (a US EPA method and a Netherlands method), which yielded chronic no effect concentrations in surface water of 4.7 mg/L (final Chronic Value; US EPA method) and 3.2 mg/L (HC_5; Netherlands method). These methods both require assessment of multiple aquatic species and trophic levels.

8.1.1.1 Derivation of the Predicted No-Effect Concentration (PNEC) for Water

The critical toxicity calue (CTV) chosen to represent effects in aquatic organisms is an acute 10-day LC_{50} of 28.1 mg/L for *Hyallela azteca*, taken from Call et al. (2001). This study was found to be reliable (see robust study summary in Environment Canada 2015b). An application factor (AF) of 10 was chosen because this is an acute value, and there were data available for more than 7 species comprising at least 3 taxonomic groups. The resulting PNEC is, therefore, 2.81 mg/L.

Several studies reported effect concentrations lower than the CTV that was chosen. Rhodes et al. reported a 102-day LOEC of 24 mg/L for reduced survival, growth and hatchability in rainbow trout. The study by Rhodes et al. (1995) is considered reliable because standard test procedures were employed and good laboratory practices were followed. However, as this chronic LOEC is only slightly lower than the acute LC_{50} from Call et al. (2001), it would result in a less sensitive PNEC once an assessment factor was applied. Therefore, it was not chosen as the CTV. Use of a regression-based endpoint (i.e., LC_{50}) rather than an endpoint based on hypothesis testing (i.e., NOEC or LOEC), also provides more certainty in the threshold for effects. Also, there are lower reported values for secondary effects in abalone (Zhou et al. 2011) but the effects do not appear to predict effects related to primary endpoints.

8.1.2 Sediment

Very few sediment toxicity data were found for DMP. One study (Call et al. 2001) reported effects on the annelid, *Lumbriculus variegatus*: a 10 day LC_{50} of 256 mg/L was reported. Neither DMP nor the analogue DEP are expected to partition significantly to suspended solids or sediments. Therefore, a PNEC was not derived for sediment.

8.1.3 Soil

Terrestrial toxicity data for DMP are compiled in Environment Canada (2015b). Data are only available for a few species.

Several studies have been conducted with DMP, exhibiting low levels of toxicity of soil-dwelling organisms. For example, a 14-day earthworm (*Eisenia fetida*) LC_{50} value of 3160 mg/kg (soil) was reported for DMP by Neuhauser et al. (1985). Neuhauser et al. (1986) reported 14-day LC50 values for DMP ranging from 1064 to 3335 mg/kg for four species of worms (*Allolobophora tuberculata*, *Eisenia fetida*, *Eudrilus eugeniae*, *Perionyx excavates*). In addition, a 56-day LC_{100}, LOEC, and NOEC for growth and

reproduction in earthworm (*Eisenia fetida*) were reported as 94400 mg/kg, 70800 mg/kg and 47200 mg/kg, respectively, after exposure to DMP in horse manure medium (Neuhauser et al. 1985). These studies indicate that DMP is not likely to be toxic to earthworms, even at high concentrations in soil. No plant toxicity data were found for DMP.

8.1.4 Wildlife

No wildlife toxicity test data are available for DMP. Exposure to wildlife, via the aquatic route, is not expected because DMP is not likely to biomagnify and uptake from drinking water is very low.

There are, however, some studies that report toxicity to mammals such as rats and mice. In a 2-year rat study (Lehman 1955) effects on growth and on the kidneys were observed. Study results are discussed in more detail below (Section 9.2.3.2). (Lehman1955 in NICNAS 2008). These types of effects are equally significant for wildlife, especially in the mustelid family like otters and mink. Body weight scaling factors are used to convert the toxicity data to the wildlife species of concern (e.g. mink). A scaling factor of 5.77 is used to convert the body weight of a rat to that of a mink (Sample et al. 1996).

Following oral administration in rats, the primary metabolites for DMP in urine were the monoester monomethyl phthalate (MMP) (78%) with some free phthalic acid (14.4%) and unchanged DMP (8.1%) (Albro and Moore 1974, in NICNAS 2008). Methanol and formaldehyde have also been identified as metabolites in vivo and in vitro.

A limited number of studies have investigated the potential carcinogenicity of DMP in mammals. Results are discussed below (section 9.2.3.2).

8.1.5 Air

Given DMP's relatively high residence time in air, inhalation effects to wildlife are possible. No toxicity studies were found for inhalation effects on wildlife, but there are a number of inhalation studies for laboratory animals.

In a 4-month rat inhalation study, exposure to concentrations of 0.68 and 1.84 mg/m^3 DMP for 4 h/d resulted in changes in respiratory rate, decreased haemoglobin, altered red blood cell count, reduced weight gain, disturbed diuresis, altered chloride in urine and increased clearance of hippuric acid at the high dose (Timofievskaya et al. 1974, in NICNAS 2008).The results of this single study of inhalation exposure is inadequate to establish conclusions on repeated inhalation toxicity.

8.1.5.2 Derivation of the Predicted No-Effect Concentration (PNEC) for Air

An evaluation of the toxicity of DEP (SCCNFP 2002) reports effects on mice from inhalation of DEP. The acute inhalation toxicity is a reported LC_{50} of 4.9 g/m^3 (4900

mg/m^3). This value has been chosen as the CTV for the effects of air exposure to wildlife. An assessment factor (AF) of 100 was chosen because this is an acute value, and to account for interspecies variation, as there were no data available for other species. The resulting PNEC is, therefore, 49 mg/m^3.

8.1.6 Secondary effects including effects on the endocrine system

Secondary effects include molecular, biochemical, cellular, and/or histological responses to chemical exposure. They include effects on gene regulation. Secondary effects can be useful for elucidating the toxic mode of action or serving as biomarkers of exposure.

There is some evidence that DMP causes secondary effects in aquatic organisms. For example, Zhou et al. (2011) found that when abalone (*Haliotis diversicolor supertexta*) gametes were exposed to DMP, the expression patterns of physiologically-related genes (e.g. 17B-HSD-11) were modified in subsequent embryogenesis. On the other hand, Staples et al. (2011) conclude secondary effects of phthalates do not appear to predict effects related to primary endpoints of survival, growth and development, or reproductive fitness; their conclusion, however, rests on studies for phthalates other than DMP, such as the medium-chain diethyl hexyl phthalate (DEHP).

There are some studies, using standard toxicity tests, indicating that DMP does not have effects on the endocrine system. For example, DMP was found to not have binding affinity for the estrogen receptor and failed to prevent estradiol binding in vitro in rat (NCTR:SDN) uteri or human oestrogen receptor α or ß ((Nakai et al. 1999; Toda et al. 2004; Blair et al. 2000) in NICNAS 2008). Additionally, monomethyl phthalate (MMP, the main metabolite of DMP) did not affect estradiol production, at concentrations up to 400 µM, in cultured rat ovarian granulosa cells (Lovekamp and Davies 2001) in NICNAS 2008). However, less conventional (i.e., non-standard) toxicity studies suggest the potential for effects on the fertilization process and subsequent embryogenesis at much lower concentrations that could indicate that EDC effects are occurring. These studies report a LOEC for decreased fertilization of 0.0194 mg/L (which is a secondary citation which cannot be affirmed), the EC_{50} (larval settlement) of ≤0.05 mg/L (Yang et al. 2009), and the findings of Zhou et al. (2011), discussed above. The reliability of these studies has not been confirmed.

8.2 Ecological Exposure

8.2.1 Measured environmental concentrations

There are few data for recent environmental concentrations of DMP in Canadian media, but the existing historical (1998-2012) data show maximum, but not necessarily representative, concentrations of 5.46 ng/L (surface water), 2 600 ng/L (wastewater effluent), and 853 ng/g (sediment). There are no data for DMP concentrations in air. Reported concentrations of DMP in soil, in Canada, are all below the detection limit for the analytical method used. Most results for the DMP concentration in WWTP sludge

are below the detection limit; the highest reported value is 900 ng/g (dry weight) (Webber and Nichols 1995).

The available measured concentrations of DMP in the Canadian environment, including wastewater effluent, are presented in Environment Canada (2015a).

8.2.2 Air

DMP has been measured in some air samples collected from regions considered to be remote from potential sources. For example, DMP was detected at concentrations of 0.040–0.223 ng/m^3 (gas phase) and 0.001–0.008 ng/m^3 (particle phase) in six air samples collected in 2004 from sites in the Norwegian Arctic (Xie et al. 2007). Morin (2003) found DMP in air at eastern Hudson's Bay in concentrations ranging from 1.12 to 2.31 ng/g.

8.2.3 Surface Water

Canadian data for the concentration of DMP in surface water are limited. Samples associated with a petroleum spill were collected from Wabamun Lake, Alberta and some measurements were taken in five rivers receiving waste water treatment systems effluent in Alberta. At Wabamun Lake, DMP was reported to be non-detectable (<0.1 µg/L) by Alberta Environment (2006), which is a relatively high detection limit for these types of compounds. Alberta Environment notes that within their sampling program, some phthalates were occasionally detected in field blanks and in trip blanks, suggesting contamination during sampling. The rivers receiving wastewater treatment systems effluent were: the North Saskatchewan, Bow, Oldman, South Saskatchewan, and Red Deer rivers. Concentrations of DMP ranged from not detected to 3.2 ng/L (specific detection limits for each phthalate not provided; Alberta Environment, 2005). Data for DMP concentrations in the Niagara River (upstream (head)/downstream (mouth)) were collected as part of the Canada-USA Niagara River Monitoring Committee (Data Interpretation Group 1999). The upstream (Fort Erie) concentration ranged from 0.93 ng/L to 6.38 ng/L; the downstream (Niagara-on-the-Lake) concentration ranged from 0.49 ng/L to 4.39 ng/L.DMP was found in one tap water sample in Japan in 1998 at a concentration of 0.08 µg/L (Hashizume et al. 2002).

In a study of samples collected in 2004 from sites in the Norwegian Arctic (Xie et al. 2007), the authors reported dissolved-phase DMP at a mean concentration of 0.033 ng/L in eight of 16 water samples. In another study (Mackintosh et al. 2006) DMP concentrations in seawater were found to be a very small fraction of DMP's solubility in water (6.7×10^{-8}%).

The scenario (below, Section 8.2.8) for exposure of aquatic organisms involves the calculation of a site-specific (industrial) predicted environmental concentration (PEC). For comparison, a PEC based on a measured environmental concentration for DMP in surface water was also selected. The concentration chosen is 4.39 ng/L (0.004 µg/L), measured at Niagara-on-the-Lake in 1997 (Data Interpretation Group 1999).

8.2.4 Marine Water

Canadian data for the concentration of DMP in marine water are limited to studies conducted in the False Creek area of Vancouver, B.C. (a former industrialized area in an urban setting). For the False Creek area, DMP concentrations were approximately 3 to 3.7 ng/L (Blair et al. 2009; Mackintosh et al. 2004, 2006).

8.2.5 Wastewater Effluent

One study from Alberta Environment (2005) reported concentrations of phthalates in treated wastewaters in Alberta. Concentrations of DMP were very low, ranging from non-detectable to 3.9 ng/L. The report notes that these samples were corrected by subtracting the concentrations of compounds found in laboratory blanks from the actual sample data. This was done to account for inadvertent sample contamination, due to the wide use of phthalate esters in the manufacture of plastics, which are prevalent in a laboratory environment.

8.2.6 Sediment

There are data for concentrations of DMP in sediment in Canada, mainly at locations in British Columbia. The concentrations range from 0.04 ng/g dry weight (Hudson's Bay, 2002 (Morin 2003)) to 853 ng/g dry weight (Vancouver 2003 (Mackintosh et al. 2006)).

8.2.7 Biota

Only a few studies report the concentration of phthalates in biota in Canada. Data collected in eastern Hudson's Bay between 2000 and 2002 yielded DMP concentrations in various biological tissues (Morin 2003). The concentration of DMP in lichen, beluga whale tissue and arctic cod were reported at 0.325 ng/g dw, 2.39 ng/g ww, and 0.346 ng/g ww, respectively. In False Creek Harbour, sediments and biota were analyzed (Lin et al. 2003). The results indicate that fish tissue show a predominance of low molecular weight phthalates, including DMP, and ranged in the 0.1 to 1 ng/g level, similar to results for eastern Hudson's Bay (Morin 2003). In another study of biota from False Creek Harbour, DMP concentrations in white spotted greenling and shiner perch ranged from 0.26 - 0.71 ng/g ww, with concentrations in spiny dogfish being below the detection limit (McConnell 2007). Concentrations of DMP in various invertebrates ranged from 0.051 – 0.47 ng/g ww (Blair et al. 2009; McConnell 2007), whereas algal concentrations were 0.33 ng/g ww (McConnell 2007).

8.2.8 Exposure scenarios and predicted environmental concentrations

Based on Section 71 submissions for DMP (Environment Canada 2014), the substance is primarily imported to Canada in ready-to-use coatings, and the main use of this phthalate in Canada is in specialty coating applications. There could be some potential in future for the formulation of these specialty coatings in Canada as the main current importers of DMP coatings (Environment Canada 2014) have their coating

manufacturing sites in Canada too. However, the releases of DMP from the potential future coating formulations in Canada are not expected to be higher than the conservative DMP releases estimated for the coating application below.

DMP is used, in particular, as a solvent in exterior fluoropolymer coating formulations that are applied to metal surfaces (e.g., coil aluminum roof tiles). These exterior coatings are also known as polyvinylidene fluoride coatings. The typical composition of these coatings is 50-60% of solids and 40-50% of solvents (OECD ESD 2009). DMP would be included in the solvent portion. Material safety data sheets that were located for two fluoropolymer coating products indicate that concentrations of DMP in those products range from 1 – 5% (Valspar 2011) and 5 – 10% (PPG Industries Inc Coatings and Resins Group, 1991). For the purpose of conducting a first-tier conservative generic exposure scenario, 10% of DMP in the coating formulation is assumed. As mentioned above, the activity involving the largest quantities of DMP in Canada in 2012, as identified through Section 71, was the import of ready-to-use coatings. This importer identified ten downstream users that apply the imported specialty coating at their sites in Canada. Among these downstream users, four users with the highest use quantities were considered, and their publicly available site information (Ontario Ministry of the Environment, Environmental Compliance Approval) were analysed. There was not much useful information available for conducting the generic exposure scenario. However, the maximum fluoropolymer coating daily usage rate, that was available for one of the sites, was applied in the exposure assessment for calculating DMP releases to water and air from industrial coating applications in Canada.

Aquatic – industrial local exposure scenario

Under this first-tier scenario, aquatic exposure to DMP is expected when the substance is released from fluoropolymer coating applications at a generic coating application industrial site to a wastewater system. The concentration of the substance in the receiving water near the discharge point can be used in evaluating the aquatic risk of the substance. It can be calculated using the equation:

$$C_{aquatic-ind} = \frac{1000 \times Q \times L \times (1-R)}{F \times D}$$

where

$C_{aquatic-ind}$: aquatic concentration resulting from industrial releases, mg/L

Q: total substance quantity used daily at an industrial site, kg/d

L: loss to wastewater, fraction

R: wastewater system removal rate, fraction

F: wastewater system effluent flow, m^3/d

D: receiving water dilution factor, dimensionless

As mentioned above, the daily use quantity of the substance at the generic site is based on the maximum 24 hours usage rate of acrylic fluoropolymer-based paints of one of the downstream users and the density of solvent-based coatings for coil applications (Crechem 2003). A loss of 100% to wastewater is selected for the purpose of this first-tier exposure scenario. This assumption is unrealistic and highly conservative. The coatings are applied in spray booths, and even if the coating transfer efficiency in the booth is low, the coating loss would still be less than 100%. No information is available on whether the downstream users have on-site treatment of their wastewater. Therefore, for the purpose of this assessment, it is assumed that the generic site is discharging its effluent to an off-site wastewater treatment system.

The potential removal rates of DMP in primary and secondary wastewater treatment systems (WWTS) are estimated using the following three computer models: SimpleTreat 3.0 (1997), STP Model 2.1 (2006) and ASTreat 1.0 (2006). The removal rates of aerated and facultative lagoons for DMP are estimated by STP-EX (2011). The most conservative estimates from the results of all four models are selected for use in estimating aquatic releases. The result of the primary removal by ASTreat 1.0 (2006) is used when assuming that this industrial coating application site discharges to a wastewater treatment system that uses only primary treatment. While the primary and secondary combined removal rate predicted by ASTreat 1.0 (2006) is used when assuming a wastewater discharge to a secondary activated sludge wastewater treatment system. The predicted removal rates by lagoons are not used in this assessment as higher removal of DMP by lagoons were predicted by STP-EX in comparison to the ASTreat 1.0 (2006) prediction for secondary treatment removal. Therefore, the more conservative estimate is used. All four selected sites of the downstream users of DMP coating are located in the same large industrial area and send their wastewater to large secondary wastewater treatment systems with activated sludge technology. One of the site locations is used for selecting the wastewater treatment system effluent flow and dilution factor for the generic scenario with the site discharging to the secondary WWTS, whereas Montreal's primary WWTS was selected for the assumptions on the primary WWTS effluent flow and its receiving water dilution factor. Montreal was selected as it is a good example of a large industrial area with the primary WWTS.

All of the inputs used to determine aquatic exposure are summarized in Table 8-1 below.

Table 8-1. Summary of input values used for the first-tier conservative exposure scenario estimating aquatic concentrations resulting from industrial release of DMP at generic coating application sites.

Input	Value	Justification and reference
Quantity used per site per day (kg/d)	104.5	Based on the coating usage rate of one of the downstream users (Ontario Ministry of the Environment) assuming 10% solvent concentration in fluoride coatings (OECD ESD, 2009); and density of 0.950 kg/L of solvent-based coatings for coil applications (Crechem 2003)
Loss to wastewater (%)	100	Unrealistic assumption for first-tier conservative approach
Primary and secondary wastewater treatment system removal efficiencies (%)	4 and 81	Predicted values for primary and secondary treatments as estimated by model ASTreat 1.0 (2006)
Primary wastewater treatment system effluent flow (m^3/d)	2.2 x 106	Average daily effluent volume of WWTS
Secondary wastewater system effluent flow (m^3/d)	171.1 x 103	Site specific wastewater treatment system data from Environment Canada internal database
Dilution factor (–)	10	Site specific ratio between flow rate of receiving water body and flow rate of wastewater treatment system. When a dilution factor was greater than 10, a maximum default value of 10 was used.

The total concentrations in water near the point of discharge of primary and secondary WWTSs are calculated to be 4.56 µg/L (0.00456 mg/L) and 11.6 µg/L (0.0116 mg/L), respectively. The PEC chosen for the characterization of risk to aquatic organisms is 0.0116 mg/L.

Atmospheric – industrial local exposure scenario

Given that DMP has a relatively long residence time in air, an air exposure scenario was developed.

The USEPA model SCREEN3 was selected to estimate a generic 1-hour maximum concentration surrounding the coating application representative industrial site for the first-tier conservative exposure scenario (SCREEN3 1995). SCREEN3 is a screening tool that requires fewer and less refined inputs than other more complex models. The

selected scenario is designed to provide an estimate based on conservative assumptions regarding the amount of substance used and released by the facility, and the facility and environmental setting where the releases occur. The full inputs used to calculate the atmospheric concentration surrounding the facility and the output of the model are presented in Table 8-2. Assuming 100% atmospheric loss and a release rate of 6.05 g/s, SCREEN3 estimates that the maximum 1-h concentration is obtained at 30 m from the source and is 28,420 µg/m^3. The 1-h maximum concentration at 100 m is 6020 µg/m3 and at 1000 m is down to 380.7 µg/m^3. The concentration at 100 m is used as the representative predicted environmental concentration ($PEC_{atmospheric}$) for this assessment as this distance corresponds to the average distance between the emissions source and the border of an industrial site (European Commission 2003).

Table 8-2: Inputs and summary outputs of SCREEN3

Parameter	Value	Notes
Emission rate (g/s)	6.05	This assumption is based on maximum 1 hour paint usage rate of one of the downstream users, 100% atmospheric loss and density of 0.950 kg/L of solvent-based coatings for coil applications (Crechem 2003)
Stack height (m)	10	Default, median for 1,085,590 stacks in the U.S. (US EPA 2004)
Stack diameter (m)	0.6	Default, median for 9,706 stacks from the Residual Discharge Information System (RDIS database).
Stack gas exit velocity (m/s)	9	Default, median for 1,085,590 stacks in the U.S. (US EPA 2004).
Stack gas exit temperature (K)	316	Median for 9706 stacks from the Residual Discharge Information System (RDIS database).
Ambient air temperature (K)	293	Default
Receptor height above ground (m)	2.5	Default, represents height of small arboreal terrestrial organisms.
Urban/Rural Option	Urban	Default, facility is situated in an urban setting.
Building downwash option	Selected	Default, provides a more conservative scenario (US EPA 1995).
Building height (m)	10	Default, represents the height of building in which production, processing or use takes place (European Commission 2003).
Minimum horizontal dimension (m)	20	Default, represents typical low rise industrial facility (Law et al. 2004).
Maximum horizontal dimension (m)	100	
Simple terrain	Selected	Default, provides a more conservative scenario than using complex terrain (US EPA 1995).
Full meteorological conditions	Selected	Default, identifies worst case conditions (US EPA 1995).
Terrain height (m)	5	Default, corresponds to one half of the stack height.
Maximum	28.4	At 30 m

Parameter	Value	Notes
concentration (mg/m3)		
Concentration at 100m (mg/m3)	6.02	At 100 m that corresponds to average distance between the emissions source and the border of an industrial site
Concentration at 1000m (mg/m3)	0.38	

8.3 Characterization of Ecological Risk

8.3.1 Consideration of Lines of Evidence

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was done for the aquatic medium to determine whether there is potential for ecological harm in Canada. The site-specific industrial scenario (considering the actual receiving water body) presented above yielded a predicted environmental concentration (PEC) of 0.0116 mg/L (Environment Canada 2015a). A predicted no-effect concentration (PNEC) was derived from the acute toxicity value of 28.1 mg/L (see the Ecological Effects section). The resulting risk quotient (PEC/PNEC) is 0.004. Therefore, harm to aquatic organisms is unlikely at this site. A risk quotient analysis was also done for the aquatic medium using a measured environmental concentration (see Table 8-3, below); the resulting risk quotient is 0.0000014.

A risk quotient analysis was also done for air. The site-specific industrial scenario (considering the coating application representative industrial site) presented above yielded a predicted environmental concentration (PEC) of 6.02 mg/m^3 at 100 metres from the site. A predicted no-effect concentration (PNEC) was derived from the acute inhalation toxicity LC_{50} of 4.9 g/m^3 (4900 mg/m^3, see the Ecological Effects section). The resulting risk quotient (PEC/PNEC) is 0.12. Therefore, harm to wildlife from inhalation is unlikely at this site.

A risk quotient analysis was not done for sediment.

Table 8-3. Summary of risk quotients for DMP obtained for different media and exposure scenarios

Media	Scenario	PNEC	PEC	RQ
Water	Industrial release	2.81 mg/L	0.0116 mg/L	0.004
Water (measured environmental conc.)	Measured environmental concentration	2.81 mg/L	0.0000044 mg/L	0.0000014
Air	Industrial release	49 mg/m^3	6.02 mg/m^3	0.12

DMP is expected to be persistent in air, but not in water, soil or sediment. DMP is expected to have low bioaccumulation potential. The moderate importation quantities of DMP into Canada, along with information on its uses, indicate potential for widespread release into the Canadian environment. Once released, it will be found mainly in air, water, and soil. Available monitoring data indicates the presence of low concentrations of DMP in most media (air, water, sediment). DMP has low potential for toxicity to aquatic organisms. Risk quotient analyses indicate that harm to aquatic organisms, through releases of DMP from facilities where it is used as a coating additive, is unlikely. Similarly, DMP released to air from industrial use is unlikely to cause harm to terrestrial wildlife through inhalation.

8.3.2 Uncertainties

DMP is a well-studied chemical but data gaps exist. Experimental data are limited for effects to soil and sediment-dwelling organisms, as well as to wildlife. The caveats are that DMP is not expected to persist in any medium, except for air, and it is not expected to partition significantly to sediment. Consequently, significant effects to wildlife, as well as to soil and sediment-dwelling organisms are not expected. Monitoring data, also sparse for these media, would be helpful to confirm the low concern surrounding effects. The data pertaining to potential endocrine activity of DMP is not definitive, so more research in this area would also be helpful. These data gaps lead to some uncertainty in risk characterization.

9. Potential to Cause Harm to Human Health

9.1 Exposure

Environment Media and Food

Ambient air, drinking water and soil

Canadian monitoring data measuring the presence of DMP in ambient air was not identified. DMP has been detected in ambient air in the North Sea, Arctic (Xie et al. 2005, 2007) and Hudson Bay (see section 8.2.2, Xie et al. 2005, 2007; Morin 2003). Note the Xie et al. 2005, 2007 surveys show greater concentrations in vapour phase vs. gaseous phase.

A summary of the data pertaining to DMP presence in Canadian surface water is presented in section 8.2.3. Additionally, DMP has been monitored in surface water samples in France and China (Teil et al. 2007; Shao et al. 2013, Liu et al. 2014; He et al. 2011; Zhang et al. 2012) but was not detected in surface water samples taken from African Countries (Adeniyi et al. 2011; Fatoki et al. 2010).

Canadian monitoring data measuring the presence of DMP in drinking water was not identified. However, DMP has been detected in one of 15 drinking water samples from California (0.54 µg/L) (Loraine and Pettigrove 2006) and was not detected nor quantified

in drinking water samples obtained in Spain and China (Bono-Blay et al. 2012, Shao et al. 2013).

DMP was not detected in any bottled water samples surveyed as part of Health Canada's total diet study (Cao 2008). Also, DMP was below either the detection or the quantification limits in surveys of bottled water conducted in France, Greece and China (Devier et al. 2013; Diana and Dimitra 2011; Guo et al. 2012).

Other international surveys have detected the presence of DMP in bottled water in Thailand, Saudi Arabia and Italy (Prapatpong and Kanchanamayoon 2010; Kanchanamayoon et al. 2012; Al-Saleh et al. 2011; Montuori et al. 2008).

According to the available data, DMP has been detected in a small portion of bottled water samples but has not in bottled water sampled in Canada. Based on this, exposure to DMP from bottled water is expected to be negligible.

DMP was detected, but not quantified, in 6 of 10 samples of agricultural soil from five Canadian provinces (limit of detection, 0.03 mg/kg dry weight) (Webber and Wang, 1995). Additionally, Zeng et al. (2009) reported mean concentrations of DMP in soil collected from residential (0.074 µg/g dw) and parkland (0.067 µg/g dw) areas of Guangzhou, China.

Due to the limited data pertaining to DMP in ambient air, drinking water and bottled water and soil, exposure estimates were not derived from these sources.

Indoor air and dust

One study measured DMP in indoor air in Canadian homes; all samples were less than the limit of detection (Zhu et al. 2007). A summary of the data pertaining to DMP presence in indoor air is outlined below.

Table 9-1: Indoor air concentrations of DMP

Location	Detection Frequency	Concentration (µg/m^3)	Reference
Canada	0% of 73 homes	< LOD (LOD not reported)	Zhu et al. 2007
Germany	100% of 59 apartments	Median: 0.436 Mean: 1.182 95th percentile: 4.648 Max: 13.907	Fromme et al. 2004
Germany	100% of 74 Kindergartens	Median: 0.331 Mean: 1.034 95th percentile: 6.249 Max: 13.233	Fromme et al. 2004
Sweden	100% of 10 homes	Median: 0.015 Mean: 0.018 Range: 0.0074 – 0.047	Bergh et al. 2011a

Sweden	100% of 10 daycare centers	Median: 0.0047 Mean: 0.0062 Range: 0.0023 – 0.014	Bergh et al. 2011a
Sweden	100% of 10 workplaces	Median: 0.0044 Mean: 0.0046 Range: 0.0028 – 0.0079	Bergh et al. 2011a
Sweden	DF not provided: 169 apartments	Median: 0.016 Mean: 0.027 Range: ND – 0.380	Bergh et al. 2011b
China	100% of 10 apartments	Mean: 1.299 Range: ND – 6.578	Pei et al. 2013

ND: Not detected below the method limit of detection

Given that DMP is of moderate volatility (DMP vapour pressure: 0.23 Pascals), exposure from air is expected to occur and is expected to be predominantly from indoor air. The recent Swedish surveys (survey of DMP in apartments and homes) were used for exposure characterization and data from apartments were used specifically as these reported higher concentrations than other homes surveyed (Bergh et al. 2011a,b). DMP concentrations reported in Bergh et al. (2011b) are lower than surveys conducted in Germany and China (Fromme et al. 2004; Pei et al. 2013), but this survey has a higher sample size (n=169 apartments vs. n= 10 apartments vs. 59 homes) and is more recent (when compared to Fromme et al. 2004).

Therefore, mean (0.027 µg/m^3) and maximum (0.380 µg/m^3) concentrations were used to estimate exposure to the Canadian general population from DMP presence in indoor air; the highest estimates, from this source, were 0.014 and 0.21 µg/kg/day (children aged 0.5 to 4 years old) for central tendency and upper-bounding concentrations, respectively (see Appendix C).

DMP has been detected in numerous surveys of house dust and a summary of the results is provided in Table 9-2 below.

Table 9-2: DMP concentrations in house dust

Location	Detection Frequency	Concentration (µg/g)	Reference
Canada	90% of 126 homes	Median: 0.12 95th percentile: 1.4 Range: ND - 22	Kubwabo et al. 2013
United States	94%of 33 homes	Median: 0.08 Range: ND - 3.3	Guo et al. 2011
Germany	97% of 30 apartments	Median: 1.5 Mean: 10.8 95th percentile: 46.4 Max: 157.9	Fromme et al. 2004
Bulgaria	92% of 177 homes	Geometric Mean: 260 Median: 280	Kolarik et al. 2008a

China	99% of 75 homes	Median: 0.2 Range: ND* – 8.2	Guo et al. 2011
Sweden	100% of 10 homes	Median: 0.04 Mean: 0.1 Range: 0.03 – 0.1	Bergh et al. 2011a
Sweden	100% of 10 daycare centers	Median: 0.1 Mean: 0.3 Range: 0.01 – 1.5	Bergh et al. 2011a
Sweden	100% of 10 workplaces	Median: 0.2 Mean: 0.2 Range: 0.05 – 1.2	Bergh et al. 2011a
Kuwait	62% of 21 homes	Median: 0.03 Geometric mean: 0.01 Range: ND – 0.1	Gevao et al. 2013

The Canadian dust survey (Kubwabo et al. 2013) was chosen as the most relevant with which to derive estimates of exposure from dust for the Canadian population. The highest estimates were <0.001 and 0.007 µg/kg/day (0 to 6-month-old children) based on median (0.12 µg/g) and 95th percentile (1.4 µg/g) dust concentrations (see Appendix C for more details).

Food and beverages

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 et al. 2011; Barros et al. 2010; Bradley et al. 2007; Gartner et al. 2009; Page and Lacroix 1992; Fierens et al. 2012; Petersen and Jensen 2010; Xu et al. 2010; Xue et al. 2010).

In Canada, phthalates were monitored in a targeted survey of butter and margarine and their packaging, as part of Health Canada's Total Diet Study (Page and Lacroix 1992, 1995). DMP was not detected in either survey (Page and Lacroix 1992 limit of detection (LOD): 1000 ppb, Page and Lacroix 1995 LOD not stated). DMP was also not detected in a recent targeted Health Canada survey conducted to evaluate the presence of phthalates in meat, fish, and cheese (average method detection limit (MDL): 2.5 ppb) (Cao et al. 2014)[5].

[5] Paige and Lacroix (1995) as well as Cao et al. (2014) included relatively lower sample sizes than other evaluated international studies. Furthermore, Paige and Lacroix (1995) was based on samples from the 1989 total diet survey (TDS) 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 TDS

DMP has been monitored in total diet surveys in the United Kingdom (LOD 2.0 – 11.5 ppb), United States (LOD: 0.1 ppb), Belgium (limit of quantification (LOQ): 0.01 – 5 ppb), Germany (0.2 - 5 ppb), China (LOQ: 2 ppb), and Taiwan (25 – 50 ppb) and DMP was detected in all surveys. Specifically, DMP was detected in 32% of 400 food samples in Belgium, 37% of 65 food samples in the United States, 4% of 261 retail food samples in the United Kingdom, 18% of 350 and 58% of 171 duplicate diet samples in Germany, >60% of 70 food samples in China, and a proportion (detection frequency not stated) of 1200 food samples in Taiwan (Fierens et al. 2012; Schecter et al. 2013; Bradley et al. 2013a; Bradley et al. 2013b; Fromme et al. 2007; Fromme et al. 2011; Guo et al. 2012; Chang et al. 2014).

The North American total diet survey (Schecter et al. 2013) was used as the critical study for exposure characterization (as analysis showed that it covered a sufficient range of foods to quantify exposure and is the closest in geographical vicinity to Canada), with data from Bradley et al. 2013a, 2013b informing data gaps (e.g. presence of DMP in a food commodity type not found in Schecter et al. 2013).

Probabilistic dietary recall intakes were derived for DMP and a summary of results and methodology are outlined in Table C2 of Appendix C and in Appendix D[6].

The group with the highest exposure was 1 – 3 year-old children with intakes of 0.0029 and 0.010 µg/kg/day at the median and 90th percentile, respectively. Amongst adults, the highest exposure was estimated for 19 – 30 year-old males with intakes of 0.0018 and 0.0046 µg/kg/day at the median and 90th percentile, respectively.

Breast milk

Recently, DMP was monitored by Health Canada in breast milk as part of the Maternal Infant Research on Environmental Chemicals (MIREC) survey. It was not detected in any breast milk samples (n=305; MDL=1ng/g; personal communication Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, November 2014). In an earlier Health Canada survey, presence of DMP was monitored in breast milk (21 mothers, 86 samples) and was not detected (detection limit 0.63 ng/g) in any of the samples (Zhu et al. 2006). However, DMP is expected to

data for these same phthalates would be considered a more representative and unbiased source of phthalate occurrence data to use in dietary exposure assessments.

[6] This estimate was based on statistical imputation of half the limit of detection (LOD) in samples in which DMP levels were found to be below the LOD. When compared to an analysis conducted with imputing a numerical value of 0 in samples in which DMP levels were found to be below the LOD, minimal impact was observed at the higher percentiles.

metabolize quickly to the monoester mono-methyl phthalate (MMP) (Koch and Calafat et al. 2009) and this may explain the lack of detection in the studies described above.

Recently, an analysis of breast milk samples obtained from 56 women in the Plastics and Personal-care Product Use in Pregnancy (P4) cohort survey showed 100% detection of MMP (LOD: 0.03 µg/L, geometric mean: 0.55 µg/L, median: 0.56 µg/L, maximum: 2.8 µg/L) (Personal Communication from EHSRD to ESRAB, Sept 2013). However, measurement of this metabolite in breast milk was affected by high field blank levels (possible contamination) and therefore was not used to quantify intakes.

Mortensen et al. (2005) obtained 36 samples of breast milk from healthy mothers in Denmark and measured the monoester MMP at concentrations (detection frequency 89 % of 36 samples) ranging from <0.01 to 1.49 µg/L (median, 0.11 µg/L; mean, 0.17 µg/L). Additionally, Main et al. (2006) obtained breast milk samples from a joint prospective longitudinal cohort study carried out in Finland and Denmark (n=65 for each country). MMP was measured at median concentrations of 0.10 and 0.09 µg/L in Denmark and Finland, respectively.

Therefore, Mortensen et al. 2005 was used for exposure characterization, and a molecular weight adjustment was used to convert intakes of MMP into an estimated intake for DMP. DMP intakes from breast milk (0 to 6 month-old infants) were estimated to be 0.012 and 0.16 µg/kg/day based on the median (0.11µg/L) and maximum (1.49 µg/L) concentrations, respectively (see Appendix C for further details).

Products used by consumers

Cosmetics and personal care products

Based on notifications submitted under the *Cosmetic Regulations* to Health Canada, DMP was notified as being present in 3 products however the submissions were all made prior to 2008 (September 2014 email from the Consumer Product Safety Directorate (CPSD), Health Canada to Existing substances Risk Assessment Bureau (ESRAB), Health Canada). DMP was notified as being present in 3 products, with concentrations between 1 and 3%. The three products are gel manicure preparation, a gel hair dye and a pump spray hair grooming product.

Health Canada (Koniecki et al. 2011) also conducted a national survey of 18 phthalates in cosmetic and personal care products on the Canadian market. A total of 18 phthalates were monitored in 252 products (including 98 baby care products) collected in several Canadian provinces (Atlantic, Ontario, Alberta, Manitoba/Saskatchewan regions) between December 2007 and April 2008. Examples of product types were fragrances, hair care products, deodorant, and nail polish (Koniecki et al. 2011). Only 5 of the 18 targeted phthalates were detected. DMP was detected in 1 of the 252 products analysed, at a concentration of 72 µg/g in 1 of 18 deodorants. The method detection limit was 0.5 µg/g.

Hubinger and Havery (2006) purchased 48 personal care products in Washington DC and detected DMP in 3 of 48 samples (LOD: 10 µ/g). In nail enamel, DMP was found at concentrations ranging from below the LOD to15 395 µg/g. A subsequent survey by the same authors in Washington DC did not detect DMP (LOD 10 µg/g) in any of the products sampled (Hubinger 2010).

Guo et al. (2013) also detected DMP in products (17% of 52 products, detection limit 0.1 µg/g) sampled in China. Specifically, DMP was detected in body and hand lotion (median: 0.1 µg/g, mean: 0.2 µg/g, maximum 4.4 µg/g), shampoo (median: ND, mean: 0.1 µg/g, maximum: 0.7 µg/g), and body wash (median: ND, mean: 0.1 µg/g, maximum: 0.8 µg/g).

Finally, Guo and Kannan 2013 also surveyed DMP presence in 170 personal care products in Albany, New York (LOD: 0.01 µg/g, 50 fold lower when compared to the Koniecki et al. 2011) and detected DMP in 11% of 170 products. The results of their analyses are presented below (see Table 9-3).

Table 9-3: Concentrations of DMP in cosmetic products as surveyed by Guo and Kannan 2013.

Product (number of products)	Concentrations DMP (µg/g)
Body wash (n=11)	Mean: 0.01 Maximum: 0.09
Shampoo (n=9)	Mean: 0.07 Maximum: 0.32
Hair conditioner (n=7)	Mean: ND
	Max: ND
Face cleaner (n=9)	Mean: 0.01
	Maximum: 0.06
Shaving gel (n=5)	Mean: ND
	Maximum: ND
Skin lotion (n=23)	Mean: 0.39
	Maximum: 5.68
Hair care (n=6)	Mean: 3.71 Maximum: 12.1
Perfume (n=12)	Mean: ND
	Maximum: ND
Skin toner (n=9)	Mean: 0.03 Maximum: 0.28
Deodorant (n=14)	Mean: 1.51 Maximum: 20.6
Face cream (n=21)	Mean: 0.52
	Maximum: 10.7
Eyeliner cream (n=4)	Mean: ND Maximum: ND
Hand cream (n=3)	Mean: ND

Product (number of products)	Concentrations DMP (µg/g)
	Maximum: ND
Sunscreen (n=5)	Mean: ND Maximum: ND
Lipstick (n=4)	Mean: 0.04 Maximum: 0.18
Nail polish (n=8)	Mean: 0.03 Maximum: 0.22
Shampoo (n=4)	Mean: 0.17 Maximum: 0.68
Lotion and oil (n=4)	Mean: ND Maximum: ND
Sunscreen (n=6)	Mean: ND Maximum: ND
Diaper cream (n=3)	Mean: 0.17 Maximum: 0.51
Powder (n=1)	ND

ND = not detected or concentration below 0.01 µg/g

Using concentrations from the Guo publications[7], Koniecki et al. (2011), and notifications submitted under the *Cosmetic Regulations* to Health Canada, estimates of daily intake of DMP from use of cosmetics and personal care products were derived for the Canadian general population (see Appendix E). ConsExpo 4.1 software was used to estimate intakes (RIVM 2007).

Representative products were selected to estimate dermal daily intake of DMP for adults (20+) and infants (0 – 0.5 months), because they are associated with leave-on application, highest frequency of use and highest DMP concentration (see Tables 9-4 and 9-5).

Table 9-4: Chronic dermal estimates of exposure from use of cosmetics.

Sentinel Products[a,b]	Concentration (µg/g)	Intake (µg/kg/day)	Reference
Hair Spray (adult)	Min: 10 000 Max: 30 000	Min: 6.6 Max: 20	Notifications under *Cosmetic Regulations*, CPSD
Nail Polish (adult)	Min: 10 000 Max: 30 000	Min: 0.30 Max: 0.90	Notifications under *Cosmetic*

[7] lower limits of detection and higher detection frequency than Koniecki et al. 2011

			Regulations, CPSD
Solid Deodorant (adult)	Mean: 1.51 Max: 72	Mean: 0.0017 Max: 0.079	Guo and Kannan 2013;Koniecki et al. 2011
Body Lotion (adult)	Mean: 0.39 Max: 5.68	Mean: 0.0027 Max: 0.039	Guo and Kannan 2013
Face Cream (adult)	Mean: 0.52 Max: 10.7	Mean: 0.0016 Max: 0.033	Guo and Kannan 2013
Solid Deodorant (Adult)	Mean: 1.51 Max: 20.6	Mean: 0.0017 Max: 0.023	Guo and Kannan 2013
Hair Mousse	Mean: 3.71 Max: 12.1	Mean: < 0.001 Max: 0.0031	Guo and Kannan 2013
Body Lotion[c] (Infant)	Mean: 0.1 Max: 4.4	Mean: 0.0032 Max: 0.14	Guo et al. 2013
Diaper cream (infant)[d]	Mean: 0.17 Max: 0.51	Mean: 2.7 Max: 8.2	Guo and Kannan 2013

[a]Only products where intakes > 0.001 µg/kg/day were presented in Table 9-4.

[b] 10% dermal absorption factor was used for all products except diaper cream (see section on Toxicokinetics for approach for characterizing dermal absorption for DMP).

[c]Used adult body lotion concentration to estimate exposure to an infant.

[d]Guo and Kannan 2013 observed DMP in diaper cream –used application frequency (4 x day, 0.3 g/application) of infant body cream to estimate exposure to diaper cream. Used 100% dermal absorption for this scenario because of potential for abraded skin.

Table 9-5: Acute dermal estimates of exposure from use of cosmetics

Sentinel Products[a]	Concentration (µg/g)	Intake (µg/kg/bw)	Reference
Hair Dye (adult)[b]	Min: 10 000 Max: 30 000	Min: 140 Max: 420	Notifications under *Cosmetic Regulations*, CPSD

[a]10% dermal absorption factor was used for all products except diaper cream (see the section on Toxicokinetics for approach for characterizing dermal absorption for DMP).

[b]Modelled non-spray/wash in permanent scenario, reported in µg/kg/bw.

For adults, the products with the highest potential for chronic dermal DMP exposure were hair spray and hair mousse (a function of high product concentrations). For infants (0 to 6 months old) diaper cream was the product with the highest potential for chronic dermal exposure to DMP. For the oral route, exposure to DMP from presence in lipstick was estimated to be < 1 ng/kg/day.

Since DMP is of low volatility (DMP vapour pressure: 0.23 Pascals), inhalation exposure is expected to be predominantly through aerosols rather than vapour during use of personal care products. Therefore, inhalation exposure to DMP from use of hair spray (1 – 3%, only aerosol product with DMP presence) was modelled. Use of hair spray

(1.5/day), containing 1 – 3% DMP, was estimated to result in mean event concentrations of 0.27 - 0.82 mg/m^3, and intakes of 0.76 - 2.3 µg/kg/day, based on minimum and maximum concentrations of DMP, respectively. Regarding inhalation exposure from vapour, due to its low volatility, DMP exposure from this route is not expected to be significant.

Biomonitoring

MMP, the monoester of DMP was monitored in urine in the Canadian Health Measures Survey (CHMS) Cycle 1 and 2 (Health Canada 2013). In both cycles, the limit of detection for MMP was 5 µg/L and MMP was seldom detected and only at higher percentiles (58 – 74 % below the LOD: Cycles 1 and 2, detection at 95th percentile and above).

Health Canada has also monitored MMP in urine as part of the Assembly of First Nations Biomonitoring survey (AFN 2013) and 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) (personal communication from Environmental Health Science and Radiation Directorate [EHSRD] to Existing Substances Risk Assessment Bureau [ESRAB], October 2013, 2014). However, the limits of detection of these three surveys were also 5 µg/L and MMP was also detected at low frequencies and at the higher percentiles.

Recently, a more sensitive method (LOD 0.2 µg/L) was developed for the children of the MIREC cohort (Unpublished data, to ESRAB from EHSRD, October 2014) and MMP was 100% detected. Another method with a more sensitive limit of detection (0.1 µg/L, 50 times lower than the LOD mentioned above) was also used to analyse biomonitoring samples by the Centers for Disease Control and Protection (CDC 2013).

Therefore, given the methodological issues outlined above, NHANES data was used as a surrogate for estimating exposure to the Canadian population (6 years and older) while MIREC CD Plus was used to estimate exposure for children 2 to 3 years old (See Tables 9-6 to 9-8).

The fractional urinary excretion (FUE) of a substance is defined as the mole ratio of the amount of metabolites excreted in urine (at 24 hrs.) to that of total parent compound ingested. As there are no human pharmacokinetic studies available for DMP, a read-across approach was used to estimate the FUE for DMP. Koch and Calafat et al. (2009) recommended using DnBP (FUE: MnBP, monoester = 0.69, Anderson et al 2001) for DEP. DEP is a similar size phthalate to DMP with a similar metabolism profile, i.e., it is expected that both DEP and DMP metabolize predominantly to their respective

monoesters: a notion that is reinforced by rodent pharmacokinetic data for both substances[8].

Based on these considerations the FUE of 0.69, for DnBP[9], was also used for DMP. Intakes were corrected for urine dilution using the creatinine correction method; a commonly used method for phthalate biomonitoring assessment (Fromme 2007, Christensen et al. 2014, US CPSC CHAP 2014, Frederiksen et al. 2014). Daily creatinine excretion rates, for participants, were estimated using the Mage equation and biomonitoring intakes presented in tables 9-6, 9-7 and 9-8 below (see Appendix F for further information on the methodology).

Table 9-6:2009-2010 NHANEs daily intakes (µg/kg/day), males (using creatinine correction)[a]

Age group	n	Geometric mean	50th	75th	95th
6-11	209	0.082	0.092	0.16	0.66[b]
12-19	225	0.039	0.042	0.087	0.29
20+	949	0.026	0.026	0.064	0.24

[a] in the event of non-detects, ½ LOD was imputed for intake calculation

[b] Relative Standard Error (RSE) > 30%

Table 9-7: 2009-2010 NHANEs daily intakes (µg/kg/day), females (using creatinine correction)[a]

Age group	n	Geometric mean	50th	75th	95th
6-11	204	0.076	0.087	0.16	0.52
12-19	189	0.029	0.032	0.057	0.19
20+	948	0.027	0.027	0.060	0.26

[a] In the event of non-detects, ½ LOD was imputed for intake calculation.

[8] 78 % of MMP cleared in urine after oral administration to rats, > 75 % - 90 % of MEP (monoester of DEP) cleared in urine after oral and gavage administration in rats and mice (see section 9.2.1.1).

[9] Rodent pharmacokinetic data (> 75 % - 90 %) for DMP and DEP supports the assignment of an FUE of 0.69 (69 %) for DMP based on read across of human pharmacokinetic data for DnBP

Table 9-8 MIREC-CD Plus (preliminary data) daily intakes (µg/kg/day), children 2 to 3 years old[a]

Age group	n	Arithmetic Mean	50th	75th	95th 95%CI
2 - 3	197	0.27	0.19	0.33	0.66

[a] This analysis relied on instrument read outs, and in the event of a read-out of zero, the next smallest value was imputed.

The highest exposed group (all sources, MIREC CD-plus) are 2-3 year-old male children with median and 95th percentile intakes of 0.27 and 0.66 µg/kg/day, respectively. For older populations the highest exposed group (all sources, NHANES) are 12-19 year old males with median and 95th percentile intakes of 0.042 and 0.29 µg/kg/day respectively.

9.2 Health Effects

9.2.1 Toxicokinetics

In this section, the toxicokinetics of both DMP and its analogue DEP are examined.

9.2.1.1 Oral route

In rats, DMP is readily and extensively absorbed through the gastrointestinal tract. Following oral administration in rats, the primary metabolites for this phthalate in urine were the monoester monomethyl phthalate (MMP) (78%), with some free phthalic acid (14.4%) and unchanged DMP (8.1%) [See Table 9-9 below] (NICNAS 2008; US CPSC 2010a).

Similarly, available data for DEP indicates that this phthalate is rapidly absorbed, distributed, metabolized, and excreted in the urine, mostly as its monoester monoethyl phthalate (MEP) following oral administration [See Table 9-9 below]. In a study in which rats and mice were orally administered [^{14}C]-DEP, radioactivity was measured 48 hours post-administration in tissues, urine, and feces. Maximum concentrations of radioactivity were observed within 20 minutes and were highest in kidney and liver, followed by blood, spleen, and fat. After 24 h, only trace levels of internal radioactivity were found. Urinary and fecal excretion reached 90 and 2.7% 48 hours post-administration, respectively (Ioku et al. 1976). In Wistar rats administered DEP (10 or 100 mg) by gavage, daily urine collections revealed that for both doses, >75% of the administered dose was excreted in the urine within the first 24 h as the monoester MEP (67–70%), phthalic acid (8–9%), and parent compound (0.1–0.4%) and between 83 and 90% of the administered dose was excreted in the urine after one week (Kawano 1980). MEP also accounted for the majority of the administered dose (~1.2 mg) of DEP in plasma and urine of juvenile dogs via the oral routes (Kao et al. 2012). About 90-96% of the administered dose was excreted in the urine over 72 h in this study.

Hydrolysis of DMP to MMP and DEP to MEP has been demonstrated *in vitro* in liver homogenates and intestinal mucosal cell preparations from rats, baboons, and ferrets,

as well as in intestinal mucosal cell preparations from humans (Lake et al. 1977; Rowland et al. 1977;White et al. 1980). Hydrolysis of DEP to MEP has also been demonstrated in mouse kidney and lung (Kayano et al. 1997), and in rat and human skin (Mint and Hotchkiss 1994).

Table 9-9 Summary of metabolites of DMP and DEP found in urine after oral administration *in vivo.*

Phthalate	Abb.	Metabolite found in urine after oral administration	Abb.	Reference (species)
Dimethyl phthalate 131-11-3	**DMP**	Dimethyl phthalate	DMP	Albro and Moore 1974 (rat) Suzuki et al. 2012 (human)[a] Kasper-Sonnenberg et al. 2012 (human) [a]
Dimethyl phthalate 131-11-3	**DMP**	Monomethyl phthalate	MMP	Albro and Moore 1974 (rat)
Dimethyl phthalate 131-11-3	**DMP**	Phthalic Acid	PA	Albro and Moore 1974 (rat)
Diethyl phthalate 84-66-2	**DEP**	Diethyl phthalate	DEP	Kawano 1980 (rat)
Diethyl phthalate 84-66-2	**DEP**	Phthalic Acid	PA	Kawano 1980 (rat)
Diethyl phthalate 84-66-2	**DEP**	Monoethyl phthalate	MEP	Suzuki et al. 2012 (human) [a] Kasper-Sonnenberg et al. 2012 (human) [a] Kao et al. 2012 (dog) Kawano 1980 (rat)

[a] 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.

Pregnancy and Lactation

Some studies conducted in pregnant women have looked at MMP and/or MEP levels in amniotic fluid. These metabolites are generally undetectable, or if present, only at trace amounts (Silva et al. 2004; Huang et al. 2009).

It has been reported that there are differences between phthalates with respect to the concentration of these substances distributed to the foetal testes following exposition during pregnancy. Monoester metabolites of smaller phthalates such as DMP and DEP were found in the highest concentrations in the foetal testes after maternal dosing.

Monoester metabolites of DEHP were found in the lowest concentrations (Clewell et al. 2010).

A review of human studies reporting the presence of phthalates in breast milk indicates the occurrence of both DEP and its monester MEP (Frederiksen et al. 2007).

9.2.1.2 Inhalation route

No toxicokinetic studies were identified in the literature for DMP or DEP.

9.2.1.3 Dermal route

In a study in which [^{14}C] phthalate diesters (including DMP and DEP; 5-8 mg/cm^2; skin not washed after exposure; site of application covered with a perforated cap) were applied topically to the dorsal side of rats, it was observed that a large part of the dose remained at the site of application (ie. retained in the skin) for all substances. Approximately 40% and 50% of the applied dose of DMP and DEP, respectively, was absorbed over a 7-day period based on percentages recovered in urine and feces. For most diesters, distribution in tissue after 7 days was generally low (between 0.5 and 1.5% of applied dose recovered in tissues). About 0.6 and 0.3% of the applied dose of DMP and 0.14 and 0.03% of the applied dose of DEP were found in muscle and adipose tissue, respectively, and less than 0.5% of the applied dose of both substances was detected in other tissues examined (brain, spinal cord, and testis) (Elsisi et al.1989). Following the application of DEP to rabbit skin (unspecified dose), approximately 49% and 1% was recovered in the urine and feces, respectively, during 4 days post-application. Less than 1% of the radioactivity was found in liver, kidney, and blood combined (RIFM 1973; NICNAS 2008; US CPSC 2010a). This indicates that absorbed short-chain phthalates in animals are distributed and cleared rapidly with limited accumulation.

Elsisi et al. (1989) reported a relationship between the side-chain length and fecal excretion where, 24 hours after dermal exposure to phthalate diesters (alkyl chains from C1 to C10), the fraction of fecal excretion increased as a function of the side-chain length. The authors indicated that fecal excretion was less than 16% of total excretion for phthalate diesters with chain length of C6 or less, and only 0.1% for DMP and 1% for DEP.

In a two-week study 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 5 consecutive days followed by five daily topical applications of the same cream containing 2% (V/V) DEP (as well as 2% dibutyl phthalate and 2% butyl paraben). Blood and urine were collected during the study and analyzed for levels of MEP. 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) then decreased to 23 µg/L after 24 h just before the subsequent application. Total percent absorbed from blood MEP concentrations was estimated to be 10% of applied dose. In urine, the

majority of MEP was excreted during the first 8 hours post-application and the average dermal absorption for DEP, estimated from daily recovery of MEP in urine, was 5.8% (Janjua et al. 2007, 2008; NICNAS 2011).

Dermal absorption and retention of DMP and DEP was also studied *in vitro* with rat and human skin. Phthalate diesters (20 mg/cm^2) were applied to the epidermis of full-thickness human breast skin or dorsal rat skin placed on diffusion cells (HHBSS used as receptor fluid) (Mint and Hotchkiss 1993; Mint*, et al.* 1994). The results showed that retention in skin was 3- to 6-fold higher in rat compared to human. Mint and Hotchkiss (1993) found that after 72 h, half of the DMP (52%) applied remained on human skin surface, compared to 27% with rat skin, and the fraction present in the skin was 5% in human skin and 30% in rat skin. With DEP, a little less than half of the applied dose (44-46%) remained on human skin surface, compared to 20% with rat skin, and fraction present in the skin was 10% in human skin and 35% in rat skin (Mint*, et al.* 1994). These results indicate that rat skin is more permeable to short-chain phthalates than human skin. Another study has reported that dermal absorption of DMP through rat skin was about 10–20 times higher than through human skin (Scott et al. 1987; 1989 Errata). The authors of this study also reported that although having comparable rates of absorption through rat skin, the in vitro absorption rate of DMP was three times higher than that of DEP through human skin.

See Tables 9-10 and 9-11 for a summary of percent dermal absorption values for DMP and DEP obtained *in vivo* and *in vitro*, respectively.

Overall, with regards to dermal absorption, although animal *in vivo* studies show dermal absorption of around 40 to 50% for short-chain phthalates, recent *in vivo* and *in vitro* studies demonstrate that absorption of DMP and DEP through human skin is significantly lower than through animal skin. This difference could be explained by species differences, such as difference in skin permeability, as shown in *in vitro* studies, and/or other factors related to the different methodology used in the various studies. Considering this along with the results by Janjua et al. (2008) indicating an average dermal absorption for DEP of 5.8% in humans, as described above, it is expected that the dermal bioavailability for short-chain phthalate in humans is not likely to be greater than 10%. This is in agreement with the dermal bioavailability identified for DEP by NICNAS in their PEC assessment report (NICNAS 2011) and in their recent evaluation of DMP in which they state that “the dermal bioavailability of DMP in humans is estimated to be no lower than that of DEP, i.e. 10%” (NICNAS 2014).

Table 9-10 Summary of dermal absorption percentages and rates for short-chain phthalates obtained in vivo

Substance	Species	Dose	Basis	Absorption (% of dose and/or absorption rate)	Reference
DEP	Human	5x 2 mg/cm^2	Urine	At least 5.8% daily over 5 days	Janjua, et al. (2008)
DEP	Human	5x 2 mg/cm^2	Blood	700-1000 µg/L/h for 8 h following first application;	Janjua, et al. (2007)

Substance	Species	Dose	Basis	Absorption (% of dose and/or absorption rate)	Reference
				10%	
DEP	Rat	1x 30-40 mg/kg	Urine+tissues	50% over 7 days	Elsisi, et al. (1989)
DMP	Rat	1x 30-40 mg/kg	Urine+tissues	40% over 7 days	Elsisi, et al. (1989)

Table 9-11 Summary of dermal absorption rates for short-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
DEP	Human	Full thickness breast skin	16.3-20.6 mg/cm^2 unoccluded	72 h	HHBSS	4.2% over 72 h Steady state: 14 µg/cm^2/h (12-72 h)	Mint, et al. (1994)
DEP	Rat	Full thickness dorsal skin	16.3-20.6 mg/cm^2 unoccluded	72 h	HHBSS	35% over 72 h, Steady state: 103 µg/cm^2/h (12-72 h)	Mint, et al. (1994)
DEP	Human	Epidermis (abdominal skin)	0.5 ml	30 h	50% EtOH	Steady state: 1.27 µg/cm^2/h Kp=1.14 x 10^{-5} cm/h	Scott, et al. (1987)
DEP	Rat	Epidermis (dorsal skin)	0.5 ml	8 h	50% EtOH	Steady state: 41.37 µg/cm^2/h Kp=37.0 x 10^{-5} cm/h	Scott, et al. (1987)
DMP	Human	Full thickness breast skin	20 mg/cm^2	72 h	HHBSS	3% over 72 h Steady state 9.4 µg/cm^2/h	Mint and Hotchkiss (1993)
DMP	Rat	Full thickness dorsal skin	20 mg/cm^2	72 h	HHBSS	20.8% over 72 h Steady state 66.8 µg/cm^2/h	Mint and Hotchkiss (1993)
DMP	Human	Epidermis (abdominal skin)	0.5 ml	30 h	50% EtOH.	3.95 µg/cm^2/h Kp=3.33 x 10^{-5} cm/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
DMP	Rat	Epidermis (dorsal skin)	0.5 ml	8 h	50% EtOH	41.6 µg/cm^2/h Kp=34.5 x 10^{-5} cm/h	Scott, et al. (1987)

9.2.2 Reproductive and developmental effects

In this section**,** the first three segments focus on reproductive and developmental effects of the male gender in three different life stages (gestational exposure [GD0-21], (pre)pubertal-pubertal [PND1-55], and adult [PND55+]) with particular focus on the male gender as DMP is a part of a larger group of substances that have been associated with causing specific antiandrogenic effects in males (rat phthalate syndrome [RPS], see Health Canada [2015a] for more details). Adverse effects observed subsequent to gestational exposure to DMP are further organized and presentedas 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[10]. Descriptions of effects within each life stage are structured such that effects occurring at the lowest doses are summarised first. The potential reproductive developmental effects of DMP in female animals are presented next in a similar manner in considering life stage and species sensitivity. When no studies were available for DMP for a particular life stage or exposure period, an analysis of health effects for its analogue DEP was conducted (Health Canada 2015a). The last segments focus on endocrine studies and reproductive and developmental effects observed in humans.

9.2.2.1 Early development: *in utero* exposure

A literature search identified six studies examining the potential toxicity of DMP during gestation in rats, with only two studies focusing on male reproductive effects during the masculinization programming window (gestational days [GD] 15-17) where any potential antiandrogenic effects would be observed. Summaries of these studies are described in Table 9-12 below.

[10] The evaluation of all toxicological information currently available was not limited to endpoints directly related to effects of specific concern for phthalate toxicity in males alone, but also included review of all potential effects of phthalate exposure in both sexes at all life stages.

In general, regardless of timing of exposure during gestation, no developmental effects were reported in foetuses at the highest doses tested. Also, no significant maternal toxicity was noted. Further observation of a lack of response of genes involved in steroidogenesis supports the hypothesis that DMP is inactive in causing toxicity to the male rat reproductive tract during gestation (Liu et al. 2005). Dermal exposure to DMP during pregnancy (GD1-20) in female rats did not affect offspring development up to doses as high as 2380 mg/kg bw/day, but caused a slight reduction in body weight gain in the pregnant rats (Hansen and Meyer 1989).

Similar results were observed when mice were used to examine the developmental toxicity of DMP (See Table 9-12). It should be noted, however, that most reproductive parameters directly pertaining to the male reproductive system as it relates to RPS associated with certain phthalates were also not measured in this species therefore no conclusions can be made regarding the particular potential of DMP to induce this syndrome in mice.

Table 9-12. Lowest observed (adverse) effect levels (LO(A)EL) of gestational exposure to DMP on male offspring (mg/kg bw/day)

Strain and species; Dose (mg/kg bw/dayay); Route; Duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[b]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
Harlan SD Rats; 0, 750; GD14-18 (Furr et al. 2014)	NE (T) NM (S)	NM	NM	NM (BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	750 (↓BW gain)
SD Rats; 0, 750; Gavage; GD14-PND3 (Gray et al. 2000)	NE (T) NE (S)	NE (AGD) NE (NR) NE (PPS)	NE (CRY) NE (HYP) NM (FER)	NE	NE
SD Rats; 0, 500; Gavage; GD12-19 (Liu et al 2005)	NM	NE (AGD) NM (NR) NM (PPS)	NM	NM	NE
CD Rats; 0, 0.25, 1.0, 5.0%, est. 0, 200, 840, 3570; Diet; GD6-15 (NTP 1989; Field et al. 1993)	NM	NM	NP	NE	LOEL=3570 (transient body wt changes, ↑ relative liver wt)

Strain and species; Dose (mg/kg bw/dayay); Route; Duration (reference)	Testosterone levels[a] (T, S)	Feminization parameters[b]	Reproductive tract malformations and/or fertility[c]	Other developmental parameters[d]	Maternal effects
CD-1 Mice; 0, 3500; gavage; GD7-14 (NTP 1983; Plasterer et al. 1985)	NM	NM	NM	NE	NE
CD-1 Mice; 0, 3500, 5000; gavage; GD6-13 (Hardin et al. 1987)	NM	NM	NM	NE	LOAEL = 5000 (28% maternal death)
Outbred Mol:Wist Rats; 0, 0.5, 1.0, 2.0 ml/kg bw/d, est 0, 595, 1190, 2380; **dermal**; GD6-15, GD1-20 [high dose only] (Hansen and Meyer 1989)	NM	NM	NM	NE	LOEL = 2380 (slight reduction in body 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) measured at varying days post birth, nipple retention (NR), 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, morphology, viability, stages of spermatogenesis) or reproductive success at adult stage after *in utero* exposure.
[d]Other developmental effects include: decreases in overall fetal body weight at PND 1 (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).
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 4 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.

Effects observed in other phthalates of similar chain length/size:

Diethyl phthalate [DEP] (1,2-Benzenedicarboxylic acid, diethyl ester: CAS# 84-66-2) was identified as the 'closest analogue' phthalate to DMP within its subcategory, based on consideration of similarities in length and nature of the ester chains (Section 2.3.2; Health Canada 2015a). Results from the same studies using DMP (similar chain length/size) appear to show comparable results (Gray et al. 2000; Liu et al. 2005). The only exception is a multi-generational diet study in rats where there was an increase in frequency of abnormal and tailless sperm in the F0 and F1 generations, with no effect

on fertility in either generation, and no effects on the testes of offspring or other parameters such as AGD (Fujii et al. 2005). Body weight gain before weaning in both F1 and F2 generations was inhibited at the highest dose (1016 mg/kg bw/day) with multiple organ weight changes, but no histopathological abnormalities were observed (Fujii et al. 2005). A study by Howdeshell and colleagues (2008) found a lack of response in testicular testosterone levels at doses as high as 900 mg/kg bw/day, although serum testosterone levels were not measured.

Results from studies using DEP in mice appear to also be similar to results from DMP studies on this species; where effects were seen on pup viability and fertility at the highest DEP dose tested (3640 mg/kg bw/day; Lamb 1987). Another study did not observe any effects in offspring after high dose (4500 mg/kg bw/day) DEP exposure of dams during GD6-13 (Hardin 1987). As with DMP, most reproductive parameters directly pertaining to the male reproductive system as it relates to RPS were not measured with DEP in mice.

No developmental studies were identified examining gestational exposure to DMP or DEP using other species.

Overall, the highest oral no-observed effect level (NOAEL) for developmental toxicity of DMP was 750 mg/kg bw/day for studies conducted within the masculinization programming window for reproductive development (Gray et al 2000; Furr et al. 2014). This effect level was also established by the US CSPC CHAP (2014). The lowest oral LOAEL for maternal toxicity was 3750 mg/kg bw/day based on transient decreases in body weight gain in a short term diet study in rats during GD 6-15 along with slight, but significant increases in liver weight at GD20 (NOAEL of 840 mg/kg bw/day; Field 1993). The highest dermal NOAEL for developmental toxicity from dermal exposure to DMP was 2380 mg/kg bw/day with slight maternal toxicity at this dose in rats (Hansen and Meyer 1989).

9.2.2.2 Exposure at prepubertal-pubertal life stage

Results from repeated-dose oral exposure studies in sexually immature rats (PND1-PND55) have shown evidence that DMP is not as potent a male rat reproductive toxicant as certain other phthalate esters (e.g. DEHP and other medium-chain phthalates). Summaries of the studies are provided in Table 9-13 below.

Oishi and Hiraga (1980) found a significant decrease in serum and testicular testosterone and dihydrotestosterone concentrations ($p < 0.05$) in treated animals, but these results are of uncertain adversity since no other effects in testes were noted (no changes in testes weights, no inhibition of spermatogenesis, and no testicular atrophy). No other studies were found using other routes of exposure.

Table 9-13. Lowest observed (adverse) effect levels (LO(A)EL) of exposure to DMP and DEP on prepubertal-pubertal males (mg/kg bw/dayay)

Strain and species; Dose (mg/kg bw/dayay); 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]
Wistar Rats; 0, 2%, est. 0, 1862 DMP (US CPSC 2010a); diet; 7 days (Oishi and Hiraga 1980)	Prepubertal (PND35)	LOAEL = 1862 (↓T) 1862 (↓S)	NE	NE	1) NE (BW) 2) NE (ROW) 3) LOEL = 1862 (↑ abs, rel liver weight)
Strain? Rats; 0, 1400 DMP; Gavage; 4 days (Foster et al. 1980)	Prepubertal based on wt ('immature' NR; 70g)	NM	NM	NE	1) NE (BW) 2) NE (ROW) 3) NM (ST)
SD Rats; 0, 500 DMP; Gavage; 4 weeks (Kwack et al. 2009)	Prepubertal-pubertal (PND35)	NM	NE	NM	1) NE (BW) 2) NE (ROW) 3) NE (ST)
F344/N Rats; 0, 37.5, 75, 150, or 300 µL, est. 0, 282, 559, 1332, 2278 DEP; **dermal**; 4 weeks (NTP 1995)	Pubertal (6 wks)	NM	NM	NE	1) NE (BW) 2) NE (ROW) 3) LOEL = 1332 (↑kidney weight) & 2278 (slight ↑ liver weight)
B6C3F$_1$ Mice; 0, 12.5, 25, 50, or 100 µL, est. 0, 630, 1314, 2594, 5212 DEP; **dermal**; 4 weeks (NTP 1995)	Pubertal (6 wks)	NM	NM	NE	1) NE (BW) 2) NE (ROW) 3) NE (ST)

[a]Hormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), or leutinizing 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, an 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).
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.

Effects observed in other phthalates of similar chain length/size:

Results from studies using DMP appear to be comparable to those from studies conducted with another phthalate of similar chain length/size, DEP. DEP also caused decreases in serum and testicular testosterone levels at very high doses (2000 mg/kg bw/day, only dose tested) in prepubertal rats after short term oral exposure (Oishi and Hiraga 1980) and some evidence of slight linearity effects in sperm in another study at 500 mg/kg bw/dayay (Kwack et al. 2009). There were also observations of subtle effects in the testes (alterations in Leydig cell cytoplasmic ultrastructure, mitochondrial swelling, and effects in the smooth endoplasmic reticulum) in pubertal rats at very high doses as well, but these changes could not be replicated *in vitro* with the metabolite of DEP, monoethyl phthalate (MEP) (2000 mg/kg bw/day; Jones et al 1993). Other studies did not observe any effects in males up to doses as high as 1600 mg/kg bw/day (Foster 1980; Gray & Gangiolli 1986; Li et al. 2000).

Due to the lack of dermal studies available using DMP, results from a 4-week study using DEP in mice and rats were used to examine potential reproductive effects of these low molecular weight phthalates at this life stage after dermal exposure. Pubertal rodents (6 weeks of age) did not appear to exhibit any effects on reproductive organs or body weight, with the exception of increased kidney and liver weights in male rats with no histopathological changes in either organ (See Table 9-12; NTP 1995).

Overall, the only LOAEL for reproductive toxicity of DMP identified for this life stage following oral exposure was 1862 mg/kg bw/day based on a significant decrease in serum and testicular testosterone and dihydrotestosterone concentrations in exposed young male rats. The lowest LOEL for systemic toxicity was 1862 mg/kg bw/day based on significant increase in absolute and relative liver weights in treated rats in the same study (Oishi & Hiraga 1980).

With regards to dermal exposure, there was no available information for DMP; the lowest NOAEL for reproductive toxicity of DEP for sexually immature rats after dermal exposure as an analogue was 2278 mg/kg bw/day with increases in kidney weights at 1332 mg/kg bw/day (LOEL) along with slightly increased liver weights at 2278 mg/kg bw/day with no histopathology in young rats (NTP 1995). No studies were identified examining the potential reproductive effects of DMP on any other species *via* any route of exposure at this life stage.

9.2.2.3 Oral exposure at the mature male adult stage

No studies were identified where DMP was administered *via* any route in the male adult rodent (PND55+) where reproductive parameters were measured. As previously mentioned, DEP was identified as the 'closest analogue' phthalate to DMP within the subcategory to use for read-across for potential hazard. Summaries of the studies are described in Table 9-14 below.

A relatively recent, OECD guideline and GLP compliant study designed to detect endocrine-mediated effects showed no effects on testosterone, testes or sperm parameters in male adult rats exposed to DEP (Table 9-14; Shiraishi et al. 2006). It should be noted that the doses used in this study were the same as those used in the multi-generational study described above (Fujii et al. 2005) where authors observed a decrease in serum testosterone levels in F0 males at 197 mg/kg bw/day and above. These results were not considered an adverse effect by the study authors as the degree of reduction was too slight to affect reproductive capacity, the extent of the reduction was greater in the mid-dose than at the high dose, and levels were all within historical controls for this strain of rat. A significant increase in incidence of abnormal and tailless sperm was also observed at the mid dose (197 mg/kg bw/dayay), but not at the higher dose in the F0 males and at the mid and high dose F1 males, but again, these slight increases did not affect the reproductive capacity of adult F1 males (Fujii et al. 2005). Further, the rates of abnormal and tailless sperm (1-1.5%) were relatively low compared to other studies using the same strain of rat where the abnormal and tailless sperm rates in untreated controls can range between 0 and 3.5% (Ateşşahin et al. 2006; Kato et al. 2006; Turk et al. 2008; Matsumoto et al. 2008).

In an NTP study (NTP 1995), no effects in fertility in either generation were observed after chronic dermal exposure to DEP (104 weeks), in either rats or mice, although systemic effects included kidney, liver and brain weight changes at the highest doses tested (See Table 9-14).

Table 9-14. Lowest observed effect levels (LOEL) of exposure to DEP on adult 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, 40, 200, 1000; gavage; 28 days (Shiraishi et al. 2006)	8 wks	1)NM (T) 2)NE (S)	NE	NE	1) NE (BW) 2) NE (ROW) 3) NE (ST)

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]
Crj:CD SD IGS Rats; 0, 600, 3000, 15000 ppm, est. 0, 40, 197, 1016 DEP (F0 males); diet; 15-17 wks (Fujii et al. 2005)	F0: 8wks	1) NM (T) 2) 197[e](S)	197[NDR] (abnormal, tailless sperm)	NE	1) NE (BW) 2) 1016 (ROW, abs. epididymis weight, 5%) 3) 1016 (↑rel. liver weight, ↓abs. adrenal weight, 12%)
SD Rats; 0, 0.2, 1.0, 5.0%, est. 0, 100, 500, 2500 DEP (HC 1994); Diet; 16 weeks (Brown et al 1978)	Not specified	NM	NM	NE	1) 2500 (↓BW, ↓food) 2) 2500 (↑ relative ROW) 3) 2500 (↑multiple organ weights)
Wistar Rats, 0, 0.57, 1.43, 2.85 DEP; Diet; 150 days (Pereira et al 2006[f])	7-8 wks	NM (T) 0.57 (S)	NM	NM	1) 0.57 (↓BW) 2) 0.57 (↓ROW) 3) ↓0.57, ↑ 1.43 (liver weight)
F344/N Rats; 0, 100, or 300 µL, est. 0, 230, 743 DEP (based on a dose conversion by US CPSC 2011); dermal; 104 weeks (NTP 1995)	6 wks	NM	NM	NE	1) NE (BW) 2) NE (ROW) 3) 743 (↓abs brain weight)
B6C3F$_1$ Mice; 0, 7.5, 15, or 30 µL, est. 0, 191, 387, 775 DEP (based on a dose conversion by US CPSC 2011); dermal; 104 weeks (NTP 1995)	6 wks	NM	NM	NE	1) NE (BW) 2) NE (ROW) 3) 775 (↓abs kidney weight & ↓monocytes)

[a]Hormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), [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, an 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] Fujii et al (2005): The decreases in serum testosterone levels were more severe and statistically significant at the mid dose ($p \leq 0.01$) than in the highest dose ($p \leq 0.05$) in parental F0 males. Levels at the low, mid, and high dose were 28%, 80%, and 50% of control levels and were all within historical controls for this strain of rat.
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.
[f] There are several inconsistencies with the results of this study and other studies by the same authors, apart from the divergence with the rest of the literature. These results are considered highly questionable.
NDR = No dose response.

As there were no available studies examining the potential reproductive effects of DMP during the adult life stage, studies using DEP were used for read across. The lowest oral LOEL for reproductive toxicity identified was 1016 mg/kg bw/day based on mild effects seen in the F0 parental males of decreases in serum testosterone and transient increases in abnormal and tailless sperm at the mid dose (but not at the high dose), as well as observations of small decreases in absolute epididymis and absolute adrenal weights at this dose in F0 males (Fujii et al. 2005). The lowest oral NOAEL for systemic toxicity of DEP was 1016 mg/kg bw/day, (increases in relative liver weight in F0 parental males at that dose were not considered adverse) (Fujii et al. 2005).

There were no reproductive effects in adult male rats after chronic dermal exposure to DEP (reproductive NOAEL of 743 mg/kg bw/day) with systemic effects including a small but significant decrease in absolute brain weight at 743 mg/kg bw/day (NOAEL of 230 mg/kg bw/day; NTP 1995).

9.2.2.4 Oral exposure in females

Six published studies on the reproductive and developmental effects of DMP in females were identified. These studies were performed in rats and mice exposed to DMP during gestation (principally between GD6-GD15 but also on GD1-GD20 and GD14-PND3) via feed, gavage or via dermal administration. No two-generation study was available.

No developmental effects were observed in the studies reviewed, even at maternally toxic dosages (LOAEL for maternal toxicity ranged from 200 to 5 000 mg/kg bw/day). The NOAELs identified for developmental toxicity ranged from 2 380 mg/kg bw/day (dermal) to 5 000 mg/kg bw/day (gavage) in rats and mice, respectively.

No reproductive effects were observed in the studies reviewed. The NOAELs identified for reproductive toxicity ranged from 750 to 5 000 mg/kg bw/day (gavage) in rats and mice.

Overall, these studies indicate no adverse effects on developmental and reproductive parameters in females after exposure to DMP at high doses (750 mg/kg bw/day and above).

Effects observed in other phthalates of similar chain length/size [DEP]:

Nine published studies on the developmental and/or reproductive effects of DEP in females were located. These studies were performed in rats and mice exposed to DEP during gestation via oral, percutaneous or subcutaneous administration, and include two two-generation studies (one in rats and one in mice). Moreover, one study aimed to determine the estrogenic potency of DEP via an *in vitro* estrogen receptor-binding assay and an *in vivo* uterotrophic assay performed in immature rats exposed via subcutaneous injection. Overall, the results of the available studies indicate that, at high doses (721-2191 mg/kg bw/day), DEP may induce developmental toxicity in females including altered growth (organs, body weights), lethality, teratogenicity (variations: supernumerary and rudimentary ribs), and functional deficits (liver). However, all these developmental adverse effects in females occurred only at doses inducing maternal toxicity and were mainly the same as those affecting males.

One of the two 2-generation studies reported reproductive toxicity in females. Reproductive toxicity (effects on reproductive development, pregnancy outcomes and reproductive related organ weight) was observed in the F1 parents only (after *in utero* and subsequent exposures).

9.2.2.5 Endocrine studies

One targeted study by Clewell et al. (2010) examined the effects of the monoester of DMP, MMP, on progesterone and testosterone synthesis in the immortalized mouse Leydig cell tumour (MA-10) assay system. MMP showed weak to no inhibition of testosterone synthesis (*ie.* no changes in expression of genes involved in the process) at concentrations up to 100 µM. In the same study, the authors tested DMP (along with four other phthalates) in pregnant rats (500 mg/kg bw/day, GD12–19) and analyzed the fetal testes for corresponding monoesters and found that levels of MMP were 2–40-fold higher in the testes than those of the more active monoesters examined. A more recent study by the same group using a rat Leydig cell line (R2C) using MMP (and the monoester of DEP, MEP) showed that both monoesters slightly reduced testosterone production at concentrations equal to and greater than 100 µM (Balbuena et al 2013). Authors inferred that comparative *in vivo* concentrations in the testes of these low molecular weight phthalates would have to be very high to inhibit testosterone in the fetal testis (greater than 500 mg/kg bw/day).

In a study by Yuan et al. (2012), human and rat testis microsomes were used to investigate the inhibitory potencies of 14 different phthalates on 3β-hydroxysteroid dehydrogenase (3βHSD) and 17βb-hydroxysteroid dehydrogenase 3 (17β-HSD3) activities, enzymes involved in androgen biosynthesis. DMP and DEP both had no

activity in rat microsomes and were only weakly active in human microsomes and did not inhibit activities by up to 50% at the highest concentrations tested (1 mM).

An *in vitro* estrogen receptor-binding assay and an *in vivo* uterotrophic assay indicate that DEP did not bind to the estrogen receptors and did not elicit estrogenic or anti-estrogenic activities (Akahori et al. 2008).

9.2.2.6 Reproductive and developmental toxicity: evidence in humans

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 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[11] (Downs and Black 1988). This allowed for a reliable, objective assessment tool that captured the dimensions of study quality across various study designs. See Appendix G for a description of the Downs and Black evaluation approach for epidemiological studies and definitions of levels of association.

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.

Several human studies have reported findings for DMP and its metabolite, MMP (See section 9.2.1), and these were evaluated accordingly. There was inadequate evidence for an association of neonatal exposure to MMP in breast milk and luteinizing hormone (LH)/free testosterone ratio in newborn boys (Main et al. 2006). No associations were reported between MMP exposure and gestational age, birth measures (e.g. birth weight, birth length, and head circumference) (Wolff et al. 2008; Suzuki et al. 2010), or defects in male infant genitalia (Main et al. 2006).

No associations were observed between urinary MMP and serum levels of reproductive hormones in men (Duty et al. 2005) or in semen parameters (e.g. DNA integrity in

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

sperm, sperm concentration, motility and morphology) (Duty et al. 2003a; Duty et al. 2003b). Buck Louis et al. (2014) found association between MMP and longer time to pregnancy based on MMP concentrations in male partners, although the evidence for this association was inadequate as only one study was available.

Rozati et al. (2008) showed significantly higher levels of serum DMP among endometriosis cases compared with controls; however, failure to adjust for confounders limited the validity of this study.

There was inadequate evidence of association between MMP and some domains of behavioral and cognitive functioning in children (e.g. attention problems, emotional control, etc.) (Engel et al. 2010), and no association was observed for MMP with social functioning (Miodovnik et al. 2011); while in some studies, the association for individual metabolites such as MMP was not reported (Engel et al. 2009).

More recent studies have examined associations between DMP and various endpoints, but these have not yet been assessed using the Downs and Black evaluation approach. Based on the authors conclusions, no associations were found between MMP and intrauterine growth retardation (Zhao et al. 2014), testosterone in both genders (Meeker and Ferguson 2014), and the timing of female puberty (Chen et al. 2013).

9.2.3 Other systemic effects[12]

While exposure to phthalates is commonly associated with adverse effects on the development of the reproductive system in laboratory animals, it is also associated with a range of systemic effects. Repeated-dose exposures to phthalates for short- and long-term duration have shown to be associated with effects in the liver and other organs such as kidney and testes.

It has been shown that phthalates induce peroxisome proliferation in the liver, as well as increased liver weight in rats and mice, and that these effects were identified as the most sensitive in several rodent studies conducted in recent decades. In some cases, liver cancer was also observed following longer-term oral administration. 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 the peroxisomal proliferation response (rodents being largely more sensitive than humans regarding the PPARα-mediated induction of peroxisome proliferation) (ECB 2008, NICNAS 2010, US CPSC

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

2010b). 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 that are likely PPARα-independent (Ito et al. 2007, Yang et al. 2007, Eveillard et al. 2009, Ren et al. 2010, IARC 2012). A detailed evaluation of the potential systemic toxicity (MOA) of phthalate exposure is available in Health Canada (2015c).

A review of studies looking at non-reproductive toxicity endpoints is presented in this section.

9.2.3.1 Repeated-dose studies

The database for repeated-dose toxicity of DMP is limited with only a few short-term and subchronic oral and dermal studies that have been identified in the literature looking at the effects of DMP on rats, mice and rabbits. The available health effects information for DMP is summarized below.

In a dose-ranging study designed to identified the maximum tolerated dose (MTD) for DMP, female CD-1 mice were administered DMP by gavage at 0, 875, 1750, 3500, 7000, 11890 mg/kg bw/day for 8 days. No effects on body weight were observed at any doses. Mortality was observed from 3500 mg/kg bw/day with 10% lethality at that dose level, 50% lethality at 7000 mg/kg bw/day, and 100% lethality at the highest dose tested. The MTD was established at 3500 mg/kg bw/day (NTP 1983). When rats were administered DMP by gavage for 14 days at up to 1000 mg/kg bw/day in another study, no effects were reported (Lake et al. 1978). However, in a second oral study in rats, changes in lipid metabolism (significant reduction in hepatic total cholesterol and total lipid content among treated animals; 31% and 9%, respectively) were observed when animals were exposed to 0.5% DMP in feed for 21 days (equivalent to 250 mg/kg bw/day based on a dose conversion based on Health Canada, 1994). However, levels of serum cholesterol were similar between control and exposed animals (Bell et al. 1978).

The LOEL for short-term oral exposure was 250 mg/kg bw/day based on changes in lipid metabolism in rats and the LOAEL was 3500 mg/kg bw/day (NOAEL of 1750 mg/kg bw/day) based on increased mortality in treated female mice.

In a short-term dermal study, a LOEL of 4800 mg/kg bw/day was reported among rabbits receiving dermal application of DMP for 33 days, based on a slight reduction in hematocrit and testes weight at that dose level. No histological changes were reported at study termination (Dow Chemical 1946). In a subchronic dermal study in which rabbits were exposed to 0, 0.5, 1.0, 2.0 or 4.0 ml/kg (0, 600, 1200, 2400, 4800 mg/kg bw/day) DMP for 90 days, pulmonary edema and kidney damage (nephritis) were observed in animals at levels of 2400 mg/kg bw/day and above (Draize et al. 1948). When male rats were exposed dermally to 0, 200, 1250, 2000 mg/kg bw/day for 90 days, nervous system and renal function changes were reported at the two highest doses (no other details on these effects were available) (Timofieyskaya 1976).

In these studies, the lowest LOAEL for repeated-dose dermal exposure was 1250 mg/kg bw/day (NOAEL of 200 mg/kg bw/day) based on changes in nervous system and renal function in male rats.

9.2.3.2 Carcinogenicity

DMP has not been classified for its potential carcinogenicity by other international agencies and chronic toxicity/carcinogenesis studies for this phthalate are limited.

In a 2-year study of female rats exposed to 0, 2.0%, 4.0%, 8.0% DMP throughdiet (equivalent to 0, 1000, 2000, 4000 mg/kg bw/day based on a dose conversion based on Health Canada, 1994), no evidence of carcinogenicity was noted. Non-neoplastic effects observed included effects on growth and on the kidneys. Growth rate (body weight gain) in the 4% and 8% groups was slightly, but statistically, decreased from controls (magnitude of change was not reported). Kidney damage was observed at the highest dose (Lehman 1955). Confidence in this study is considered low due to the age of the study and insufficient detail provided.

The National Toxicology Program (NTP) (1995) has also conducted a study of the tumour initiation and promotion activity of dermally applied undiluted DMP in male mice. DMP was tested as initiator with and without the known skin tumour promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) and as promoter with and without the known skin tumour initiator 7,12 -dimethylbenzanthrancene (DMBA). In the initiation study, mice were administrated 0.1 ml DMP on the skin once during week 1, followed by application of 0.005 mg TPA, 3 times/week for 8 weeks, then 0.0025 TPA 2 times/week for 44 weeks for a total of 52 weeks of promotion. In the promoter study, mice were treated once in week 1 with 0.05 mg DMBA, followed by applications of 0.1 ml DMP, 5 times/week for a total of 52 weeks. No evidence of initiation or promotion of skin carcinogenesis was observed. The incidence of squamous cell papilloma or carcinoma in both the DMP initiation group (0/50) and the DMP promotion group (1/50, squamous cell papilloma) were similar to the vehicle control (0/50).

The available data suggest that DMP is not likely to induce tumours in experimental animals exposed through the oral or dermal route.

Carcinogenicity studies conducted with other phthalates of similar chain length/size:

DEP has not been classified for carcinogenicity by any organization. In addition to a one year dermal study in male mice in which DEP was shown to lack initiator or promoter activity (as is the case for DMP) (NTP 1995), the NTP has also conducted long term dermal carcinogenicity studies with DEP in both rats and mice.

In the rat study, undiluted DEP was applied to the shaved intrascapular skin of male and female F344/N rats at 0, 100 or 300 µL/animal-day (equivalent to 0, 230, 743 mg/kg-bw/d in males; 0, 379, 1170 mg/kg bw/day in females; based on a dose conversion by the US CPSC 2011), five times per week for 104 weeks (NTP, 1995). No evidence of

carcinogenicity was reported in either sex. However, the authors noted that the sensitivity of the study was reduced in males since survival at terminal sacrifice was significantly reduced in all groups (survival in males: 8%, 12%, and 12%, at 0 µl, 100 µl, and 300 µl, respectively). A treatment-related increase of minimal to mild epidermal acanthosis was noted in both sexes at the site of application, which was considered an adaptive response to irritation. During an evaluation conducted after 15 months of exposure (interim sacrifice), a small but significant decrease in absolute brain weight was reported in males at the highest dose tested (about 5-6% lower than control, no histopathological changes reported) (NTP 1995). The NOAEL for non-cancer effects in this study was identified at 230 and 1170 mg/kg bw/day for male and female rats, respectively.

In the mouse study, DEP dissolved in acetone was applied to shaved intrascapular skin of male and female B6C3F1 mice at 0, 7.5, 15 or 30 µL/animal-day (equivalent to 0, 191, 387 or 775 mg/kg bw/day in males; 0, 209, 415 or 834 mg/kg bw/day in females; based on a dose conversion by US CPSC 2011), five days per week for 103 weeks. Survival at terminal sacrifice and mean body weights of dosed mice were similar to controls. While there was no evidence of toxicity or neoplasia at the application site, a significant increase in incidence of non-neoplastic proliferative lesions (basophilic foci) was observed in the liver of mid dose males. A significant increase in combined hepatocellular adenoma or carcinoma was also observed in high dose males, although it was within the range of historical controls. Increases in incidence of combined hepatocellular adenoma or carcinoma were also observed in females exposed at the low and mid dose but not at the highest dose. Due to the lack of dose-response trend in females and because the incidence rate in high dose males was within the range of historical controls, the NTP indicated that the marginal increases in hepatocellular neoplasms in mice were considered to be uncertain findings providing only equivocal evidence of carcinogenic activity (NTP 1995). At 15-month interim sacrifice, a reduction in mean body weight (8% lower than controls) was noted in females at the highest dose, and a significant increase in relative kidney weight was noted in females at the two highest doses. The NOAEL for non-neoplastic effects in this study was identified at 775 and 415 mg/kg bw/day for male and female mice, respectively.

In conclusion, the available information indicates that DEP is not likely carcinogenic.

9.2.3.3 Genotoxicity

Mixed results have been obtained for *in vitro* and *in vivo* genotoxicity assays with DMP.

In *in vitro* assays, mixed results were observed with DMP in bacterial mutation assays using *Salmonella typhimurium* strains TA98, TA 100, TA 1535 and TA 1537, with and without metabolic activation. In some studies, DMP was not mutagenic (Zeiger et al. 1985; Kozumbo and Rubin 1991; Kubo et al. 2002). In some tests, DMP induced mutations in *Salmonella typhimurium* strains TA100 or TA 1535 in the absence, but not the presence, of metabolic activation (Kozumbo et al. 1982; Seed 1982; Argawal et al. 1985). In an 8-azaguanine resistance assay, DMP was weakly mutagenic both in the

presence and absence of metabolic activation (Seed 1982). In mouse lymphoma cell mutation assays and an assay for sister chromatid exchange in Chinese hamster ovary (CHO) cells, negative results were reported without metabolic activation but positive results were observed in the presence of metabolic activation (Chemical Manufacturers Association 1986; Loveday et al. 1990; Barber et al. 2000). Negative results were observed in a transformation assay with Balb/3T3 cells and in assays for chromosomal aberration in CHO cells and human leukocytes, with and without metabolic activation, respectively (Tsuchiya and Hattori 1976; Loveday et al. 1990; Barber et al. 2000).

Some *in vivo* studies where DMP was administered on the skin or via the intraperitoneal (IP) route have been identified in the literature. DMP produced negative results in dominant lethal assays in mice following both IP and dermal administration (Timofieyskaya 1976; Yurchenko and Gleiberman 1980). Likewise, no chromosomal damage was seen in the bone marrow of mice in a chromosome aberration assay using DMP via IP injection. However, a small but significant increase in chromosome aberrations was observed in the liver of rats following dermal exposure for 1 month in this study (Yurchenko 1977).

9.2.3.4 Evidence of systemic toxicity in humans

Available information on the potential systemic effects of phthalates on humans was reviewed (Health Canada 2015b). See Appendix G for a description of the Downs and Black evaluation approach for epidemiological studies and definitions of levels of association.

There was inadequate evidence for associations of MMP and diabetes (Lind et al. 2012a), effects on cardiovascular function (Lind and Lind 2011; Olsen et al. 2012; Shiue 2013; Trasande et al. 2014), and obesity in elderly women (Lind et al. 2012b). There was inadequate evidence for an inverse association between MMP and waist circumstance in children (Wang et al. 2013).

The levels of indoor dust DMP and corresponding urinary metabolite MMP were not associated with allergic symptoms (asthma, allergic rhinitis, eczema etc.) (Kolarik et al. 2008b; Hsu et al. 2012; Hoppin et al. 2013).

More recent studies have found associations between DMP and various endpoints, but these have not yet been assessed using the Downs and Black evaluation approach. Significant associations were reported between DMP in floor dust and allergic rhinitis in children (Bamai et al. 2014), but no significant associations were found for other related outcomes and in multi-surface dust. Significant associations were reported between MMP and blood pressure considering both genders together (Shiue 2014a,b; Shiue and Hristova 2014) and in men alone (Shiue and Hristova 2014). However, no statistically significant association was found in women alone (Shiue and Hristova 2014).

9.3 Characterization of Risk to Human Health

9.3.1 DMP

DMP has not been classified for its potential carcinogenicity by other international agencies. While chronic toxicity/carcinogenesis studies for DMP are limited, the available data suggest that DMP is not likely to induce tumours in experimental animals exposed through the oral or dermal route.

Consideration of the available information on genotoxicity indicates that mixed results have been observed in *in vitro* and *in vivo* assays. However, phthalates are generally considered to be non-genotoxic substances.

The health effects database for DMP shows that there is no evidence of adverse effects on developmental, reproductive or other organ systems after exposure. No effects were observed on the developing male as it related to the rat phthalate syndrome (RPS) at doses up to 750 mg/kg bw/day, as well as no effects on other developmental parameters outside this syndrome at doses as high as 3570 mg/kg bw/day. It cannot be excluded that effects would not be observed at higher doses, similar to those used in older life stages where decreases in serum and testicular testosterone levels were observed in pubertal rats (1000 mg/kg bw/day) although the dose levels may not be relevant to humans. There were also no reproductive effects observed in adult males when exposed to DEP, an analogue of DMP, and there appeared to be no differences in effects between different routes of exposure (oral *versus* dermal). Based on the available information at this time, there does not appear to be a life stage that is more sensitive than another.

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 DMP or DEP were available (See Tables 9-15 and 9-16 for a summary of critical effects of DMP (or DEP) used for risk characterization).

An examination of the potential developmental toxicity of DMP showed that this short-chain phthalate also had no effect on the developing female or the reproductive capacity of adult females at relatively high doses.

Table 9-15. Summary results of reproductive and/or developmental effects studies based on oral exposure to DMP

Life Stage	Species	Effect (mg/kg bw/day)	LOEL (mg/kg bw/day)	NOEL (mg/kg bw/day)	Reference
in utero	Rat	No developmental effects observed. No effects on **RPS parameters** (GD14-PND3)	NA	750	Gray et al. (2000); Furr et al. (2014)
		LOEL (Maternal) = 3750 transient body weight	NA	3750	NTP (1989)

		changes, ↑ relative liver weight (GD6-15)			[NICNAS and US CPSC]
(pre)pubertal	Rat (7 d)	**A significant decrease in serum and testicular testosterone[a]**, dihydrotestosterone concentrations and ↑ absolute, relative liver weight	1862 (LOAEL)	NA	Oishi & Hiraga (1980)
Adult	Rat DEP (F0, 8 wk)	↓ serum testosterone, transient increases in abnormal and tailless sperm at the mid dose, (not high), ↓ in absolute epididymis, adrenal weights	1016	197	Fujii et al. (2005)

[a]These results are of uncertain adversity since no other effects in testes were noted (no changes in testes weights, no inhibition of spermatogenesis, and no testicular atrophy).
NA = Not applicable

Table 9-16. Summary results of reproductive and/or developmental effects studies based on dermal exposure to DMP

Life Stage	Species	Effect (mg/kg bw/day)	LOEL (mg/kg bw/day)	NOEL (mg/kg bw/day)	Reference
in utero	Rat (GD1-20)	LOEL (Maternal) = 2380 (slight ↓body weight). No effects on pups	NA	2380	Hansen and Meyer (1989)
(pre)pubertal	Rat DEP (4 wk)	Systemic LOEL = 1332 ↑relative kidney and liver (2278) weights, no testicular pathology observed	NA	2278	NTP (1995)
adult	Rat DEP (2 yr)	Systemic LOAEL**=** 743 ↓abs brain weight, no testicular pathology observed	NA	743	NTP (1995)

NA = Not applicable

Following repeated-dose exposure, the lowest LOAEL for subchronic dermal exposure was 1250 mg/kg bw/day (NOAEL of 200 mg/kg bw/day) based on changes in nervous system and renal function in male rats exposed for 90 days. The lowest LOAEL for chronic dermal exposure identified from a 2-year study conducted in rats with the analogue DEP was 743 mg/kg bw/day (NOAEL of 230 mg/kg bw/day) based on small but significant decrease in absolute brain weight in males. In a corresponding mouse study, the lowest LOAEL from chronic exposure was identified at 834 mg/kg bw/day (NOAEL of 415 mg/kg bw/day) based on reduction in mean body weight in females.

See Table 9-17 for a summary of critical effects of DMP that will be used for risk characterization.

Table 9-17. Summary table of critical systemic effects after dermal exposure to DMP

Endpoint	Species	Effect	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Reference
Subchronic	Rat (90 days)	Changes in nervous system and renal function in males	1250	200	Timofieyskaya (1976)
Chronic	Rats DEP (2 years)	Small but significant decrease in absolute brain weight in males	743	230	NTP (1995)
Chronic	Mice DEP (2 years)	Decrease in mean body weight in females	834	415	NTP (1995)

The predominant source of exposure to DMP, for the general population,is expected to be from breast milk and food, with indoor air and dust also being contributors. Dermal and inhalation (aerosol) exposure to cosmetics and personal care products were also evaluated for adults (20+) and infants (0 to 6 months). Finally, metabolite concentrations of DMP in human urine were evaluated and reverse dosimetry was used to convert these concentrations into DMP intake estimates; this provides an estimate of systemic exposure from all sources. Central tendency and upper-bound intakes and respective margins of exposure for the relevant populations and sources are presented in Table 9-18.

Table 9-18. Summary of margins of exposure to DMP for subpopulations with highest exposure.

Age Group and Exposure Scenario	Central tendency (upper bounding) estimate of exposure (µg/kg per day)	Level and basis for NOAEL (mg/kg-bw/day)	Margin of Exposure (MOE)[d]

Children (males) 2 - 3 years: Biomonitoring, MIREC CD Plus	0.19 (0.66)	NOAEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males	Over 1 million (348 485)
Infants 0- 6 months, breast milk fed: environmental media and food, oral and inhalation	0.019 (0.26)	LOAEL = 1862 (pubertal, 7 days oral, DMP) ↓ serum and testicular testosterone, dihydrotestosterone concentrations and ↑ absolute, relative liver weight (no NOAEL)	Over 1 million
Infants 0 – 6 months: diaper cream, dermal	2.7[a] (8.2)[a]	NOAEL = 200 (subchronic dermal, DMP) Changes in nervous system and renal function in males	74 074 (24 390)
Adults (females) 20+ years: Biomonitoring, NHANES	0.027 (0.26)	NOAEL = 415 (chronic dermal, DEP) Decrease in BW of 8% in females)	Over 1 million
Teens (males) 12-19 years: Biomonitoring, NHANES	0.042 (0.29)	NOAEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males	Over 1 million (793 103)
Teens 12-19 years: environmental media and food, oral and inhalation	0.0085 (0.091)	NOAEL = 750 (*in utero* oral DMP) Highest dose tested for potential RPS effects	Over 1 million[b]
Adults 20 + years: hairspray, dermal	66[ac] (200)[a]	NOEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males	3485 (1150)
Adults 20 + years: hair dye, dermal	1400[ac] (4200)[a]	NOAEL = 2380 (short term dermal, DMP) slight ↓body weight in dams	1700 (567)

[a] External dermal exposure estimates
[b] This margin is also protective for potential effects of DMP (based on effects observed with DEP) on males of this age group which occur at higher doses.
[c] Lower-bound estimate: based on minimum concentration
[d] 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 as they not only address potential systemic effects of DMP, but also slight effects on the reproductive system that occur at higher doses than those used in risk characterization. Further, selection of an RPS-specific NOAEL of 750 mg/kg bw/day for potential developmental effects was chosen as a conservative, precautionary point of departure as other available studies with higher NOAELs did not

examine the parameters indicative of the mode of action of concern for this substance grouping.

9.3.2 Considerations

For DMP the predominant source of exposure is from breast milk and food, with indoor air and dust also being contributors. Additional, sources of exposure are personal care products, including cosmetics.

With respect to the use of adhesive, sealants, and coatings which contain DMP, exposure would not be considered to be of concern for human health based on the following:

Dermal absorption of short-chain phthalates in rats is low (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 of DEP and DMP in other tissues (adipose and muscle) is extremely low after 7 days (0.3 to 0.6% of applied dose; Elsisi et al. 1989).

This is consistent with the assessments of other jurisdictions that have focused their assessment on repeated exposures (ECHA 2013a; US CPSC CHAP 2014).

9.4 Uncertainties in Evaluation of Risk to Human Health

There is some uncertainty associated with the use of DEP to characterize human health effects of DMP when there was no available toxicological information for its specific life stage or duration and/or route of exposure.

There are limited to no studies via any route of administration on neurodevelopmental toxicity, nor is there any two-generation study available for DMP. The remaining studies available for DMP related to reproductive-developmental toxicity are generally limited to one species (rat), one dose, and mostly in males. There is some uncertainty associated not only with the potential biological significance of effects, but also in sensitivity of

effects after exposure to this substance group in both female and male humans, but current information does not allow for conclusions to state otherwise.

There is a lack of repeated-dose studies of short to long-term duration via inhalation as well as limited carcinogenicity studies by the oral and dermal route for DMP. Consequently, there is uncertainty surrounding the potential carcinogenicity and chronic toxicity of this phthalate. However, there is available information from carcinogenicity studies for the analogue DEP to address this endpoint.

Although a rigorous evaluation approach was conducted with the available human epidemiological data, uncertainty still exists in the relevance of these studies implicating the potential hazard of certain phthalates 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 shows 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).

There are uncertainties associated with estimating intakes of DMP from environmental media due to minimal monitoring data available 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.

For quantification of food exposure from DMP presence in food, U.S. and U.K. surveys were used for analysis; as a result, uncertainty exists as these intakes are extrapolated for the Canadian general population. There is also uncertainty associated with exposure estimates calculated from DMP monoester (MMP) presence in breast milk and infant formula. This uncertainty is related to the quantification of exposure (conversion of metabolite exposure to parent phthalate exposure) and evaluating margins of exposure between exposure intakes derived from metabolite exposure (to infants ingesting breast milk and formula containing MMP) to toxicology studies evaluating effects of parent phthalate exposure.

There are a number of assumptions that have been made to derive intake estimates from biomonitoring data which represent a source of uncertainty; i.e., assumption that spot urine samples are representative of steady state daily concentrations, 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.

Additionally, there is uncertainty related to the use of NHANES derived DMP intakes as a surrogate for the Canadian population and the use of read-across (MnBP FUE used for MMP) in deriving exposure estimates. However, confidence in the biomonitoring database for DMP is high as it represents a substantially large number of data points collected recently in North American individuals.

Margins of exposure for inhalation exposure to aerosol hair spray were not assessed because of insufficient inhalation toxicity data and robust toxicity studies evaluating chronic oral exposure were not identified (precluding route to route extrapolation).

Uncertainty also exists regarding the use of an external dermal dose as an endpoint to evaluate the risk associated with internal intakes from biomonitoring data (all sources and routes), when dermal absorption of this substance is expected to be less than 100% in rats (<10 %, see section 9.2.2). However, the magnitude of margins of exposure (348 485 to > 1 million), are considered adequate to address this uncertainty. Additionally, it is important to note that rat skin is thought to be more permeable than human skin for a similar phthalate (DEP) leading to presumably lower systemic doses in humans (see section 9.2.2).

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. In the case of inconsistencies in duration scenarios, provided that the daily

exposure is being compared with health effect levels from animal studies of longer duration, confidence is high that the derived MOEs areconservative.

Uncertainty is recognized in the potential oral bioavailability of DMP after administration and therefore the estimated systemic exposure at which effects were observed in animal studies, however limited information exists that oral absorption of short-chain phthalates are close to 100% (see section 9.2.1) and MOEs are considered adequate to account for this uncertainty.

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Appendix A. Empirical and Modelled Data for the Biodegradation of DMP

Table A-1. Summary of key empirical data regarding the biodegradation of DMP.

Medium	Fate process	Degradation value	Degradation endpoint / units (Method)	Reference
Surface water				
River water (urban Japan)	Aerobic biodegradation (Handai Method)	49.3% biodegraded by river water	Primary degradation (Cultured microbial isolates); Existing phthalate in water or supplemented. 100 µg in 5 mL river water, 25oC; 7d incubation	Hashizume et al. 2002
Water/sediments				
Fresh water sediments (9:1 River water to sediment)	Aerobic biodegradation; 12-14°C in the dark	t½ (d) = 2.5 d	Primary degradation (OECD 301)	Kickham et al. 2012
Fresh water sediments (9:1 River water to sediment)	Aerobic biodegradation; 12-14°C in the dark	rate = 0.28 (± 0.07) d-1	Primary degradation (OECD 301)	Kickham et al. 2012
Subsurface sediment slurry	Sulphate reducing environment; isolation/enrichment of bacterial species (Thauera sp.)	22% of DMP degraded in 60 d under sulphate reducing conditions	Thauera sp. Pure isolate yields slow and incomplete degradation in sulphate reducing conditions.	Cheung et al. 2007
Acclimated sediment organisms	Aerobic biodegradation, shake flask	86% ±12% (28 d) [>99%]	Primary [ultimate]	Sugatt et al. 1984
Acclimated sediment organisms	Aerobic biodegradation, shake flask	t½ (d) = 1.9	half-life	Sugatt et al. 1984
Acclimated sediment organisms	Aerobic biodegradation, shake flask	0.364 (SD 0.015)	Rate constant per day	Sugatt et al. 1984
Marine sediments (enriched microbes)	Primary aerobic biodegradation	>85% (74 d); K = 0.0587 day-1; t½ = 11.8	% degradation (74d); 18oC	Peng and Li 2012
Sediment and fresh water cyanobacteria	Primary degradation rate compared to control	*A. flos-aquae* (strain): 4.89±0.16/69.63±1.49;	Sediment and fresh water cyanobacteria	Primary degradation rate compared to control

Medium	Fate process	Degradation value	Degradation endpoint / units (Method)	Reference
Soil				
Soil microbes (enriched)	Aerobic degradation in culture by *Pseudomonas fluorescens* FS1	25 to 400 mg/L initial conc. t½ range = 6.17 – 10.39 h.	Concentration dependent rate of biodegradation	Zeng et al. 2004
Soil microbes (enriched)	Aerobic degradation in culture by *Pseudomonas fluorescens* FS1	At < 200 mg/L initial conc. and incubation 7 d at 30oC, t½ = 6.48 h	Concentration dependent rate of biodegradation	Zeng et al. 2004
Sewage sludge				
Sludge (Activated)	Aerobic biodegradation (Composting)	75% (75 to 90 d), 100% (135 d)		Amir et al. 2005
Sludge (Lagoon)	Aerobic biodegradation (Composting)	180 d	not degraded	Amir et al. 2005
Sludge Anaerobic WWT digester	Anaerobic biodegradation (37 ^{o}C)	>90%	Primary degradation (4 d)	Wang et al. 2000
Sludge Anaerobic WWT digester	Anaerobic biodegradation (37 ^{o}C)	78%	Methane (% theoretical)	Wang et al. 2000
Sludge Anaerobic WWT digester	Anaerobic biodegradation (37 ^{o}C)	23.9	half-life (h)	Wang et al. 2000
Sludge (WWT)	Anaerobic degradation (35 ^{o}C)	>90% (LOD 0.5 ppm)	Primary degradation (40 d)	Shelton et al. 1984
Sludge (WWT)	Anaerobic degradation (35 ^{o}C)	82%	Methane (% theoretical)	Shelton et al. 1984
Activated Sludge	Aerobic biodegradation (25 ^{o}C)	90% (3 d); 100% (5d) 100 mg/L; t½ =21 h; Rate constant (h-1) = 0.033	Primary degradation	Wang et al. 1996
Activated Sludge	Aerobic biodegradation	<0.1% adsorbed; 93% degraded by microbes. Rate = 0.031 kg/day (DMP)	Primary biodegradation, solubility and adsorption to particulate.	Roslev et al. 2007
Acclimated, activated sludge	Aerobic biodegradation	>90% (10 d); K = 0.3028 day^{-1}; t½ = 2.29 d	Primary biodegradation, % after period of days (d), rate and t½.	Wang et al. 2004

Medium	Fate process	Degradation value	Degradation endpoint / units (Method)	Reference
Other				
Defined medium	Algal bioassay: initial density of algal cells of 10^6 /ml for biodegradation / accumulation experiments	85% loss from aqueous fraction. Final conc. = 13.4 mg/L; Rate constant (h^{-1}) = 0.484/h (second order).	DMP = 100 mg/L (2% degraded abiotically). Combination of bioaccumulation and biodegradation measured by loss of DMP from aqueous solution. After 24 h accumulation decreases and maximum biodegradation achieved by 72 h. Rates supplied.	Yan et al. 1995

Abbreviations: $t_{½}$, half-life; d^{-1}, per day; h^{-1}, per hour; conc., concentration; SD, standard deviation; K, rate constant for degradation in soil, sediment or other medium.

Table A-2. Summary of key modelled data regarding the ultimate biodegradation of DMP.

Degradation endpoint or prediction	Test method or model basis	Extrapolated half-life ($t_{1/2}$ = days)	Reference
3.05[a] "biodegrades fast"	Sub-model 3: Expert Survey (qualitative)	<180	BIOWIN 2010
0.86[b] "biodegrades fast"	Sub-model 5: MITI linear probability	<180	BIOWIN 2010
0.91[b] "biodegrades fast"	Sub-model 6: MITI non-linear probability	<180	BIOWIN 2010
1[b] "biodegrades fast"	Probability	< 180	DS TOPKAT 2004
0.86 "biodegrades fast"	% BOD (biological oxygen demand)	<180	CATALOGIC 2012

[a]Output is a numerical score from 0 to 5.
[b]Output is a probability score.

Appendix B. Empirical Data for the Aquatic Toxicity of DMP

Table B-1 Organism Toxicity Values

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish				
Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	LC_{50}	56 (38-83)	CMA 1984f
Rainbow trout, *Oncorhynchus mykiss*	Acute (96 h)	LC_{50}	56	Adams et al. 1995*
Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h) juvenile	LC_{50}	50 (static)	Adams et al. 1995*
Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h) juvenile	NOEC, survival	15.3 (static)	Adams et al. 1995*
Bluegill sunfish, *Lepomis macrochirus*	Acute (96 h) juvenile	LC_{50}	67 (static)	CMA 1984f
Bleak, *Alburnus alburnus*	Acute (96 h)	$LC(I)_{50}$	100-115	Linden et al. 1979
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC_{50}	121 (static)	Adams et al. 1995*
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC_{50}	39 (flow-through)	Adams et al. 1995*
Fathead minnow, *Pimephales promelas*	Acute (120 h)	LC_{50}	38 (32 – 45)	ECHA c2007-2013
Fathead minnow, *Pimephales promelas*	Acute (144 h)	LC_{50}	38 (32 – 45)	ECHA c2007-2013
Fathead minnow, *Pimephales promelas*	Acute (96 h)	LC50	56	US EPA 2010
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	NOEC, survival	66 (static)	Adams et al. 1995*
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	NOEC, survival	16 (flow-through)	Adams et al. 1995*
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC50	29 (static)	Adams et al. 1995*
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC50	120 (static) (68-210)	CMA 1984f
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC50	39 (flow-through) (33-46)	CMA 1984f
Fathead minnow, *Pimephales promelas*	Acute (96 h) juvenile	LC50	39 (flow-through)	Reference?
Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h) juvenile	NOEC, survival	3.2 (flow-through)	Adams et al. 1995*
Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h) juvenile	LC50	56 (flow-through)	Adams et al. 1995*
Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h) juvenile	NOEC, survival	38 (flow-through)	Adams et al. 1995*
Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	LC50	29 (flow-through)	CMA 1984e
Sheepshead minnow, *Cyprinodon variegatus*	Acute (96 h)	LC50	58 (47-68)	Heitmuller et al. 1981
Rainbow trout, *Oncorhynchus mykiss*	Chronic (102 d)	NOEC, hatchability,	11	Rhodes et al. 1995*

		survival, or growth		
Rainbow trout, *Oncorhynchus mykiss*	Chronic (102 d)	LOEC, hatchability, survival, or growth	24	Rhodes et al. 1995*
Invertebrates				
Abalone, *Haliotis diversicolor supertexta*	Acute (9 h)	EC_{50} (embryo toxicity, blastula stage)	55.71	Yang Z. et al. 2009a.
Abalone, *Haliotis diversicolor supertexta*	(96 h)	NOEC (96h); reduced larval metamorphosis	0.02	Liu et al. 2009*
Abalone, *Haliotis diversicolor supertexta*	(96 h)	LOEC, embryo abnormalities	40	Yang et al. 2009*
Abalone, *Haliotis diversicolor supertexta*	(96 h)	LOEC, larval settlement	0.05	Yang et al. 2009*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	LOEC, decrease in ATPase activities (sperm)	0.01 (10 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	NOEC, decrease in ATPase activities (sperm)	0.001 (<1 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	LOEC, sperm morphology	0.1 (100 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	NOEC, total lipd egg levels	0.1 (100 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	NOEC, egg morphology	0.001 (1 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	LOEC, T2 and T3 fertilization capabilities	0.01 (10 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	NOEC, T1 fertilization capabilities	0.001 (<1 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	LOEC, embryo abnormalities T2 and T3	0.001 (1 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	NOEC, embro abnormalities T1	0.1 (100 ppb)	Zhou et al. 2011*
Abalone, *Haliotis diversicolor supertexta*	Acute (60 min)	LOEC; hatch success rates (T1, T2, T3, respectively)	0.1 (100 ppb; T1); 0.01 (10 ppb, T2); 0.01 (10 ppb; T3)	Zhou et al. 2011*

Mysid shrimp, *Americamysis bahia*	Acute (96h)	LC50	68.6 (static)	Adams et al. 1995*
Mysid shrimp, *Americamysis bahia*	Acute (96h)	NOEC, immobility	22.2 (static)	Adams et al. 1995*
Mysid shrimp, *Americamysis bahia*	Acute (48h)	EC_{50}	76 (static) (54-130)	CMA 1984e
Water flea, *Daphnia magna*	Acute (48h)	LC_{50}	>52	ECHA c2007-2013
Water flea, *Daphnia magna*	Acute (48h)	EC_{50}, immobility	45.9 (static)	Adams et al. 1995*
Water flea, *Daphnia magna*	Acute (48h)	NOEC, immobility	<23.5(static)	Adams et al. 1995*
Water flea, *Daphnia magna*	Acute (48h)	IC_{50}, immobility	284	Oehlmann et al. 2009 (Jonsson and Baun 2003)*
Water flea, *Daphnia magna*	Acute (48h)	EC_{50}	33	LeBlanc 1980
Annelid, *Lumbriculus variegatus*	Acute (10 d)	LC_{50}	246	Call et al. 2001*
Amphipod crustacean, *Hyalellaazteca*	Acute (10 d)	LC_{50}	28.1	Call et al. 2001*
Midge,*Chironomus tentans*	Acute (10 d)	LC_{50}	68.2	Call et al. 2001
Polychaete, *Pomatoceros lamarckii*	NS	LOEC; decrease in fertilization	1.94	Dixon et al. 1999*
Polychaete, *Pomatoceros lamarckii*	NS	LOEC; chromosome separations in oocytes at anaphase	0.0194 (19.4 µg/L)	Wilson et al. 2002*
Midge, *Paratany-tarsus partheno-genetica*	Acute (96 h)	LC_{50}, immobility	377 (static)	Adams et al. 1995*
Midge, *Paratany-tarsus partheno-genetica*	Acute (96 h)	NOEC, immobility	<100 (static)	Adams et al. 1995*
Midge	Acute (48 h)	EC_{50}	390 (static) (330-450)	CMA 1984e
Harpacticoid, *Nitocra spinipes*	Acute (96 h)	$LC(I)_{50}$	53-72	Linden et al. 1979
Water flea, *Daphnia magna*	Chronic (21d)	NOEC, survival and reproduction	9.6	Rhodes et al. 1995*
Water flea, *Daphnia magna*	Chronic (21d)	LOEC, survival and reproduction	23	Rhodes et al. 1995*
Algae				
Green alga, *Desmodesmus subspicatus*	Chronic (72h)	EC_{10}, biomass	116	ECHA c2007-2013
Green alga,	Chronic (72h)	EC_{50},	204	ECHA c2007-2013

Desmodesmus subspicatus		biomass		
Green alga, *Desmodesmus subspicatus*	Chronic (72h)	EC_{90}, biomass	358	ECHA c2007-2013
Green alga, *Desmodesmus subspicatus*	Chronic (72h)	EC_{10}, growth rate	193.09	ECHA c2007-2013
Green alga, *Desmodesmus subspicatus*	Chronic (72h)	EC_{50}, growth rate	259.76	ECHA c2007-2013
Green alga, *Desmodesmus subspicatus*	Chronic (72h)	EC_{90}, growth rate	349.43	ECHA c2007-2013
Green algae, *Pseudokirchneriella subcapitata*	Chronic (96 h)	EC_{50}, cell count decrease	142	Adams et al. 1995*
Green algae, *Pseudokirchneriella subcapitata*	Chronic (96 h)	NOEC, cell count decrease	<64.7 (static)	Adams et al. 1995*
Green Algae,*Chlorella pyrenoidosa*	Chronic (96 h)	EC_{50}; growth	313	Yan et al. 1995*
Algae	Chronic (96h)	EC_{50}	145.6 (static) (95.4-240.2)	CMA 1984e
Other				
Micro-organisms	(30 min)	EC_{20}, respiration rate	400 (calculated)	ECHA c2007-2013
Gymnodinium breve		96h TLM ^	125, 185 (2 assays)	Wilson et al. 1978 #
Gymnodinium breve		96h EC_{50} (median growth limit concentration)	96, 54 (2 assays)	Wilson et al. 1978 #

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 low 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

based on nominal concentrations

^ Median Tolerance Limit (same as LC_{50})

Appendix C. Estimates of Daily Intake for the Short-chain Grouping

Table C-1. Central Tendency (Upper-bounding) estimates of daily intake of DMP for the general population. Estimated intake (µg/kg/day) of DMP by various age groups

Route of exposure	0–0.5 year[a] Breast milk 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]	-	-	-	-	-	-	-	-
Indoor air[k]	0.0066 (0.093)	0.0066 (0.093)	0.0066 (0.093)	0.014 (0.21)	0.011 (0.16)	0.0063 (0.084)	0.0054 (0.076)	0.0047 (0.066)
Drinking water[l]	-	-	-	-	-	-	-	-
Food and beverages[m]	0.012 (0.16)	0	0	0.0029 (0.010)	0.0028 (0.0076)	0.0022 (0.0061)	0.0018 (0.0046)	0.0011 (0.0034)
Soil[n]	-	-	-	-	-	-	-	-
Dust[o]	<0.001 (0.0070)	<0.001 (0.0070)	<0.001 (0.0070)	<0.001 (0.0050)	<0.001 (0.0023)	<0.001	<0.001	<0.001
Total Oral intake	**0.019 (0.26)**	**0.0066 (0.10)**	**0.0066 (0.10)**	**0.017 (0.23)**	**0.014 (0.17)**	**0.0085 (0.090)**	**0.0072 (0.081)**	**0.0058 (0.069)**

[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 38 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Median and 90th dietary intake estimates (food) for the < 6 months age group, as presented in Table C2, were used to represent dietary intake for this age group (applicable to the non-formula fed group).

[b] Infants 0-6 months assumed to ingest 0.742 litre breast milk/day (USEPA, 2011). Two Canadian studies did not detect DMP in breast milk. The first was part of the Maternal Infant Research on Environmental Chemicals (MIREC) survey (n=305; MDL=1ng/g; personal communication Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada, November 2014). The other samples (86) were collected in 2003-2004 from 21 mothers over a 6-month postpartum period in Kingston, ON, Canada (limit of detection, 0.63 ng/g; Zhu et al. 2006). Additionally, in a recent Health Canada study evaluating breast milk studies from the MIREC cohort, DMP was not detected in 305 samples. MMP (metabolite of DMP) was detected in 100% of breast milk samples obtained from the P4 cohort, however due to high field blank contamination, these results were not used to quantify intakes. Therefore Mortensen et al. 2005 (detection of MMP in 32 of 36 samples obtained from Danish women) was used for exposure characterization and median (0.11 ug/L) and maximum concentrations (1.49 ug/L) were used to calculate intakes. The concentrations of MMP have been multiplied by the ratio of the molecular weight of dimethyl phthalate to the molecular weight of monomethyl phthalate (194.2/180.2) to convert the intake into a DMP equivalent intake (ug DMP/kg-bw/day) so that it can be compared to a toxicological endpoint derived from a study conducted with DMP. Other data were reported by Main et al. (2006).

[c] In the P4 study, MMP (metabolite of DMP) was detected in 100% of infant formula samples; the median was 0.51 ug MMP/L and the maximum was 1.1 ug MMP/L (Personal Communication from EHSRD to ESRAB, Sept 2013) however, due to high field blank contamination these results were not used to quantify intakes. Additionally Mortensen et al. 2005 showed non detection of MMP in 10 formula samples. Therefore intakes for this population, from exposure to DMP in formula were not quantified.

[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 14 mg of soil and 41 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Median and 90th dietary intake estimates (food) for the 1 to 3 years age group, as presented in Table C2, 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 21 mg of soil and 41 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Median and 90th dietary intake estimates (food) for the 4 to 8 years age group, as presented in Table C2, 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 1.4 mg of soil and 2.2 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th dietary intake estimates (food) for the 14 to 18 years age group, as presented in Table C2, 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 1.6 mg of soil and 2.5 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th dietary intake estimates (food) for the 19 to 30 years age group, as presented in Table C2, 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 1.5 mg of soil and 2.5 mg of dust per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th dietary intake estimates (food) for the 51 to 70 years age group, as presented in Table 2, were used to represent dietary intake for this age group.

[i] A mean concentration of 0.3 ng/m^3 (n=10) was reported in sampling of air collected 9 metres above sea level in the North Sea in 2004 (Xie et al., 2005). A report of DMP in Arctic air was also identified (Xie et al., 2007). Canadians are assumed to spend 3 hours per day outdoors (Health Canada, 1998). However given the low concentrations reported, and the non-Canadian data, intakes from this source were not quantified.

[j] Scientific notation is included in parentheses for values that were not true zeros or were rounded.

[k] DMP was not detected in 73 randomly selected residential houses in Ottawa in the winter of 2002-2003 (limit of detection in pg/m^3 for phthalates) (Zhu et al. 2007). Indoor air values reported in Swedish apartments by Bergh et al. (2011b) were used as a surrogate. The mean concentration of DMP reported in indoor air was 27 ng/m3 and the maximum was 380 ng/m^3. Studies considered in the selection of critical data included Fromme et al. (2004); Pei et al (2013); Bergh et al. (2011a). Canadians are assumed to spend 21 hours per day indoors (Health Canada, 1998).

[l] No Canadian data on the levels of DMP in drinking water were identified. DMP was not detected in bottled water in Canada.

[m] Probabilistic intakes (median and 90th) were incorporated into a dietary intake table for comparison purposes. (Intakes and methodology are outlined in Table C2 and Appendix D). Note gender and age groups do not match fully; therefore the highest intake from within an age group was inputted into the table: e.g. Male intakes (19 – 30 years) were inputted into the 20 – 59 years (unisex) column because this age group had the highest intake of all groups in the 19 – 50 year range.

[n] Webber and Wang (1995) detected DMP in 6 of 10 samples of agricultural soil from five provinces in Canada; limit of detection, 0.03 mg/kg dw, however, due to the date of the study estimates of exposure were not derived. Concentrations of DMP in soil in China were also identified (Zeng et al. (2009).

[o] The amount of indoor dust ingested each day is based on Wilson et al. (2013). The median concentration (0.12 ug/g) and 95th percentile (1.4) concentrations of DMP identified in indoor dust was used for exposure characterization (Kubwabo et al. 2013).

Table C-2. Probabilistic dietary exposure estimates to DMP (ng/kg/day)

DRI group	Median	90th percentile
< 6 months	0	0
6 months-1 yr	F	F
1 - 3 yrs	2.9	10.02
4 - 8 yrs	2.82	7.57
M: 9 -13 yrs	2.14	5.9
F: 9 -13 yrs	1.7	4.93
M: 14 - 18 yrs	2.21	6.11
F: 14 - 18 yrs	1.55	4.42
M: 19 - 30 yrs	1.81	4.64
F: 19 - 30 yrs	1.29	4.09
M: 31 - 50 yrs	1.42	4.14
F: 31 - 50 yrs	1.14	3.53
M: 51 - 70 yrs	1.09	3.4
F: 51 - 70 yrs	0.82	2.88
M: > 71 yrs	0.73	2.59
F: > 71 yrs	0.67	2.32

F denotes that coefficients of variation associated with intake estimates were not sufficiently low to allow for reporting the intake value.

Appendix D: Derivation of dietary intakes

Occurrence data – DMP

Occurrence data for DMP 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 DMP in food that was reported as less than the analytical LOD were assigned values of ½LOD. 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

DMP 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 phthalates 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 DMP 989 foods, 23 recipes were matched with the list of 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 E: Dermal chronic exposure estimates for cosmetic and personal care products

Table E-1 Dermal and Cosmetic and personal care products estimates

Product Type	Min/Mean % - Max %	Min Chronic Exposure (mg/kg/day)	Max Chronic Exposure (mg/kg/day)	Reference
Hair Spray (adult)	1 - 3	0.0066	0.020	Notifications under *Cosmetic Regulations*
Nail Polish (adult)	1 - 3	3.00E-04	9.0E-04	Notifications under *Cosmetic Regulations*
Body Cream, Lotion, Moisturizer (infant)	0.00001 - 0.00044	3.2E-06	1.4E-04	Guo et al. 2013
Deodorant/Antiperspirant	ND –	-	7.9E-05	Guo and

Solid (adult)	0.0072			Kannan 2013
Body Cream, Lotion, Moisturizer (adult)	0.000039 - 0.000568	2.7E-06	3.9E-05	Guo and Kannan 2013
Face Cream, Lotion, Moisturizer (adult)	0.000052 - 0.00107	1.6E-06	3.3E-05	Guo and Kannan 2013
Body Cream, Lotion, Moisturizer (adult)	0.00001 - 0.00044	6.8E-07	3.0E-05	Guo and Kannan 2013
Deodorant/Antiperspirant Solid (adult)	0.000151 - 0.00206	1.7E-06	2.3E-05	Guo and Kannan 2013
Body Cream, Lotion, Moisturizer (infant)	0.000017 - 0.000051	5.4E-06	1.6E-05	Guo and Kannan 2013
Hair Mousse (adult)	0.000371 - 0.00121	9.4E-07	3.1E-06	Guo and Kannan 2013
Facial Toner (adult)	0.000003 - 0.000028	2.1E-08	2.0E-07	Guo and Kannan 2013
Hair Shampoo (adult)	0.00001 - 0.00007	1.8E-08	1.3E-07	Guo et al. 2013
Hair Shampoo (adult)	0.000007 - 0.000032	1.3E-08	5.9E-08	Guo and Kannan 2013
Liquid shower soap (adult)	0.00001 - 0.00008	3.7E-09	2.9E-08	Guo et al. 2013
Nail Polish (adult)	0.000003 - 0.000022	9.0E-10	6.6E-09	Guo and Kannan 2013
Hair Shampoo (infant)	0.00001 - 0.00007	9.3E-10	6.5E-09	Guo and Kannan 2013
Hair Shampoo (infant)	0.000017 - 0.000068	1.6E-09	6.3E-09	Guo and Kannan 2013
Facial Cleanser (adult)	0.000001 - 0.000006	5.9E-10	3.5E-09	Guo and Kannan 2013
Liquid shower soap (adult)	0.000001 - 0.000009	3.7E-10	3.3E-09	Guo and Kannan 2013

Appendix F: Derivation of daily intakes for DMP based on biomonitoring

MIREC CD+

Equation 1:

$$\text{Daily intake}\left({}^{\mu g}/_{\text{kg bw.day}}\right) = \frac{C_{\text{metabolite}}\left(\frac{\text{moles}}{\text{g Cr}}\right) \times \text{CER}\left(\frac{\text{g}}{\text{day}}\right) \times MW_{\text{parent}}\left(\frac{\text{g}}{\text{mole}}\right)}{\text{FUE} \times \text{BW (Kg)}}$$

Where,

$C_{metabolite}\left(\frac{moles}{g\ Cr}\right)$ = Molar concentrations of the metabolite

CER = Creatinine excretion rate using Mage equation

MW = Molecular weight of DMP, 194 g/mol

FUE = Fractional urinary excretion values of MMP: 0.69

BW = Body weight of the participant

Step 1: Converting urinary metabolite concentrations into moles/g Cr unit

Equation2

$$C_{metabolite}\left(\frac{moles}{g\ Cr}\right) = \frac{C_{metabolite\ Cr}\left(\frac{\mu g}{g\ Cr}\right)}{MW_{metabolite}\left(\frac{g}{mole}\right)}$$

A. *Converting urinary MMP concentrations (DEP daily intake estimation)*

$$C_{MMP}\left(\frac{moles}{g\ Cr}\right) = \frac{C_{MMP\ Cr}\left(\frac{\mu g}{g\ Cr}\right)}{180\ (g/mole)}$$

Step 2: Compute CER for individual participants using Mage equation

Step 3: Estimate daily intake using Equation 1.

NHANES

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 the Taylor Series Linearization approach as recommended by the NHANES analytical guidelines. All analyses were weighted using the NHANES survey weights (environmental subsample) in order to be representative of the U.S. population. Phthalates concentrations that were below LOD were assigned a value of LOD/2.

Estimation of creatinine excretion rate (CER): For each study 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 NHANES sample. The 2009-2010 and 2011-2012 NHANES

phthalates datasets had 58 and 49 children who exceeded the 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 each phthalate was estimated for each participant using the following equation (David et al. 2000; Koch et al. 2007):

$$\text{Daily intake } (\mu g/kg\ bw/day) = \frac{UC_{Cr}\left(\frac{\mu g}{g\ Cr}\right)}{MW_M} \times \frac{CER\ \left(\frac{g}{day}\right) \times MW_D}{BW\ (kg) \times FUE} \qquad \text{Equation 1}$$

The UC_{Cr} is the creatinine adjusted urinary monoester concentration and the BW refers to the body-weight. MW_D and MW_M are the molecular weights of the diester and monoester. DMP each has a single monoester metabolite measured in NHANES (MMP). The molecular weights were 194.19, and 180.16 g/mole for DMP and MMP respectively.

The fractional urinary excretion (FUE) is defined as the fraction of the diester exposure dose excreted as monoesters in urine, calculated on mole-basis (0.69 for MMP).

For each selected phthalate diester, the daily intake for each study participant was computed using equation 1. Arithmetic and geometric means, and selected percentiles along with their 95% confidence intervals of daily intake, were produced for the U.S. population by age group and sex. Descriptive statistics were computed using SUDAAN proc DESCRIPT.

Appendix G. 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 G-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.

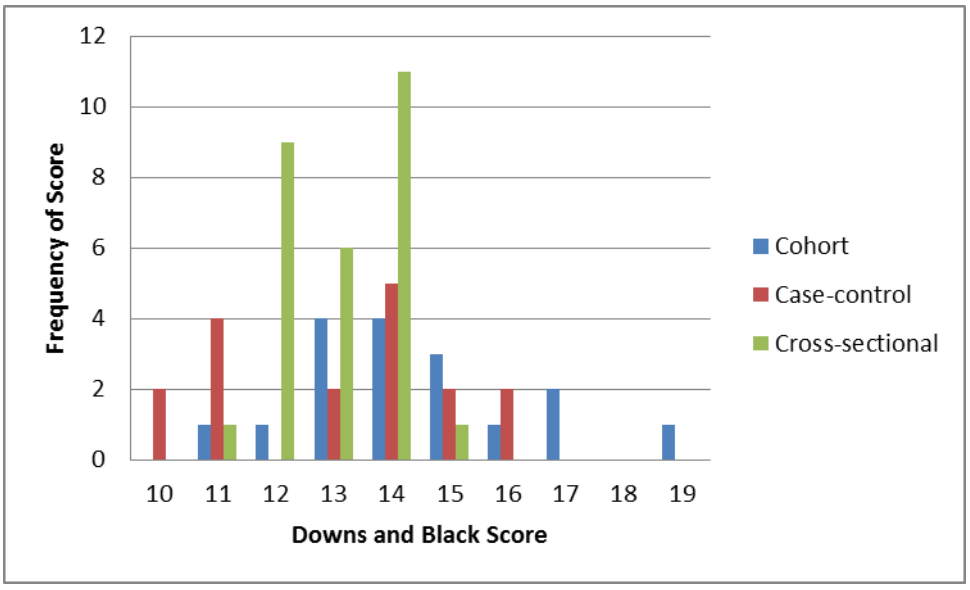

Figure G-1. Distribution of Downs and Black scores by study design.

Guidance for level 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.