# Proposed Approach for Cumulative Risk Assessment of Certain Phthalates under the Chemicals Management Plan

Health Canada
Environment Canada

August 2015

Canada

## Contents

# 1 Purpose

The purpose of this document, and the content within, is to conduct peer-review and consultation of the considerations of the proposed approach for assessment of cumulative risk (human health and ecological) from combined exposures to certain phthalates, including key considerations for assessment. The document provides a summary of the current international initiatives for the cumulative risk assessment[1] (CRA) of phthalates and of the approaches considered to be most relevant for the assessment of cumulative risk from combined exposures to certain phthalates under the Government of Canada's Chemicals Management Plan (CMP). The content should not be viewed as final release by the Government of Canada. The content is subject to change resulting from feedback received during the review and consultation process and further data availability. The content/methodology of the subsequent draft CRA released by the Government of Canada may differ from what is presented here.

## 1.1 Background

On October 8, 2011, the Government of Canada announced[2] its intention to address nine groupings of substances through the second phase of the CMP, the Substance Groupings Initiative (Canada 2011). The Government of Canada plans to assess and, where appropriate, manage the potential human health and ecological risks associated with these nine groupings of substances. One of the groupings listed in the notice of intent includes fourteen phthalate substances. A brief group profile of these substances is available through the Chemical Substances website[3] describing the considerations for the development of the group for assessment under the *Canadian Environmental Protection Act, 1999* (CEPA 1999), and the rationale for considering them to be a priority (Canada 2012).

The Phthalate Substance Grouping is based on chemical similarity and similarity in uses of these substances in plasticizers, adhesives, sealants, paints and coatings, plastic and rubber materials, and automotive parts in Canada that could result in exposure to the general population, including children. Assessment as a group allows for better

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[1] Cumulative risk assessment – The analysis, characterization and possible quantification of the combined risks to health or the environment from multiple agents or stressors.

[2] *Canada Gazette*, Part I, October 8, 2011 http://www.gazette.gc.ca/rp-pr/p1/2011/2011-10-08/html/notice-avis-eng.html#d127

[3] Phthalate Group Profile
http://www.chemicalsubstanceschimiques.gc.ca/group/phthalate/profil-eng.php

hazard characterization and considerations of aggregate exposure and cumulative risk, where warranted.

The selection of the 14 phthalate substances initially covered under the Substance Groupings Initiative was based on the categorization[4] process completed in 2006 and new information received as part of the first phase of the CMP. Consideration is also being given to 14 additional phthalates that were deemed to have the potential to inform the risk assessment and potentially contribute to a cumulative risk. Other phthalates on *Canada's Domestic Substances List* (DSL), or that have been notified for use in Canada under the *New Substances Notification Regulations (Chemicals and Polymers)* may also be considered in the CRA. Several jurisdictions internationally are addressing the cumulative risk of phthalates. The United States Environmental Protection Agency (US EPA) tasked the National Academy of Science (NAS) with reviewing the health effects of phthalates and evaluating if a CRA of phthalates be conducted and how. As a result, the National Research Council formed the Committee on Health Risks of Phthalates and published Phthalates and Cumulative Risk Assessment: The Task Ahead in 2008 (NAS 2008), which concluded that a CRA of phthalates is warranted and the United States Consumer Product Safety Commission released their assessment in 2014. The Danish EPA and the Australian Department of Health have also released CRA reports based on health effects of phthalates. The Government of Canada is proposing a cumulative approach for certain phthalates in this grouping. Hazard information is being collected on 14 additional phthalate substances (total of 28), because preliminary information found in the public literature, including assessments by other international jurisdictions, indicates that their mode of action is likely to be similar to that of other phthalates currently in the grouping, and may represent a potential for exposure to the general population of Canada and to the Canadian environment. The 28 phthalates and their associated subgroups are outlined in Table 1-1, Table 1-2, and Table 1-3**.** The subgroups were formed to inform read-across[5] approaches for hazard characterization for substances with limited data, and to reflect differences across substances in the grouping with respect to their mode of action and environmental fate and behaviour. Additional information can be obtained from the Government of Canada's Chemical Substances website at: http://www.chemicalsubstanceschimiques.gc.ca/group/phthalate/index-eng.php.

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[4] Categorization http://www.chemicalsubstanceschimiques.gc.ca/glossary-glossaire-eng.php#c

[5] Read-Across Approach – The technique of using data from a similar chemical(s) to predict endpoint or property information for one or more substances that lack empirical data. Read-across can be qualitative or quantitative.

**Table 1-1 Subgroup 1 – Short Chain Phthalate Esters (carbon backbone length of 1 or 2)**

| CAS RN | Chemical Name (DSL) | Acronym | Substance Type |
|---|---|---|---|
| 131-11-3 | 1,2-Benzenedicarboxylic acid, dimethyl ester | DMP | Discrete |
| 84-66-2 | 1,2-Benzenedicarboxylic acid, diethyl ester | DEP | Discrete |

Abbreviations: DSL, Domestic Substances List

**Table 1-2 Subgroup 2 – Medium Chain Phthalate Esters (carbon backbone length of 3 to 7[a])**

| CAS RN | Chemical Name (DSL) | Acronym | Substance Type |
|---|---|---|---|
| 131-16-8 | 1,2-Benzenedicarboxylic acid, dipropyl ester | DPrP | Discrete |
| 84-69-5 | 1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester | DIBP | Discrete |
| 5334-09-8 | 1,2-Benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester | CHIBP | Discrete |
| 84-64-0 | 1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester | BCHP | Discrete |
| 84-74-2 | 1,2-Benzenedicarboxylic acid, dibutyl ester | DBP | Discrete |
| 85-68-7 | 1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester | BBP | Discrete |
| 84-61-7 | 1,2-Benzenedicarboxylic acid, dicyclohexyl ester | DCHP | Discrete |
| 27987-25-3 | 1,2-Benzenedicarboxylic acid, bis(methylcyclohexyl) ester | DMCHP | Discrete |
| 71888-89-6 | 1,2-Benzenedicarboxylic acid, di-$C_{6-8}$-branched alkyl esters, $C_7$-rich | DIHepP | Isomeric Mixture[b] |
| 27554-26-3 | 1,2-Benzenedicarboxylic acid, diisooctyl ester | DIOP | Isomeric Mixture |
| 27215-22-1 | 1,2-Benzenedicarboxylic acid, isooctyl phenylmethyl ester | BIOP | Isomeric Mixture |
| 117-81-7 | 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester | DEHP | Discrete |
| 84-75-3 | 1,2-Benzenedicarboxylic acid, dihexyl ester | DnHP | Discrete |
| 111381-89-6 | 1,2-Benzenedicarboxylic acid, heptyl nonyl ester, branched and linear | 79P | UVCB[c] |
| 68515-48-0; 28553-12-0 | 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich; 1,2-Benzenedicarboxylic acid, diisononyl ester | DINP1,2[d] | Isomeric Mixture |
| 68515-40-2 | 1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters | B79P | UVCB |
| 16883-83-3 | 1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1- | B84P | Discrete |

| CAS RN | Chemical Name (DSL) | Acronym | Substance Type |
|---|---|---|---|
| | (1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester | | |
| 523-31-9 | 1,2-Benzenedicarboxylic acid, bis(phenylmethyl) ester | DBzP | Discrete |

Abbreviations: DSL, Domestic Substances List
[a] Carbon backbone length refers to the number of carbon atoms within the longest straight chain; for chains that are branched, the carbon backbone length will be less than the total number of carbons.
[b] A phthalate isomeric mixture consists of phthalate molecules with varying alkyl chain lengths and branching, but with a defined distribution.
[c] A phthalate UVCB (Unknown or Variable Composition, Complex Reaction Products or Biological Materials) consists of phthalate molecules with varying alkyl chain lengths and branching, but the composition and distribution of the alkyl chains is variable.
[d] DINP is considered as a medium-chain phthalate for the purposes of the health assessment, and as a long-chain phthalate for the purposes of the ecological assessment.

**Table 1-3 Subgroup 3 – Long Chain Phthalate Esters (carbon backbone length equal to or greater than 8)**

| CAS RN | Chemical Name (DSL) | Acronym | Substance Type |
|---|---|---|---|
| 68515-48-0; 28553-12-0 | 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich; 1,2-Benzenedicarboxylic acid, diisononyl ester | DINP1,2[a] | Isomeric Mixture |
| 68648-93-1 | 1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters | 610P | UVCB |
| 26761-40-0; 68515-49-1[b] | 1,2-Benzenedicarboxylic acid, diisodecyl ester | DIDP | Isomeric Mixture |
| 117-84-0 | 1,2-Benzenedicarboxylic acid, dioctyl ester | DnOP | Discrete |
| 68515-43-5 | 1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters | D911P | UVCB |
| 3648-20-2 | 1,2-Benzenedicarboxylic acid, diundecyl ester | DUP | Isomeric Mixture |
| 111381-91-0 | 1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear | D911P-2 | UVCB |
| 68515-47-9 | 1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich | DTDP | UVCB |
| 85507-79-5 | 1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear | DIUP | UVCB |

Abbreviations: DSL, Domestic Substances List
[a] DINP is considered as a medium-chain phthalate for the purposes of the health assessment, and as a long-chain phthalate for the purposes of the ecological assessment.
[b] Two CAS RNs are associated with a single common name.

# 2 Cumulative Risk Assessment Approaches

Cumulative risk assessment (CRA) is defined as the analysis, characterization and possible quantification of the combined risks to health or the environment from multiple agents or stressors (US EPA 2003).

Substances that have a common effect can be grouped together for evaluation of aggregate exposures of multiple agents and cumulative risks. With respect to human health, co-occurrence of exposures to chemicals can occur via multiple sources, pathways, and routes of exposures over different exposure durations. For an ecological assessment co-occurrence of exposures to chemicals can occur in various media (e.g., water, sediment, soil, and air) through releases from multiple sources to the same geographic area.

The World Health Organization (WHO) and the International Program on Chemical Safety (IPCS) Framework for Risk Assessment of Combined Exposures to Multiple Chemicals (Meek et al. 2011), addresses the human health outcomes of combined exposures to multiple chemicals. The objective of the framework is to develop a "fit for purpose" assessment that uses only the resources necessary. This framework exercises the default assumption that the substances act by dose addition, and it outlines a tiered approach, as illustrated in Figure 2-1. The WHO/IPCS framework can be applied in consideration of the methods available and the level of refinement possible based on the data available for conducting each of the hazard and exposure assessments and subsequent risk characterization.

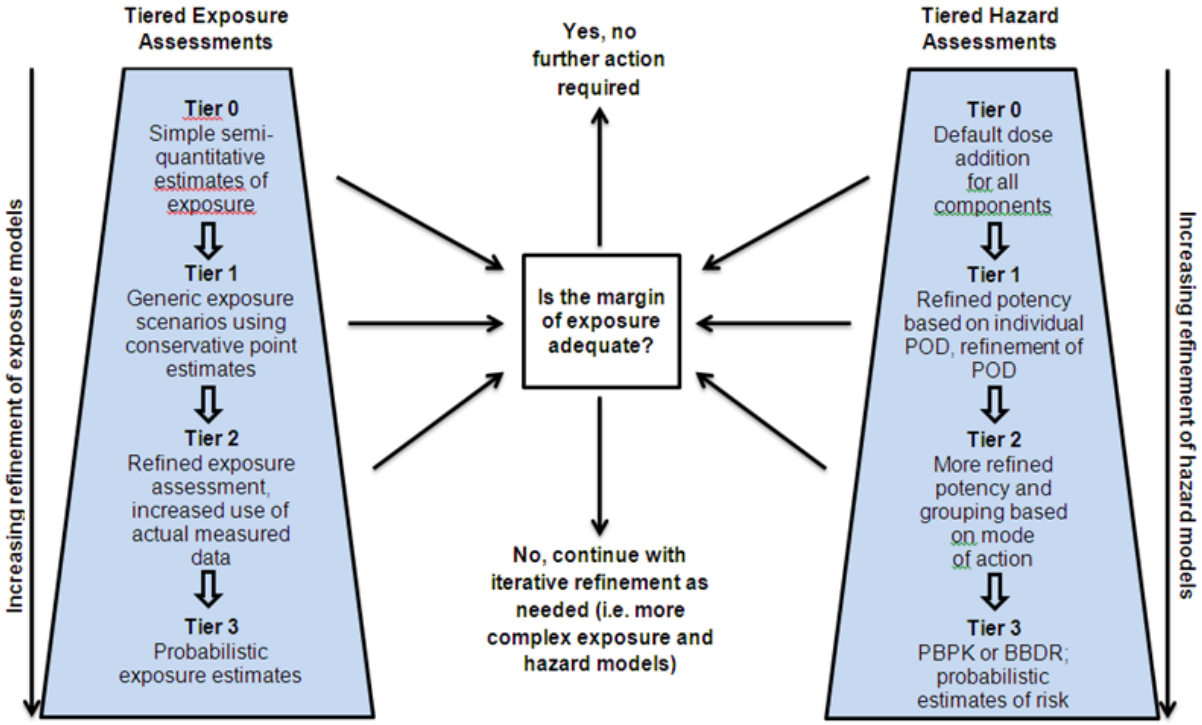



**Figure 2-1 Schematic of the WHO/IPCS Framework for Risk Assessment of Combined Exposures to Chemical Mixtures (Meek et al. 2011)**

While approaches for cumulative risk characterization may be considered in the context of multiple tiers, each higher level is increasingly dependent on the incorporation of additional data to inform both the exposure and hazard assessments. Identification of those inputs that add the most value are critical in ensuring meaningful and efficient progression throughout each tier of the framework. Through the work of case studies comparing the outputs of exposure and hazard tiers, it was demonstrated by the WHO/IPCS that the most gains can be achieved through refinements in exposure due to the simple assumptions and/or surrogate data employed in the lower exposure assessment tiers. Relative to exposure refinements, hazard refinements are more limited in the absence of mode of action data or toxicokinetic and toxicodynamic data (Meek 2013). In the case of ecological risk assessments, there may be considerable value in hazard refinements because differences in sensitivity between organisms can be substantial and present a great deal of uncertainty if ecotoxicity data are limited.

There are three potential approaches to consider for characterizing hazard associated with combined exposures to multiple chemicals; dose (or concentration) addition, response addition (or independent action) or integrated addition. In the dose addition

approach, it is assumed that the substances in the assessment group act through a common mode of action thereby yielding toxicologically similar effects. In this approach, the components of the assessment group are dilutions of one another whereby one chemical can be replaced with a fraction of an equally effective concentration of another chemical without changing the overall combined effect (NAS 2008). Therefore, substances in an assessment group act together to produce an effect but they do not enhance or diminish each other's actions. Response addition, also referred to as independent action in the literature, is used for those substances in the assessment group that act independently through separate modes of action and act on different target cells, tissues or organs (US EPA 2002; NAS 2008; Hannas et al. 2012). Integrated addition is used for those groups of chemicals that have both similar and dissimilar modes of action.

The level of knowledge supporting the hypothesis of similarity of adverse effects can range from the observation of a common adverse effect across the assessment group to a more in-depth understanding of a common mode of action at the tissue or biological system level, to a higher level of knowledge of the mechanism of action at the cellular or subcellular level. The higher the level of mechanistic knowledge of the adverse effects, the higher the tier of hazard assessment that is achievable.

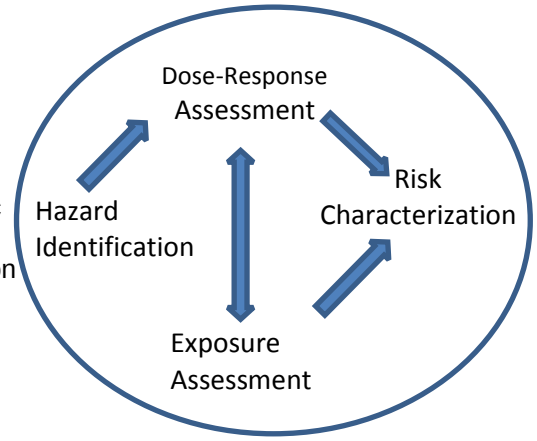
The risk assessment paradigm for CRA has the same four components as a traditional single-chemical assessment including hazard identification, dose-response assessment, exposure assessment and risk characterization. However, there are specific considerations that are required when conducting a combined exposure assessment, including the assessment of exposure to multiple chemicals across multiple sources and routes. The hazard identification requires consideration of effects from toxicological interactions, while the exposure assessment will need to account for multiple exposure sources, pathways and routes. Figure 2-2, adapted from US EPA (2003) and Teuschler (2011), depicts the risk assessment paradigm and some considerations when evaluating combined exposures from more than one chemical.

**Hazard Identification:**

- Identify effects for consideration
- Identify data gaps
- Toxicological interactions: antagonistic/synergistic or additive
- Common mode of action
- Tier of assessment possible

**Exposure Assessment:**

- Account for internal dose of substances at target tissue
- Account for multiple exposure routes and pathways
- Determination of co-occurrence/co-exposures
- Tier of assessment possible




**Dose-Response Assessment:**

- Incorporate toxicological judgment of similar toxicity between substances
- Consideration of benchmark doses where data permits

**Risk Characterization:**

- Evaluate data support for assumptions of similarity of toxicity
- Determine appropriate method(s) to estimate risk
- Consider assumptions and uncertainties when interpreting risk estimates

**Figure 2-2 Risk assessment paradigm considerations for combined exposures adapted from US EPA 2003 and Teuschler 2011**

Internationally, there are several CRA initiatives for phthalates. A brief overview of activities with respect to CRA is outlined below in Table 2-1 to illustrate the approaches and methods that have been published and that have been considered in outlining possibilities for advancing with a CRA of certain phthalates under the Government of Canada's CMP.

## 2.1 Cumulative Risk Assessment Initiatives

CRAs of phthalates, focused on human health, have been conducted by several national organizations including the Australian Department of Health, the Danish EPA, and the recently completed assessment by the United States Chronic Health Advisory Panel (CHAP). Appendix A provides a comparison across the various assessments, both regulatory and non-regulatory, of the chemicals considered in each of the CRAs, the assumptions and approaches that were used, a summary of the exposure and hazard assessment considerations, as well as the risk assessment outcome. A summary of each of the methods is presented in Section 3.

### 2.1.1 Australia

The Australian Department of Health's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) has completed cumulative assessments for DINP (NICNAS 2012), DBP (NICNAS 2013), DMP (NICNAS 2014a) and DMEP (NICNAS 2014b). A cumulative Margin of Exposure (MOE) approach was used for all assessments with a Tier 1 level of refinement as outlined by the WHO/IPCS framework (Meek et al. 2011). The assessments were conducted under the assumption that phthalates act by a similar mode of action for each of the endpoints considered and act by dose addition. Endpoints considered in the CRA include systemic toxicity for DINP, and developmental toxicity and fertility-related toxicity for all four assessments.

The exposure assessment focused on the oral and dermal routes with deterministic estimates modelled for six-month-old infants for scenarios of co-occurrence to various mixtures of plasticizers in toys and cosmetics. The estimated cumulative MOEs indicate an adequate margin of safety for six-month-old infants for each of the four cumulative phthalate assessments. As a result of the four CRAs, it was concluded that current risk estimates do not indicate a health concern from combined exposures of children to a mixed phthalate plasticizer in children's toy and childcare articles and to phthalates in body lotion at a phthalate concentration of 0.5%. However, it is noted that at 0.75% DEP in body lotions and above, the cumulative MOE for risk of fertility-related effects in six-month-old infants is below 100 and is of concern. An overview of the four CRAs are outlined in Appendix B.

### 2.1.2 Danish EPA

The Danish EPA undertook an assessment of four phthalates, bis (2-ethylhexyl) phthalate (DEHP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP) and diisobutyl phthalate (DIBP), all of which had been previously individually classified as reproductive category 1b (adverse effects on sexual function and fertility or on development). In addition, each substance had been reported to affect testicular functions, to have known adverse effects on sexual differentiation during development and found to exert antiandrogenic effects. The Danish EPA then evaluated the combined exposures from each of the four phthalates from articles intended for use indoors and articles that may come into direct contact with the skin or mucous membranes (EU 2008; Danish EPA 2011; ECHA 2012a).

The Danish EPA's CRA for phthalates is based on the assumption that the chemicals in the assessment act by dose addition and that all chemicals in the chemical group act on the same biological site (receptor/target organ), by the same mechanism of action and that they differ only in their individual potency. The differences in potency were adjusted for by calculating individual Derived No Effect Level (DNEL) for each of the four phthalates. Exposure was characterized by the sum of the internal exposure estimates for background exposure from articles, dust and indoor air and food for three age groups: two-year-olds, six- and seven-year-olds, and adults. The focus of the

toxicity portion of the assessment was on antiandrogenic or reproductive effects. Such effects included decreased anogenital distance (AGD), nipple retention, and sperm and testosterone effects. No Observable Adverse Effect Levels (NOAELs) and Lowest Observable Adverse Effect Levels (LOAELs) were identified for antiandrogenic effects from developmental studies and used in the calculation of the DNEL for both external and internal doses. The DNEL internal was calculated so that exposure data by different routes could be considered.

A Risk Characterization Ratio (RCR), which is similar to a Hazard Index (HI) approach and will be outlined in detail in Section 3, was used to determine the magnitude of the risk as a result of cumulative phthalate exposure as outlined in the assessment document (ECHA 2011). The lowest median value was used for calculating a lower exposure scenario, the highest median value was selected for the mid-range scenario and the 95$^{th}$ percentile was selected for a realistic worst-case exposure estimate. An RCR exceeding 1 indicates that the risk is not sufficiently controlled.

A RCR was also derived using biomonitoring data established for both adults and children. These biomonitoring data were collected before the legislation of phthalates in food contact materials was enacted (2008) but after voluntary agreement to phase out phthalates in tubes for milk (transportation and hoses for milking) and foils for food; these data may therefore be an overestimate of current exposures. It is also noted that some of these data were collected prior to the EU ban of some phthalates in toys and childcare articles from 2007, and before an emergency ban on six phthalates in toys and childcare articles for children under three years of age (Danish EPA 2011).

As a result of the Danish CRA for DEHP, BBP, DBP and DIBP, a proposal for restriction on phthalates was recommended (Danish EPA 2011). Specifically, the Danish EPA released a proposal for restriction in August of 2011 to address the potential for risk posed by the four phthalates. Subsequently, the Danish EPA placed a ban on articles intended for use indoors in unsealed applications and articles that may come into direct contact with the skin or mucous membranes containing one or more of the 4 phthalates in a concentration greater than 0.1% by weight of any plasticized material. A ban was also placed on all phthalates in toys and childcare articles for children 0–3 years of age at concentrations greater than 0.05% (Danish EPA 2013).

### 2.1.3 United States Consumer Product Safety Commission

The *Consumer Product Safety Improvement Act* (CPSIA) of 2008 requires that the United States Consumer Product Safety Commission (CPSC) study the effects on children's health of phthalates and their alternatives used in children's toys and childcare articles. More specifically, the CPSC (2010) outlined the requirement for the CHAP to complete an examination of the broad range of phthalates, a total of 14, used in products for children.

The report to the US CPSC prepared by the CHAP released in July 2014 outlines the approach to the CRA of phthalates (US CPSC 2014). Five substances, DBP, DIBP, BBP, DEHP and DINP, were included for assessment based on their adverse effect on male sexual differentiation, described as the phthalate syndrome. Consistent with the NAS (2008), the grouping of substances was not only based on structural similarity, but on the common adverse effects of the spectrum of effects described as the rat phthalate syndrome (RPS).

The CHAP concluded that the assumption of dose addition was appropriate based on the evidence in experimental data and that the Hazard Index approach offered flexibility for varying data and was used for estimating cumulative risk (US CPSC 2014).

The Hazard Index (HI) was calculated using daily intake estimates based on biomonitoring data for pregnant women and infants. Potency Estimates for Antiandrogenicity (PEAA) were derived for each substance, whereby a Point of Departure (POD) is selected and an Uncertainty Factor (UF) is applied.

Three cases were considered by CHAP for calculation of the HQ and the subsequent HI using various data for POD selection. Case 1 includes published Reference Doses (RfDs) for antiandrogenicity [PODs based on decreased testosterone synthesis and Nipple Retention (NR)] from *in vivo* data from Kortenkamp and Faust (2010) for the PEAA values in HQ. Case 2 is based on relative potency assumptions across phthalates. Testosterone-modulated effects (decreased testosterone production) from Hannas et al. (2011a; 2011b) were used to derive a PEAA with DEHP selected as the index chemical and DIBP, DBP and BBP assumed to be equipotent. A UF of 100 (factor of 10 for each inter-species extrapolation and inter-individual variation) was applied to each of the substances. Case 3 is based on the *de novo* analysis of individual phthalates for reproductive and developmental endpoints within the rat phthalate syndrome by CHAP (PODs based on AGD, NR and reproductive tract malformations, decreased spermatocytes and spermatids) with a UF of 100 applied to each substance (US CPSC 2014).

The result of the CHAP assessment, using the three cases to calculate the HI, indicates that there is clear evidence that both pregnant women and infants are exposed to mixtures of phthalates. The assessment estimated that approximately 10% of pregnant women in the US and approximately 5% of infants have HI exceeding a value of 1 across all three cases for which there may be a concern for adverse health effects.

There are several health-focused papers that have looked at CRAs of phthalates that have also been published.

The evaluation conducted by Benson et al. (2009) included six phthalates — DBP, DIBP, BBP, DEHP, DPP and DINP — in a CRA using biomonitoring data for both the US and German populations. Dose addition was assumed for these phthalates and both the HI method and the relative potency applied to the HI method were used to

calculate the cumulative risk; in this case, DEHP was selected as the index chemical. The database for each substance was reviewed for reproductive effects to males during the *in utero* critical developmental window, and NOAELs and LOAELs were identified; subsequently, benchmark doses (BMDs) were derived using the US EPA software (version 1.4.1c) when appropriate data was available (US EPA 2008b). A substance-specific UF was applied to the POD, and RfDs were established and used to derive the HQ. The Benson et al. (2009) assessment concluded that median exposures resulted in an HI of 0.07 and 0.02 for the US and German populations, respectively. Using the 95$^{th}$ percentile, resulted in an HI of 0.04 resulted for the US population and using a maximum value (95$^{th}$ percentile could not be determined) resulted in an HI of 0.8 for the German population.

Kortenkamp and Faust (2010) conducted a CRA on 15 antiandrogenic substances, including five phthalates (DBP, DIBP, BBP, DINP, DEHP) using a lower tiered HI approach. PODs for antiandrogenicity from peer-reviewed scientific literature (NOAELs, BMDs) were identified and substance-specific UFs applied. Human intake estimates (median and 95$^{th}$ percentile) were established using peer-reviewed biomonitoring data from European and US populations. The HI derived for the five phthalates was 0.12 and 0.2 for the median and 95$^{th}$ percentile, respectively.

A paper from Taiwan published by the National Cheng Kung University, Meiho University and the Ministry of Health and Welfare (Chang 2014) conducted an assessment of the dietary risk from the combined exposures to several phthalates following a severe plasticizer-contaminated food incident in Taiwan, which prompted the recall of approximately 900 products from approximately 40000 Taiwanese retailers. The seven phthalates were BBP, DEP, DEHP, DIBP, DIDP, DINP and DBP. The phthalates were identified as having dose additive effects (Hannas et al. 2011; Howdeshell et al. 2008) and an HI was calculated for both antiandrogenic effects and hepatic effects. Intakes of phthalates were calculated using the results of a survey of plasticizers in 1200 diet samples, including infant foods (formula, non-staple and supplementary), beverages, milk and dairy products, animal fat, vegetable oils and health supplements. The estimated Average Daily Dose (ADD) was calculated for the 50$^{th}$, 95$^{th}$ and 99$^{th}$ percentiles based on gender and age-specific ingestion rates of foodstuffs and the measured concentrations from the Nutrition and Health Surveys in Taiwan from 2001–2002 and 2005–2008. Existing Tolerable Daily Intakes from the European Food Safety Authority (EFSA) and the World Health Organization (WHO) and RfDs from the US CPSC were selected for antiandrogenic and hepatic effects.

The analysis investigated the relative contribution of substances and specific food sources. The results of the HI calculated for hepatic effects indicate that at the 95$^{th}$ percentile the HI is less than 1 for all population age groups, and at the 99$^{th}$ percentile the HI exceeds 1 for 0- to 3-year-old males and females and 4- to 6-year-old females. The HI for antiandrogenic effects at the 95$^{th}$ percentile exceeded 1 for 0- to 3-year-old males and females and 4- to 6-year-old females; for 4- to 6-year-old males, it was just under 1, compared to the 99$^{th}$ percentile, where all age groups under age 65 exceeded

an HI of 1. The study concluded that the health of younger Taiwanese may be adversely affected by exposure to phthalate-contaminated food.

# 3 Cumulative Risk Assessment Methods for Consideration

As outlined in the category approaches for health and the environment (Health Canada 2015; Appendix C), there are similarities in toxicological and ecotoxicological modes of action across many of the phthalates. Therefore, it is proposed to focus on CRA methods based on dose (or concentration) addition for hazard characterization. There are several methods available that are applicable for assessing cumulative risk from combined exposures to chemicals that act via dose addition. Taking into consideration the flexibility of the methods, consistency with the current risk assessment practices and alignment with international CRA approaches, the Hazard Index method (HI), the Margin of Exposure (MOE) method and the Relative Potency Factor (RPF) are considered potential methods.

## 3.1 Hazard Index Method

The Hazard Index[6] (HI) method is a summation of the individual Hazard Quotients (HQs) for each individual chemical. This approach accounts for multiple chemicals and multiple exposure sources, pathways and routes using dose addition. The HQ can be derived for each chemical and for each exposure route. The HQ is the ratio of exposure to a reference value (e.g., NOAEL or LOAEL divided by a UF) as follows:

$$HQ = \frac{Exposure}{Reference\ Value}$$

The HI can then be calculated for the assessment group by summing the HQ of all substances. An HI index greater than 1 would indicate a potential concern. The HI is calculated according to the following equation where *n* is the number of substances in the assessment group (Wilkinson 2000; Kortenkamp 2010):

$$HI = \frac{Exposure1}{Reference\ Value1} + \frac{Exposure2}{Reference\ Value2} + \frac{Exposure3}{Reference\ Value3} ..etc\ or,$$

[6] Hazard Index method (HI) – A summation of the individual hazard quotients (HQ) for each substance in the assessment group.

$$\mathrm{HI} = \sum_{i=1}^{n} \frac{\text{Exposure i}}{\text{Reference Value i}}$$

The HI method can be applied to distinguish which pathways may be driving an assessment (pathway aggregate HQ) or the chemicals that contribute the most to the risk (chemical aggregate HQ), as illustrated in Figure 3-1 and Figure 3-2.

**Illustration of the two methods for calculating a Hazard Index**

| Approach: by chemical | **Pathway A Hazard Quotient** | **Pathway B Hazard Quotient** | **Pathway C Hazard Quotient** | Chemical Aggregate Hazard Quotient |
|---|---|---|---|---|
| **Chemical A** | | | | |
| **Chemical B** | | | | |
| **Chemical C** | | | | |
| **Chemical D** | | | | |
| Pathway Aggregate Hazard Quotient | | | | Hazard Index |

**Figure 3-1 Cumulative Hazard Index by chemical (across pathways) then sum for all chemicals**

| Approach: by pathway | **Pathway A Hazard Quotient** | **Pathway B Hazard Quotient** | **Pathway C Hazard Quotient** | Chemical Aggregate Hazard Quotient |
|---|---|---|---|---|
| **Chemical A** | | | | |
| **Chemical B** | | | | |
| **Chemical C** | | | | |
| **Chemical D** | | | | |
| Pathway Aggregate Hazard Quotient | | | | Hazard Index |

**Figure 3-2 Cumulative Hazard Index by pathway (sum of chemicals) then aggregate across pathways**

Consideration as to which type of data are available and which endpoints are proposed to be used are both important as these will have impacts on the outcome of the estimate based on the strength of the data used and the UFs applied. Interpretation of the results will also require consideration of the strengths and limitations of the database to determine the need for further refinement. The HI method is a relatively simple and transparent approach and allows flexibility as separate UFs can be applied to each

substance considered in the CRA. Results must be interpreted while ensuring that the overall uncertainty of the group is not inflated through the application of UFs across all substances in the group, particularly when there are numerous substances being considered.

The US EPA peer consultation workshop on the CRA of phthalates determined that the HI method could be a valuable approach as part of a cumulative assessment of the human health impacts of phthalates due to its flexibility (US EPA 2011b). Some of the strengths that have been identified for the HI method include the relative simplicity as well as flexibility through the ability to accommodate many different types of chemicals (Kortenkamp and Faust 2010). The data input requirements include derivation of an RfD or equivalent, through the identification of LOAELs, NOAELs or other PODs and then the application of substance-specific UFs. The application of UFs requires expert judgment and further interpretation of the outputs (US EPA 2011b). The endpoint selected for derivation of the reference value for each chemical in the group is not required to be uniform across the group, thereby allowing variable data within the assessment group. Of note, when the data quality permits, the calculation of BMDs addresses some of the limitations associated with traditional PODs. BMDs account for the shape of the dose–response curve, are more independent of study design elements such as dose choice or spacing, and can be more easily compared across multiple chemicals (US EPA 2013).

The HI method can be overly conservative depending on the inputs used to derive the HQ, in particular at lower tiers with many assumptions, and does not take into account toxicokinetic or toxicodynamic differences between the chemicals. As a result of the Peer Review Workshop held by the US EPA (2011b), Exxon Mobil (2010) observed that the HI method is overly conservative and crude. They also found that the method is not defined and does not use transparent criteria for implementation, considers only whether similar endpoints are affected, and assumes dose addition even at low doses for which the dose–response curve may not be defined (Exxon Mobil 2010). Nevertheless, the HI method has been identified as a useful tool for screening purposes; for example an HI greater than 1 can lead to further refinements in the inputs rather than an indication of adverse effects (Dourson et al. 2013).

In summary, the HI method offers the benefit of being simple and flexible and allows for an indication of which substance or substances in the assessment group, or which source, pathway and route, can be the predominant contributors to the overall risk. Identification of the substances or source, pathways and routes that are drivers of the assessment is beneficial for informing the risk assessment. In addition to the numerous papers published using the HI method (Kortenkamp and Faust 2010; Benson 2009; Chang et al. 2014), there are several examples of the HI method applied in CRA of phthalates by several organizations, as previously illustrated.

## 3.2 Margin of Exposure Method

The cumulative MOE method is a relatively straightforward approach that affords flexibility in the application that can be used across multiple tiers of assessment as the data allows. It is also a method that has been used internationally by the Australian Department of Health (NICNAS 2012) and uses approaches that are currently employed by Health Canada. The MOE approach, however, does not include UFs for each individual substance; therefore, the limitations of the database for each substance are not quantified within the assessment of cumulative risk. Consequently, the HI method is preferred over the MOE method. It is, however, recognized that the limitations of the database are considered when evaluating the adequacy of the MOE. The strengths and limitations of the approach are further highlighted in Table 3-1.

## 3.3 Relative Potency Factor Method

Relative Potency Factors[7] (RPFs) are typically calculated for similar effects in order to determine relative potency between chemicals through a common measure and the method assumes the substances are acting through a common mode of action resulting in a common effect (US EPA 2002; US EPA 2011b). A risk estimate is developed assuming dose addition using the RPF approach. In order to calculate an RPF, an Index Chemical (IC) is chosen within the assessment group, and doses of additional chemicals are adjusted to Index Chemical Equivalent Doses (ICEDs) using RPFs for the assessment group chemicals. This method requires sufficient data to identify a common measure of effect in order to establish relative potency of the chemicals in the assessment group in addition to selection of an IC for the group. Considerations in selecting the IC include:

- the adequacy of the toxicological database of the IC;
- the similarities of the IC to the other chemicals considered in the chemical group; and
- consideration as to how much the IC is representative of the chemicals in the group.

The RPF, or scaling factor, can be derived using a ratio of a POD of the chosen IC to that of the individual chemical. For example, the ratio of the effective dose (i.e. $ED_{10}$) resulting in an increase of 10% in adverse effect of the component to the $ED_{10}$ of the IC can be used, as illustrated in the equation for RPF below.

---

[7] Relative Potency Factor (RPF) – Method that sums the doses of each component of the assessment group after scaling the doses using relative potency factors that are developed in relation to the potency of an index chemical.

$$\mathrm{RPF} = \frac{EDx\ index}{EDxi}$$

The challenge in using the RPF approach for phthalates based on the current state of the science lies in the varying potency across effects within the rat phthalate syndrome for the phthalates grouping. Due to the fact that the potency across phthalates is not the same for various effects, the RPFs will vary between phthalates depending on the chosen endpoint; therefore, careful consideration of the representative endpoints is required. In the absence of a common effect that can be compared across the phthalates in the chemical group, the RPF approach cannot be recommended at this time. However, if the data becomes available for a common measure of effect across the assessment group, consideration can be given to the use of an RPF method.

All of the methods previously discussed are based on the basic assumption of a dose-additive behaviour of the mixture. Each has associated strengths and limitations, as outlined in Table 3-1. Each approach relies on the data available to determine the tier of assessment that is achievable. It is therefore recommended that, based on the information available at this time, the HI method is best suited for the CRA of phthalates based on the relative simplicity of the approach, in addition to the flexibility of the method allowing for UF to be applied for each member in the assessment group. Moving forward, application of the RPF approach can be considered if further data becomes available.

Further details on the use of the HI method are provided in the following sections, which describe the proposed human health and ecological approaches for CRA of phthalates.

**Table 3-1 Summary of available dose-addition-based methods for cumulative risk assessment and their respective strengths and limitations**

| Approach | Strengths | Limitations |
|---|---|---|
| **Hazard Index** | • Simple and flexible<br>• Does not require selection of the same endpoint or point of departure for each chemical in the assessment group<br>• Accommodates varying data on substances in assessment group<br>• Different uncertainty factors can be applied to each chemical in the group, as appropriate<br>• Allows for identification | • Can be overly conservative<br>• Toxicokinetic or toxicodynamic differences are not considered |

| Approach | Strengths | Limitations |
|---|---|---|
| | of percent contribution of each substance, which permits identification of target chemicals for risk management | |
| **Margin of Exposure** | • Simple and flexible<br>• Can be used across multiple tiers of assessment<br>• Similar to methods currently used in screening assessments under CEPA 1999. | • Highly reliant on quality of available hazard data<br>• Not possible to apply different uncertainty factors to the different substances in the assessment group |
| **Relative Potency Factor** | • Allows for consideration of potency of substances in assessment group | • More complex<br>• Increased reliance on hazard data requirements<br>• Selection of index chemical requires an adequate toxicological database<br>• Requires available hazard data for a common effect across all members of the substance group<br>• Assumes similarly shaped dose–response curves |

# 4 Proposed Approach for Considering Cumulative Effects of Phthalates in a Human Health Risk Assessment

The following section outlines the various considerations for the human health CRA of phthalates under the CMP. Considerations for inclusion into the CRA from a hazard perspective will be outlined and the identification of substances that exhibit common adverse effects of the rat phthalate syndrome acting via a common mode of action identified using the substance grouping and category approach will be summarized. Consideration of inclusion into the CRA from an exposure perspective will be outlined through the identification of exposure filters to illustrate which substances are proposed to be included in the CRA. The proposed methods, guiding framework, and exposure and hazard considerations for the CRA will be presented.

## 4.1 Selection Considerations for Inclusion of Phthalates in a Human Health Cumulative Risk Assessment

### 4.1.1 Mode of Action

As outlined by the National Academy of Science (NAS) and the CHAP assessment of phthalates exposures to phthalates have been shown to result in disturbances in androgen-mediated development of the reproductive system in males *(in utero)* with biological pathways leading to common effects characterized by the spectrum of effects of the rat phthalate syndrome (NAS 2008; US CPSC 2014). Although the complete mode of action (MOA) of phthalate toxicity has not been established, there are key events that have been proposed. A more detailed description of the MOA can be found in Figure 4-1 below, and in the corresponding proposed Category Approach Document (Health Canada 2015). While this proposed MOA has not been fully established, the key event of metabolism of phthalates to the monoester and transport to the fetal testis resulting in cellular responses in either the Sertoli cells or the Leydig cells has been confirmed. As a result of the cellular responses of the Sertoli or Leydig cells, common adverse effects are seen on the developing male rat characterized by the effects of the RPS.

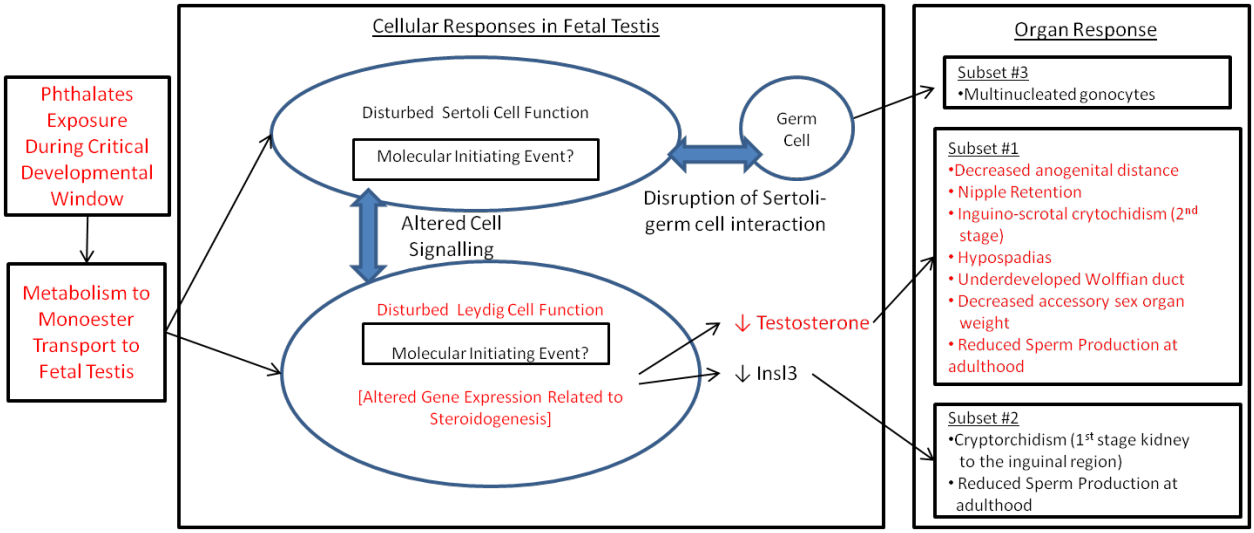



**Figure 4-1 Representation of cellular targets of the "rat phthalate syndrome" and associated changes in gene expression and subsequent hormonal and organ responses**

The important mechanistic events highlighted in red form the basis of the structure activity relationship (SAR) analysis (with considerations from NAS 2008; Sharpe 2001; Martino-Andrade and Chahoud 2010; Foster 2005)

The effects observed in the RPS can be used as a basis for the selection of effect(s) for inclusion in the CRA, as this encompasses the effects of androgen insufficiency with additional effects on fetal germ cells, which also encompass effects that correlate with

the human TDS. This is in line with the recommendations by the NAS, whereby the committee determined that a CRA should focus on adverse health outcomes as opposed to the pathways that lead to the adverse health outcomes. It is understood that there may be multiple pathways that can lead to an effect, and limiting the scope to a specific pathway can be too restrictive (NAS 2008). This is also reflected in the CRA of phthalates completed by the CHAP, which identified male developmental and reproductive toxicity via an antiandrogenic mode of action — as described by the rat phthalate syndrome — as the critical effect (US CPSC 2014).

The scope of the CRA of phthalates may focus on the rat *in utero* life stage and those effects within the RPS that are a result of disturbances of androgen-mediated development. This approach is protective of effects in adolescents and adult males for which exposures at higher doses induces testicular effects, as rodents are most sensitive to antiandrogenic effects *in utero* (US CPSC 2014).

### 4.1.2 Substance group – Category definition

Certain phthalates of interest are considered to have 'data gaps' since there are no studies available to assess effects on the developing male reproductive system during this critical window. To facilitate addressing these data gaps, a SAR analysis across the 28 phthalates of interest using available studies has been developed and, based on the SAR analysis, subgroups of phthalates are proposed relating to effects on the developing male reproductive system in rats (Health Canada 2015). The subgroups, along with other considerations, are subsequently used to facilitate read-across for effects on the developing male reproductive system for phthalates lacking relevant health effects studies. The subgroups of phthalates were established using an SAR trend analysis for three lines of evidence related to the effects and key events of the proposed MOA for RPS. These are:

a) gene expression data: *in vivo* studies investigating the potential for induced gene expression (mRNA) changes related to steroidogenesis in the fetal testes;
b) *in vivo* studies for alterations in testicular testosterone production in fetal rat testes; and
c) toxicity studies measuring decreased AGD as an indicator of androgen insufficiency during the critical development window (GD 15-17) in male rat offspring.

The substances have been grouped into three subgroups based on the carbon backbone chain length being short (carbon backbone of 2 or less), medium (carbon backbone between 3 and 7), and long (carbon backbone of 8 or more); and the proposed subgroups for the phthalates of interest as shown previously in Section 1, Table 1-1, Table 1-2 and Table 1-3. The full details on the formation of subgroups and the trend analysis using the three lines of evidence can be found in the Proposed Category Approach Document for Phthalates (Health Canada 2015). As a result of data

analysis using all three lines of evidence, it has been established that those substances in subgroups 1 and 3 do not exhibit evidence of androgen insufficiency. Those substances in subgroup 2, with a carbon backbone between 3 and 7 carbons in length, show evidence of androgen insufficiency, with the most potent phthalates having backbones between 4 and 6 carbons in length. Therefore, the focus of the CRA may be those substances that have been established to be in subgroup 2, as outlined previously in Table 1-2.

### 4.1.3 Considerations for Addressing Data Gaps

The information currently available for phthalates ranges from data rich to data poor, and methods used to fill data gaps have been developed and will be applied using the chemical category approach, as outlined in the Draft Approach for Using Chemical Categories and Read-Across to Address Data Gaps for Effects on the Developing Male Reproductive System (Health Canada 2015). As outlined above, distinct categories, or subgroups, have been derived with the focus of the CRA on those in subgroup 2, the medium-chain phthalate esters that show evidence of androgen insufficiency. In the category approach, not every chemical needs to be tested for every endpoint. Instead, the overall data for that category can prove adequate to support a hazard assessment. The purpose is to use the overall available data set to estimate hazard for the untested chemicals within the phthalate grouping (OECD 2014). The advantages of the approach include determining hazard potential on the basis of the evaluation of the category as a whole rather than based on measured data for any one particular chemical alone. This is particularly useful (a) where category member(s) lack data for one or more endpoints, or (b) where category members have issues with data adequacy (i.e. low-quality studies).

Health Canada proposes to approach the hazard characterization of phthalates by using a quantitative read-across for the developmental endpoints specifically related to androgen insufficiency using the closest analogue to the phthalate in question within a subgroup (Health Canada 2015). This approach will allow for the consideration of substances for inclusion in the CRA where empirical data is lacking.

### 4.1.4 Hazard Filter

Substances for which RPS effects have been observed will be identified through the evaluation of the toxicological profile for rats for the 28 phthalates of interest. Substances identified to have common adverse effects within the RPS as a result of alterations will then move through the exposure filter for inclusion into the CRA. The read-across approach as outlined above is proposed to be used to fill data gaps for substances for which data are not available (Health Canada 2015).

### 4.1.5 Exposure Filter

In addition to determining the considerations for inclusion from a hazard perspective, a similar process for exposure considerations will also be taken into account in determining whether a substance is proposed to be included in the CRA, as outlined in Table 4-1. Three key exposure aspects will be considered for each subpopulation of interest, for which two of the three considerations must be met for inclusion based on the information available at this time. Firstly, for inclusion into the CRA, substances may have evidence of presence in Canadian commerce or be reasonably anticipated to be in Canadian commerce. This will be determined using manufacture or import data from Section 71 surveys of CEPA 1999 for identification of those substances in Canadian commerce. Detection in biomonitoring data (i.e. urine) or environmental media or food monitoring surveys from Canadian or foreign surveys can also be used as indicators of presence or reasonably anticipated to be in Canadian commerce.

The second exposure filter for inclusion in the CRA will focus on those phthalates that lead to co-occurrence or co-exposure. This is determined by those phthalates that are present in multiple media (consumer, personal care and health products, dust, food, etc.) and/or measured in biomonitoring samples which can lead to combined and co-exposures. In addition, detection at high frequency in consumer product surveys and presence of phthalate in a significant market share of consumer products also provides evidence of co-exposure to products.

The third exposure filter is that of relevance of the duration of exposure. Exposures from the substance must occur through an appropriate or relevant route of exposure and for the identified duration of exposure.

**Table 4-1 Exposure filters and considerations for inclusion into the cumulative risk assessment of phthalates**

| Exposure Filter | Evidence/Considerations |
|---|---|
| Evidence of presence or reasonably anticipated to be in Canadian commerce | Manufacture or import in Canada: information from Section 71 surveys of CEPA 1999<br><br>Detection in biomonitoring data (i.e. urine) or environmental media or food monitoring surveys<br><br>Use characterization |

| | |
|---|---|
| Evidence of co-occurrence/co-exposure | Detection at high frequency in multiple consumer product surveys;<br>Presence in significant market share of consumer products;<br>Canadian biomonitoring data (i.e. urine);<br>Canadian environmental media data;<br>Canadian food monitoring data;<br>Foreign environmental media or food monitoring surveys |
| Relevance of exposure | Relevance of duration of exposure<br>Relevance of exposed population |

Finally, all of the above-mentioned exposure considerations will be evaluated holistically, evaluating the total exposure picture of the substance in question, in considering inclusion into a CRA. For example, high production volume of a substance, presence in products used by consumers and/or environmental media and food, and detection in biological samples provide a strong case for inclusion into a CRA. Although some substances may not meet all exposure considerations, they may be included in the CRA given sufficient evidence of potential for exposure. Proposed Approach for Human Health Cumulative Risk Assessment

## 4.2 Proposed Approach for Human Health Cumulative Risk Assessment

The process for determining which substances will be proposed for inclusion in the CRA of phthalates will consider application of both hazard and exposure filters. Figure 4-2 is a decision tree outlining the process for proposed inclusion into the CRA for phthalates.

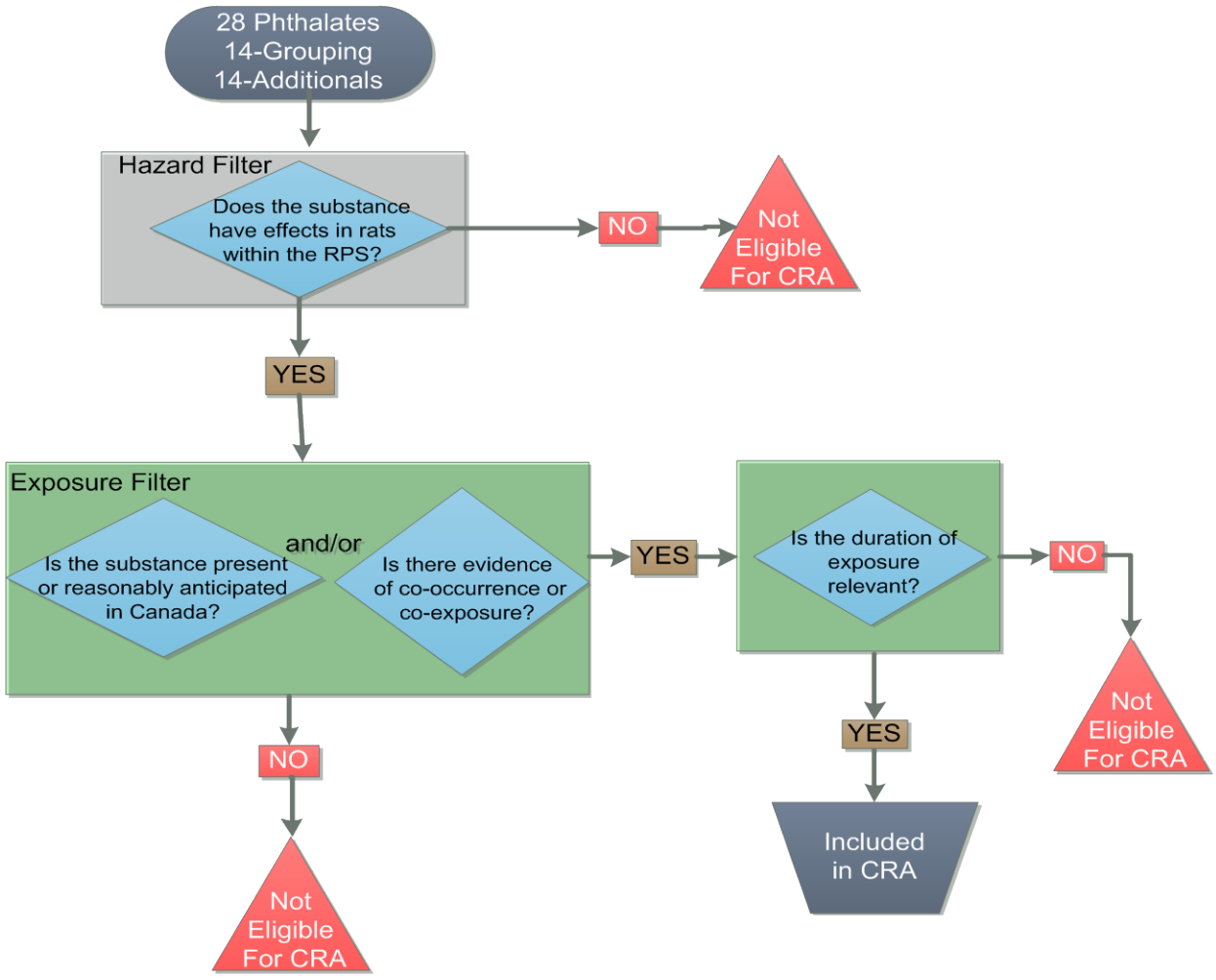



**Figure 4-2 Decision tree for application of the hazard and exposure filters to determine which substances will be included in the cumulative risk assessment of phthalates.**

Once the substances have been determined to meet the considerations for inclusion in the CRA, there are several additional factors to be considered related to the methods to be applied in the assessment. In a component-based approach, effects of the substances in the assessment group are assumed to be based on the individual components; therefore, it is necessary to determine the joint adverse effects of the components when applying this approach. Phthalates will be assessed using the component-based approach, whereby each phthalate will be considered an individual

component of the mixture of phthalates within the substance grouping for which cumulative exposures can occur.

Health Canada's CRA of phthalates will observe the WHO/IPCS Framework for Risk Assessment of Combined Exposures to Multiple Chemicals (Meek et al. 2011), whereby the CRA will begin with simple assumptions for both hazard and exposure in a lower-tiered assessment and refine to a higher-tiered assessment as required and as the data allows. The considerations for the application of the WHO/IPCS combined exposures framework is summarized previously in Figure 2-1. The considerations for each of the exposure and hazard assessments are outlined in addition to the options available for risk characterization at each assessment tier.

It is recognized that the available hazard and exposure information may not coincide with the same assessment tier level. As a result, for example, the available information for the hazard assessment may only allow for a lower-tiered assessment, whereas the exposure assessment information may allow for a higher-tiered assessment to be conducted.

The lower-tiered assessments will focus on the use of the HI approach for the characterization of cumulative risk considering the overall strengths and limitations of the approach, as outlined previously in Table 2-1. Refinement into the higher tier and exploration of the RPF approach will be considered if the appropriate data is available.

## 4.3 Hazard Characterization Considerations

### 4.3.1 Selection of Endpoints

In relation to the selection of a common adverse effect associated with the MOA, the NAS (2008) discussed which effects should form the basis of a CRA. The NAS (2008) and the US EPA (2011b) peer review panel outlined the following two options:

1. Use the RPS as a whole, whereby any of the effects in the syndrome would be considered to affect androgen action. This would subsequently require aggregation of the various effects, which have different levels of toxicity based on the varying dose ranges used among the substances in the grouping. Difficulties in filling data gaps for a variety of effects can lead to increases in uncertainty for read-across and comparison between effects of varying potency across the substances in the grouping. Difficulties arise when not all effects are measured within the same dose range.

2. Focus on a representative endpoint of the RPS and base the CRA on a single common outcome, for example, decreased AGD, decreases in fetal testosterone, or the use of gene expression data implicated in the MOA leading to the endpoint of concern. This would allow for a common comparison of effects between all members of the substance group. When substance-specific information is not

available, data gaps will be filled for a representative endpoint using the read-across methods outlined in the previous section.

The assessment completed by the CHAP (US CPSC 2014) used both of these approaches. Case 1 and Case 3 used PODs selected from effects within the RPS. In Case 2, DEHP was selected as the IC with a POD derived from an analysis of multiple studies examining effects with the RPS. An RPF was then determined for the other group members with respect to the IC (DEHP) based on *ex vivo* testicular testosterone production assay, as described in Hannas et al. (2011a,b). Table 4-2 is an overview of the information available on the effects observed for the subgroup 2 medium-chain phthalate esters that are within the RPS and outlines which phthalates are proposed to be used for read-across in the absence of information. Health Canada is currently examining the available data to determine which approach or combination of approaches is most appropriate.

**Table 4-2 Effects in rats within the rat phthalate syndrome for subgroup 2 medium-chain phthalate esters**

| Phthalate | Testosterone levels[a] (T, S) | Feminization parameters[a] | Reproductive tract malformations and/or fertility[c] | State of the Science (SOS) Package and Section |
|---|---|---|---|---|
| DPrP<br>131-16-8 | NM | AGD | CRY | Saillenfait et al. (2011) |
| DIBP<br>84-69-5 | T | AGD<br>NR<br>PPS | CRY<br>HYP<br>TP<br>FER | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.2 |
| CHIBP<br>5334-09-8 | T<br><br><br><br>Using DIBP as analogue | AGD<br>NR<br>PPS<br><br>Using DIBP and DCHP as analogues | TP<br>FER<br>CRY<br>HYP<br><br>Using DIBP and DCHP as analogues | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.2 and 9.2.3. |
| BCHP<br>84-64-0 | T<br><br><br><br>Using DBP and DCHP as analogues | AGD<br>NR<br>PPS<br><br>Using DBP and DCHP as analogues | CRY<br>TP<br>FER<br><br>Using DBP and DCHP as analogues | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.3 and see DBP below. |

| Phthalate | Testosterone levels[a] (T, S) | Feminization parameters[a] | Reproductive tract malformations and/or fertility[c] | State of the Science (SOS) Package and Section |
|---|---|---|---|---|
| DBP<br>85-68-7 | T<br>S | AGD<br>NR<br>PPS | CRY<br>TP<br>FER | Wine et al. (1997); Mylchreest et al. (1999, 2000); Barlow et al. (2004); Lee et al. (2004); Lehmann et al. (2004); Zhang et al. (2004); Jiang et al. (2007). Mahood et al. (2007); Howdeshell et al. (2008); Hutchison et al. (2008a,b); Boekelheide et al. (2009); Clewell et al. (2009); Wakui et al. (2013) |
| BBP<br>85-68-7 | T | AGD<br>NR<br>PPS | CRY<br>HYP<br>TP<br>FER | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.8 |
| DCHP<br>84-61-7<br><br>DMCHP<br>(read across)<br>27987-25-3 | T | AGD<br>NR<br>PPS | HYP<br>TP<br>FER | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section:9.2.3 and 9.2.4 |
| DIHepP<br>71888-89-6 | NE | AGD<br>NR<br>PPS | CRY<br>HYP<br>TP<br>FER | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.9 |
| DIOP<br>27554-26-3 | T | NR | CRY<br>HYP<br>TP | Saillenfait et al. (2013) |

| Phthalate | Testosterone levels[a] (T, S) | Feminization parameters[a] | Reproductive tract malformations and/or fertility[c] | State of the Science (SOS) Package and Section |
|---|---|---|---|---|
| | | | FER | |
| BIOP<br>27215-22-1 | NE<br><br><br><br>Using DIOP, DIHepP, and MBzP as analogues | AGD<br>NR<br>PPS<br><br>Using DIOP, DIHepP, and MBzP as analogues | TP<br>FER<br><br><br>Using DIOP, DIHepP and MBzP as analogues | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.2 and 9.2.3. |
| DEHP<br>117-81-7 | T | AGD<br>NR<br>PPS | CRY<br>HYP<br>TP<br>FER | Grey et al. (2000); Parks et al. (2000); Akingbemi et al. (2001); Moore et al. (2001); Wolfe & Layton (2003); Borch et al. (2004); Wilson et al (2004); Liu et al. (2005); Shirota et al. (2005); Andrade et al. (2006); Culty et al. (2008); Grey et al. (2009); Lin et al. (2009); Vo et al. (2009); Christiansen et al. (2010); Hannas et al. (2011c); Li et al. (2013); Saillenfait et al. (2013) |
| DnHP<br>84-75-3 | T | AGD<br>NR<br>PPS | CRY<br>HYP<br>TP<br>FER | Saillenfait et al. (2009a,b; 2013); Hannas et al. (2012) |
| UVCB c7-9 Mix<br>111381-89-6 | T<br>S<br><br>Using DINP as analogue | AGD<br>NR<br><br>Using DINP as analogue | TP<br>FER<br><br>Using DINP as analogue | Draft SOS for DINP Environment Canada, Health Canada 2015b; Section 9.2.2 |
| B79P<br>68515-40-2 | T<br>S | AGD | CRY | Draft SOS for Medium Chain |

| Phthalate | Testosterone levels[a] (T, S) | Feminization parameters[a] | Reproductive tract malformations and/or fertility[c] | State of the Science (SOS) Package and Section |
|---|---|---|---|---|
| | Using MBzP and DINP as analogues | Using MBzP and DINP as analogues | Using MBzP and DINP as analogues | Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.11 |
| DBzP<br>523-31-9 | NE<br><br>Using MBzP as a surrogate | AGD<br><br>Using MBzP as a surrogate | CRY<br><br>Using MBzP as a surrogate | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.7 |
| B84P<br>16883-83-3 | T<br><br><br>Using BBP, MBzP, and DIBP as analogues | AGD<br>NR<br>PPS<br><br>Using BBP, MBzP and DIBP as analogues | CRY<br>HYP<br>TP<br>FER<br><br>Using BBP, MBzP, and DIBP as analogues | Draft SOS for Medium Chain Phthalates Environment Canada, Health Canada 2015a; Section: 9.2.8 |
| DINP<br>28553-12-0;<br>68515-48-0 | T<br>S | AGD<br>NR | TP<br>FER | Draft SOS for DINP Environment Canada, Health Canada 2015b; Section 9.2.2 |

[a] Hormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), or leutinizing hormone (LH).
FER – 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, vacuolization of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.
NE – No Effect; AGD – Anogenital Distance; NR – Nipple Retention; CRY – Cryptorchidism; HYP – Hypospadias; TP – Testicular Pathology; PPS – Preputial Separation

### 4.3.2 Point of Departure Selection

Health Canada proposes using a tiered approach to the hazard characterization, beginning with a lower-tiered assessment and refining to a higher tier if required and as the data allows. The selection of PODs are proposed to be informed by the assessment of individual phthalates in the SOS reports. A tier 0 assessment is very simple and the most conservative tier. For instance, the lowest effect level within the RPS suite of effects would be selected, and data gaps would be filled using the assumption that the

data-poor substance has the same potency as the most toxic substance of the group. However, the read-across approach developed by Health Canada and outlined in the Category Approach document (Health Canada 2015) demonstrates that hazard characterization should be at a Tier 1 level, based on the available information and observed differences in potency within the subgroup. A Tier 1 hazard characterization entails the use of the most sensitive effect within the RPS for each substance and data gaps addressed using quantitative read-across methods, as outlined in Canada (2015). The most appropriate nearest neighbour is identified within the subgroup for any of the developmental endpoints within the RPS. PODs can also be refined through the derivation of BMD/BMDLs for substances where the data quality allows, in order to increase the confidence and accuracy within this level of assessment. If the margins are determined to be inadequate, then further refinement to a Tier 2 assessment will be explored if the data allows.

A Tier 2 hazard characterization requires additional refinement for selecting the POD, as illustrated in Figure 2-1, through further analysis of the data to determine a representative endpoint or marker within the RPS, such as AGD or NR, to allow for a common comparison of effects across the substance grouping. In this context, relative potency across the substances would be addressed through the consideration of a single common effect, consistent with the Tier 1 assessment data gaps filled using the read-across methods as described. The difficulties in applying the RPF approach for phthalates lies in the varying potency for the phthalates grouping across effects within the RPS. Due to the fact that the potency is not the same for each effect across the phthalates, the potency will vary between phthalates depending on the chosen endpoint. Therefore, the endpoint(s) within the RPS must be selected carefully. This approach could be applied to a suite of effects within the RPS in order to address the varying potencies across the effects. However, data is not currently available for a measure of a common effect across the substances in the chemical group; therefore, the RPF approach cannot be conducted at this time. However, based on further understanding of the MOA of the phthalates grouping, a common measurement such as the initiating event in the adverse outcome pathway or measurement of effects of activity on a target organ could be examined. A common measure could then allow for comparison of potency across the phthalate chemical group, for example, an *in vitro* system examining testosterone production and relative gene expression changes to support MOA analysis. The work published by Clewell and colleagues (2010) and further elaborated on more recently by Balbuena and colleagues (2013) highlights how the potency of a battery of phthalates with different alkyl chain structures may be measured by comparison of phthalate-induced inhibition of testosterone synthesis.

Based on the current availability of data moving to a tier 3 assessment, the hazard assessment requires in-depth MOA analysis to provide probabilistic estimates of hazard by consideration of kinetics and dynamics through the use of physiologically-based pharmacokinetic (PBPK) or biologically-based dose response (BBDR) models. Currently, this information is not available; therefore, this tier of assessment is not possible as this time.

Health Canada proposes applying the HI method in the lower-tiered assessments to assess the cumulative risk of phthalates to the Canadian population, which is in alignment with the approaches taken internationally, including the recently released CHAP report. Consideration will be given to using an RPF approach for the estimation of cumulative risk if data for which all substance group members are measured for a common effect become available.

## 4.4 Exposure Characterization Considerations

Aggregate assessment of individual phthalates in the SOS reports are proposed to be used to characterize the important sources, pathways and routes of exposures appropriate for use in a CRA. The tiered approach as outlined by the WHO/IPCS framework (2011) (Figure 2-1) will also be applied for the derivation of estimates of exposures with refinements to the extent possible to ensure that estimates reduce compounding conservative assumptions across the substances included in the CRA. Appropriate refinements may include using measures of central tendency vs. upper bounding metrics, as appropriate. Estimates of exposures will not be limited to those that have biomonitoring data available. Deterministic estimates and probabilistic estimates, where sufficient data is available, will be considered for substances that have a common mode of action, as previously discussed, and that have no biomonitoring data. In most cases, for substances with biomonitoring data, exposure will be estimated in parallel with the deterministic and probabilistic intake estimates for environmental media and products used by consumers.

Subsequent to the application of the hazard filters, the exposure filters outlined in Table 4-1, were applied to subgroup 2 medium-chain phthalate esters and were evaluated for applicability for inclusion into the CRA based on the information available. Table 4-3 outlines each line of evidence applied for the exposure filter, the information available for each substance and the proposed recommendation for inclusion into the subset for CRA.

**Table 4-3 Exposure filter lines of evidence and information to determine potential inclusion in cumulative risk assessment**

| **Substance** | **Manufacture, use, import in Canada (S.71)[1]** | **Evidence of co-occurrence/ co-exposure[2] (Biomonitor-ing)** | **Evidence of co-occurrence/ co-exposure[3] (Dust)** | **Potential exposure routes** | **Inclusion in cumula-tive risk assess-ment** |
|---|---|---|---|---|---|
| DPrP | No | Not monitored | No | N/A | No |
| DIBP | Yes | Yes | Yes | Inhalation (IA), oral (D), oral (F, BM), | Yes |

| Substance | Manufacture, use, import in Canada (S.71)[1] | Evidence of co-occurrence/ co-exposure[2] (Biomonitor-ing) | Evidence of co-occurrence/ co-exposure[3] (Dust) | Potential exposure routes | Inclusion in cumula-tive risk assess-ment |
|---|---|---|---|---|---|
| | | | | products used by consumers (D) | |
| CHIBP | No | Not monitored | No | N/A | No |
| BCHP | No | Not monitored | No | N/A | No |
| DBP | Yes | Yes | Yes | Inhalation (IA), oral (D), oral (F, BM), consumer products | Yes |
| BBP | Yes | Yes | Yes | Inhalation (IA), oral (D), oral (F, BM), products used by consumers | Yes |
| DCHP | Yes | No | Yes | Inhalation (IA), oral (D) | Yes |
| DMCHP | No | Not monitored | Yes | Oral (D) | Yes |
| DIHepP | Yes | Not monitored | Yes | Oral (D) | Yes |
| DIOP | Yes | Not monitored | Yes | TBD | Yes |
| BIOP | No | Not monitored | No | N/A | No |
| DEHP | Yes | Yes | Yes | Inhalation (IA), oral (D), oral (F, BM), products used by consumers | Yes |
| DnHP | No | Not monitored | Yes | TBD | Yes |
| 79P [UVCB | Yes | Not | Not | TBD | NSI |

| Substance | Manufacture, use, import in Canada (S.71)[1] | Evidence of co-occurrence/ co-exposure[2] (Biomonitor-ing) | Evidence of co-occurrence/ co-exposure[3] (Dust) | Potential exposure routes | Inclusion in cumula-tive risk assess-ment |
|---|---|---|---|---|---|
| mix (C7 - C9)] | | monitored | monitored | | |
| B79P | Yes | Not monitored | Yes | Oral (D) | Yes |
| B84P | Yes | Not monitored | Not monitored | Oral (D) | NSI |
| DBzP | No | Not monitored | Yes | Oral (D) | Yes |
| DINP1,2 | Yes | Yes | Yes | Oral (D), Oral (F), products used by consumers (D) | Yes |

[1] S.71 coupled with extensive searches of N. American and European databases (e.g. REACH, IUR, SPIN). Use characterization is qualitative, evaluating multiple lines of evidence to deduce the Canadian in-commerce status of a chemical.
[2] Approximately 100% detection in biomonitoring of metabolites in urine samples (P4 study, CHMS, NHANES, and MIREC)
[3] Co-occurrence analysis of phthalates in the Canadian House Dust Study (2007 – 2010) (Memo to file EHSRD to ESRAB May 2014)
TBD – to be determined later; IA – indoor air; F – food; BM – breast milk; D – dust; NSI – not sufficient information

The pivotal information that determined substances for inclusion into the CRA were industry data collected under Section 71 of CEPA 1999, detection in North American biomonitoring surveys (CHMS, MIREC, P4, NHANEs), and detection in the Canadian House Dust Study (Canada 2013; Health Canada 2013; Arbuckle et al. 2014; CDC 2014; personal communication EHSRD to ESRAB, November 2013). For phthalate parent compounds (DEHP, DIBP, DBP, BBP, DINP), with close to a 100% detection in various biomonitoring surveys, there is sufficient evidence for co-exposure; these substances will therefore be assessed for cumulative risk. Furthermore, although a significant number of phthalates within the assessment group has not been monitored in biomonitoring samples, they are found to be in commerce in Canada. These substances are also found at close to 100% detection in the Canadian House Dust Study, a survey of 126 homes across Canada between 2007 and 2010 (Kubwabo et al. 2013, Memo to file EHSRD to ESRAB May 2014). These substances (DIHepP, B79P, DCHP) will also be included in the assessment of cumulative risk based on in-commerce status coupled with close to 100% detection in dust samples from Canadian homes. Finally, due to reporting limits and difficulties in capture of import activity, the S.71 survey may not capture all in-commerce activity. As a result, substances that fit

the profile of non-reporting to S.71 and close to 100% detection in dust samples will also be assessed for cumulative risk (DMCHP, DIOP, DBzP, DnHP).

There are three populations of interest for which exposures will be estimated and cumulative risk will be calculated. Pregnant women, characterized as women aged twelve and up; infants and toddlers, 0 to 6 months, and 7 months to 4 years of age; and adults, as outlined in Table 4-4. In terms of duration of exposure from manufactured articles such as adhesives, sealants and coatings, acute dermal exposure would not be considered to be of concern for human health based on evidence showing that dermal absorption in rats is low (below 10%), human skin is even less permeable than rat skin, retention in skin is three- to six-fold higher in rats than humans (Mint and Hotchkiss 1993; Mint et al. 1994). Regardless of route of exposure, phthalates in general are not considered acute toxicants, with $LD_{50}$ levels from dermal exposure being at minimum two- to five-fold higher than oral values, which in turn are also high (Draize et al. 1948; David et al. 2001; Monsanto Company 1970 cited in US EPA 2006, 2010). Since phthalates metabolize relatively fast showing no accumulation, and excretion is rapid, within hours to days (Phokha et al. 2002; Clewell et al. 2009), acute exposures are not considered relevant for a CRA; therefore, only sources that will lead to short-term, sub-chronic and/or chronic exposures will be assessed in the context of a CRA. It should also be noted that no other jurisdictions have addressed phthalate exposure and risk from acute, one-time, exposures (ECHA 2013; US CPSC CHAP 2014, NICNAS 2012).

Moving forward, Health Canada proposes using a tiered approach for characterizing the exposure for each of the individual substances in the assessment group. As illustrated above, the data available for each substance varies; however, the estimates will be refined as much as is required and to the extent that the data allows.

Neither a Tier 0 nor a Tier 1 assessment is applicable, as sufficient data is present to increase confidence and accuracy in the exposure characterization. A Tier 2 assessment includes the generation of deterministic (e.g. dust, indoor air, products used by consumers) and probabilistic estimates (food) for each of the sources of exposure and routes. These estimates of exposure will be generated using a combination of measured and modelled data. Tier 2 exposure assessments will be conducted in a refined manner, as adding conservative assumptions (users only, $95^{th}$ percentile metrics etc.) compounds conservativeness. Deterministic environmental media and probabilistic food exposure assessments will be conducted independently of deterministic product exposure assessments, as these methods generally tend to overestimate exposure when compared to biomonitoring intakes. HQs developed from deterministic and probabilistic exposure estimates for environmental media and food, respectively, will be added to assess cumulative risk. Deterministic product hazard quotients (only products where there is evidence of co-exposure to multiple phthalates will be evaluated, e.g. toys where multiple phthalates are detected) will be added to assess cumulative risk. Tier 2 exposure assessments will incorporate biomonitoring data and may incorporate probabilistic methods to calculate intakes of co-exposed

phthalate parents based on metabolites present in urine. Biomonitoring hazard quotients will be added to evaluate cumulative risk.

A summary of both the hazard and exposure considerations are presented in Table 4-4 outlining the reproductive and developmental effects identified as the basis for the selection of the hazard endpoint, POD metric selections, the route(s), pathway(s) and example sources of exposure for each exposure population included in the CRA.

**Table 4-4 Hazard and exposure considerations and potential relevant populations for assessing cumulative risk**

| Considerations | CRA1 | CRA2 | CRA3 |
|---|---|---|---|
| **Tox life-stage** | *In utero* | Pre-pubertal–pubertal | Adult |
| **Relevant Population(s)** | Pregnant women (ages 12+) | Infants/Toddlers 0–4 years of age; Children 5–12 yrs of age | Adult males; Pregnant women |
| **Relevant duration of exposure** | Chronic; Sub-chronic; Short Term | Chronic; Sub-chronic ; Short Term | Chronic; Sub-chronic; Short Term |
| **Route (hazard study basis)** | Oral | Oral | Oral |
| **Basis for Hazard Endpoint Selection** | Reproductive-developmental effects related specifically to the rat phthalate syndrome including, but not limited to: AGD, NR, PPS, CRY, HYP, testicular pathology, effects on testosterone levels, and/or effects on fertility | Reproductive-developmental effects related specifically to the rat phthalate syndrome including, but not limited to: AGD, NR, PPS, CRY, HYP, testicular pathology, effects on testosterone levels, and/or effects on fertility | Reproductive-developmental effects related specifically to the rat phthalate syndrome including, but not limited to: AGD, NR, PPS, CRY, HYP, testicular pathology, effects on testosterone levels, and/or effects on fertility |
| **Point of Departure Selection** | Use of LOAELs/NOAELs, but when the data is robust, fulfilling the criteria for generating BMD/BMDLs, these will be | Use of LOAELs/NOAELs, but when the data is robust, fulfilling the criteria for generating BMD/BMDLs, these will be developed for | Use of LOAELs/NOAELs, but when the data is robust, fulfilling the criteria for generating BMD/BMDLs, these will be developed for the sentinel effects |

| Considerations | CRA1 | CRA2 | CRA3 |
|---|---|---|---|
| | developed for the sentinel effects described above | the sentinel effects described above | described above |
| **Route and Pathway of Exposure** a: Environmental media | Oral: food, dust; Inhalation: indoor air | Oral: breast milk, food, drinking water, dust; Inhalation: indoor air | Oral: food, dust, drinking water; Inhalation: indoor air |
| **Route and Pathway of Exposure** b: products used by consumers | Dermal: (potential products: personal care products, textiles) | Oral - Toys (potential products: mouthing toys) Dermal – (potential products: cosmetics, natural health products and drugs, including personal care products, textiles) | Dermal: (potential products: personal care products, textiles) |
| **Route and Pathway of Exposure** c:Biomonitoring | Biomonitoring: all sources, pathways and routes | Biomonitoring: all sources, pathways and routes | Biomonitoring: all sources, pathways and routes |

## 4.5 Uncertainties of the Health Approach

Empirical health effects data for medium-chain phthalates range from robust to very limited and create uncertainty in the evaluation of risk to humans. There is some uncertainty associated with the use of analogues to characterize the human health effects of phthalates with limited or no available toxicological information. This lack of available toxicological information applies to DMCHP, CHIBP, BCHP, DBzP, B84P, BIOP and B79P. It is also noted that the majority of the reproductive and developmental toxicity data for these medium-chain phthalates is generally limited to one species (rat) and to males. There is some uncertainty associated with not only the potential biological significance of effects, but also the sensitivity of effects after exposure to this substance group in both female and male humans. Studies used for risk characterization for medium-chain phthalates ranged from high-quality OECD Guideline studies to those with limited information. This uncertainty was addressed in the selection of precautionary target MOEs, where required. Although a rigorous evaluation approach was conducted with the available human epidemiological data, uncertainty still exists as to the relevance of these studies implicating the potential hazard that certain phthalates pose to humans. When conducting a CRA the results must be interpreted while ensuring that the overall uncertainty of the group is not inflated through the application of UFs across all substances in the group, particularly when there are numerous substances being considered.

Several uncertainties exist regarding exposure data. Specifically, a majority of biomonitoring data evaluate spot urine samples, and the applicability of spot urine data was discussed by the US EPA peer-review panel (2011). The short half-life of phthalates and the subsequent variation of the internal levels of phthalates, which can change by an order of magnitude, can result in large variations in the data. The use of 24-hour urine samples, to factor in the variation of spot samples, may in fact be more informative. However, the major population-level surveys, such as the US NHANES and Canada's CHMS, measure urine concentrations using spot urine samples and, consequently, have strong sample size and statistical power. These population-level surveys are thus informative and cannot be precluded from analysis. Additionally, specific to phthalates, metabolites may overlap; however, biomonitoring intake calculations have been conducted using specific metabolites to each parent compound in order to reduce uncertainty in this regard.

Several uncertainties also exist with deterministic and probabilistic estimates; specifically, variability and uncertainty is observed at each point of the exposure algorithms (e.g. product frequency, body weight, product amount, environmental concentrations and intake rates). Thus, when assessing total exposure, from environmental media for example, variability and uncertainty is compounded. In the context of CRAs, adding exposure intakes calculated from deterministic and probabilistic methods may compound not only the variability and uncertainty of the underlying exposure estimate but also the conservativeness of the cumulative exposure estimate. This is evident because aggregate deterministic and probabilistic estimates (environmental media/food plus products used by consumers) generally overestimate biomonitoring intakes (from all sources).

# 5 Proposed Approach for Considering Cumulative Effects of Phthalates in an Ecological Risk Assessment

Similar to the human health assessment of phthalates, for the ecological assessment of these substances, the potential for cumulative effects is being considered to assess the risk posed by phthalates. At the time that this document was prepared (autumn 2014), no ecological CRAs for phthalates had previously been published internationally. However, there are many examples where the cumulative ecological risks posed by other groups of substances have been assessed by the Government of Canada or by other jurisdictions internationally. Where sufficient information is available to consider cumulative effects of a group of substances, this is generally considered to provide a much more scientifically robust consideration of risk than assessments on a substance-by-substance basis.

Internationally, one of the best-known examples of cumulative ecological risk assessment is the use of toxic equivalency factors for assessing polychlorinated biphenyls (PCBs) and dioxins and furans in mammalian wildlife (Van den Berg et al. 2006). There are also several examples from Canada. The assessment of nonylphenol and its ethoxylates used a toxic-equivalents approach to consider the risk posed by

combined exposures of these substances (Environment Canada and Health Canada 2001). Various assessments of petroleum-based substances use an additive-toxic-unit approach for considering the cumulative effects of the various components in complex hydrocarbons through the use of the model PETROTOX (2009). Currently under the Substance Groupings Initiative of Canada's Chemicals Management Plan, several draft screening assessments of inorganic substances (e.g., cobalt-, selenium- and boron-containing substances) are being developed based on a moiety approach, to consider the potential ecological risk from all sources of those particular metal ions.

In this section, an approach for examining the ecological risk posed by co-exposure to multiple phthalates at varying levels is proposed.

## 5.1 Criteria for considering a cumulative ecological risk assessment

Traditionally, programs assessing and managing chemicals have focused on the assessment of individual substances. However, multiple chemicals are typically used at any given location or locations in close proximity to each other and may be released concurrently into the environment. Where similar chemicals are potentially exerting combined effects on organisms through a common mode of action, it may be more appropriate to consider assessing risk from the cumulative exposure, rather than considering each individual substance in isolation.

In determining whether to conduct a CRA, the most important consideration is whether there is co-occurrence of the substances in one or more environmental media. Sources of information that can indicate potential for co-occurrence may include:

- relevant sources and potential releases of the substances;
- fate and distribution in the environment (including persistence and potential for bioaccumulation);
- physico-chemical properties of the substances that may influence their behaviour and solubility in the environment;
- exposure modelling; and
- measured environmental concentrations or monitoring data.

Information available on any or all of these aspects suggesting a potential for co-occurrence may indicate that it would be appropriate to consider cumulative risk.

Once the decision has been taken to consider cumulative risk, selection of which cumulative assessment method to use will depend on whether or not there is a common mode of action among the substances being assessed, and what sort of data are available to characterize the effect and exposure concentrations of each constituent.

## 5.2 Rationale for conducting a cumulative risk assessment of phthalates

In the case of phthalates, there are several lines of evidence to suggest the potential for co-occurrence. Their uses, releases and degradation processes all indicate potential for co-occurrence through wastewater treatment system effluents. Environmental concentration data also indicates that many phthalates are co-occurring in the Canadian environment.

There is evidence to suggest that all of the phthalates under consideration share a common mode of toxic action in aquatic organisms. Therefore, CRA methods based on concentration addition are appropriate for use with these substances.

The following sections discuss the evidence for a common mode of action and co-occurrence of phthalates in further detail.

### 5.2.1 Modes of action for ecotoxicity of phthalates

It has been speculated that the mode of action for acute toxicity of the shorter-chain phthalates is likely narcosis[8], i.e., lipophilicity-driven baseline toxicity (Adams et al. 1995; Parkerton and Konkel 2000; Call et al. 2001). Narcosis is generally considered to represent the minimal toxicity of every substance (Escher and Hermens 2002). Call et al. (2001) found that the results of their acute invertebrate toxicity tests with DMP, DEP, DBP and BBP, in which the measurement of toxicity increased with increasing hydrophobicity (or log $K_{ow}$), were consistent with toxicity predictions based on a generic equation for narcosis-inducing chemicals; correlation of results was very good, with $R^2$ values of 0.962 to 1.000. Adams et al. (1995), who studied the toxicity of several phthalates to various species, including fish, invertebrates and algae, noted that they did not observe any major differences in sensitivity between the species. This again suggests a non-specific, narcotic mode of action. Parkerton and Konkel (2000) examined acute-to-chronic ratios (ACRs) for four shorter-chain phthalates based on empirical data for eight different aquatic species. They found that the ACRs were quite similar across species, most ranging between 2 and 6, though ACRs as high as 15 were

[8] Narcosis – A nonspecific mode of action that is reversible, is correlated with hydrophobicity of the substance, and is thought to occur through physical effects to cell membranes. Effects of narcosis in organisms typically include progressive lethargy, unconsciousness, and subsequent death. Also referred to as baseline toxicity, narcosis is caused by a wide variety of organic chemicals.

calculated. This similarity in ACRs across different species suggests that a similar mode of action, such as narcosis, is also responsible for chronic effects of phthalates.

However, there appears to be some disagreement in the literature on whether phthalates would be considered Type I nonpolar narcotics or Type II polar narcotics. Some studies suggest that diesters, such as phthalates, may have greater toxicity than that expected from nonpolar (Type I) narcotics. In binary joint toxicity studies, Veith and Broderius (1990) found that diesters were less than additive with both octanol and phenol, suggesting that their mode of action is different from that of nonpolar narcotics (e.g., octanol), and possibly even different from polar narcotics (e.g., phenol). Adams et al. (1995) also note that esters as a class, and particularly lower molecular weight phthalate esters, appear to have excess toxicity relative to other neutral organic nonspecific narcotics. They suggest that the lower molecular weight phthalates might be classified either as polar narcotics or as Class III chemicals (i.e., unspecific reactivity mode of toxic action). Estimated critical body residues (CBRs) for various phthalates were found to be one to two orders of magnitude lower than CBRs for other nonpolar narcotic chemicals when compared for the same test organism and endpoint (Parkerton and Konkel 2000). Also, quantitative structure activity relationships (QSARs) developed for several phthalates showed variation in slopes between species, whereas QSARs for nonpolar narcotics typically have a fairly constant slope across species (Parkerton and Konkel 2000).

Parkerton and Konkel (2000) propose that differences in species toxicity might be explained by differences between species in terms of biotransformation capacity (i.e., *in vivo* hydrolysis) and contributions of resulting metabolites to the toxicity. They note that estimated CBRs for parent phthalates in fish are comparable to those reported for other polar organic chemicals, but that if biotransformation products are considered, the estimated CBRs are in the range reported for nonpolar narcotics.

More recently, Kipka and DiToro (2009) have developed a model using polyparameter linear free energy relationships to describe the partitioning of narcotic chemicals to target lipids. They found that this model can be used to predict acute median lethal concentrations of polar, as well as nonpolar, narcotic chemicals to aquatic organisms because it does not use the log $K_{ow}$ to describe partitioning. Therefore, this may be a good model for estimating acute toxicity of short-chain phthalates, regardless of which non-specific mode of action they follow.

In the case of the longer-chain phthalates, acute and chronic toxic effects are generally not seen, with the exception of chronic studies on daphnids (Rhodes et al. 1995). It has been generally recognized that there is a “solubility cutoff” for the higher-molecular-weight phthalates, whereby the water solubility of these substances is lower than the aqueous concentration required to accumulate internal concentrations high enough to reach a critical body residue concentration that can elicit adverse effects (Rhodes et al. 1995; Parkerton and Konkel 2000; Call et al. 2001). Adams et al. (1995) suggested that either limited water solubility or structural differences that interfere with binding at target

sites might account for the lack of toxicity observed in the higher molecular weight phthalates. Although adverse effects have typically not been observed with exposures to individual longer-chain phthalates, it is possible that these substances could still contribute to cumulative effects through a narcotic mode of action. It has been noted that although very hydrophobic substances with low water solubility may be unable to reach sufficiently high chemical activity to cause adverse effects in organisms on their own, these substances can still be expected to contribute to baseline toxicity in a complex mixture (Escher and Hermens 2002; Mayer and Reichenberg 2006). This may be the case with the longer-chain phthalates.

Chronic adverse effects that are seen in daphnids have been speculated to result from physical entrapment of the organisms in surface films. Rhodes et al. (1995) indicate that inhibition of reproduction is commonly the most sensitive endpoint in chronic toxicity studies with daphnids. However, in their evaluation of daphnid chronic toxicity with 14 different phthalates (12 of which are among those being considered in the CRA), in no case was reproduction more sensitive than survival. They argue that this suggests the mortality was due to physical means, rather than an internal effect. In their literature review, Staples et al. (1997a) note that in daphnid toxicity studies that used solubilizers to help disperse the higher molecular weight phthalates, toxic effects were reduced. This again lends support to the theory that when chronic effects are observed in daphnids for these substances, it is due to the physical effect of entrapment. The environmental relevance of these types of effects are discussed further in the SOS reports for DINP and the long-chain subgroup with respect to assessing these substances individually. However, for the purposes of assessing combined exposures to multiple phthalates, toxicity data based on physical effects would not be included in the calculation of cumulative risk quotients. A concentration addition approach assumes that substances in the assessment group are contributing to a combined internal dose. In the case of physical entrapment, these effects are not a result of internal concentrations and, therefore, cannot be assumed to contribute to an additive effect. Data on physical effects are another line of evidence that could be considered in making conclusions on those phthalates with very low water solubility. Such considerations would need to take into account whether conditions in the environment would be likely to result in the formation of surface films of phthalates.

At least two phthalates, BBP and DEHP, have been observed to bind to steroid receptors in fish. In a study with zebrafish embryos, Chen et al. (2014) found that BBP possessed estrogenic activity, and in rainbow trout, BBP was observed to cause vitellogenin induction (Christiansen et al. 2000). DEHP was reported to impair oocyte maturation and ovulation in zebrafish, resulting in reduced fecundity (Carnevali et al. 2010), and was also found to alter spermatogenesis in zebrafish, affecting reproduction (Corradetti et al. 2013). Estrogenic activity of BBP has also been observed in amphibians (e.g., Mathieu-Denoncourt et al. 2015). Other phthalates (DBP and DINP) do not appear to be estrogenic on their own, but in the presence of 17-β-estradiol they have been observed to increase estrogenic activity (Chen et al. 2014). However, the information on estrogenic activity of phthalates in aquatic organisms is limited, has only

been reported for a small number of phthalates, and in most cases has not been demonstrated to result in population-level effects (such as growth, reproduction, or survival). Furthermore, such effects are substance-specific and structure-dependent and can affect organisms at different life stages through different mechanisms of action. Therefore, it is not proposed to account for this potential separate mode of action (e.g., through a response addition approach) in the cumulative approach being proposed here.

Therefore, we are assuming that all phthalates are acting through a common non-specific mode of action, i.e., narcosis, and could be considered together in a CRA based on concentration addition. This does not preclude the possibility that some phthalates are also acting through other modes of action (e.g., estrogenic activity). However, due to the lack of data on other modes of action for most phthalates, these other potential modes of action would not be considered in this proposed approach. However, potential estrogenic activity may be considered as a separate line of evidence in the Phthalate Substance Grouping assessment.

### 5.2.2 Potential for co-occurrence of phthalates in the environment

There are several types of information that should be considered in determining whether substances have the potential to have concurrent exposure in the Canadian environment. These include evidence of common sources and uses, evidence that the substances are present in Canadian commerce, evidence for potential releases, evidence of similar environmental fate, evidence that they are present in environmental media, and evidence of co-occurrence in those media.

Phthalates are widely used in the manufacture of flexible plastics and as additives to various products, occurring in virtually every major product category (Call et al. 2001). Although there are various attractive forces that hold phthalates within plastics, they are not covalently bound in polymeric matrices; therefore, over long periods of time, phthalates are able to migrate from plastic products into the environment (Adams et al. 1995). From the submissions received under the Section 71 survey for phthalates (Environment Canada 2014), it appears that at least some of the companies that manufacture or use phthalates are involved with more than one type of phthalate, suggesting the potential for co-occurrence of phthalate substances in their effluents. However, production of phthalates, compounding into plastics, and many other industrial uses of phthalates in Canada occur as batch processes. Therefore, the duration and frequency of these batches and the degradation rates of the various phthalates will also affect the likelihood of co-occurrence in industrial effluents. Responses to the Section 71 survey suggest that most facilities involved with phthalates that produce liquid effluents release these to wastewater collection systems (Environment Canada 2014). The contribution of phthalates from various sources in wastewater systems provides the potential for co-occurrence of various phthalates. In addition to releases of industrial effluents, phthalates may enter the wastewater collection system from down-the-drain releases of consumer products containing

phthalates (e.g., hair care products, skin care products, fragrances, etc.). It is expected that any releases to wastewater from consumer products would be relatively continuous. Not all releases from consumer products would necessarily be to wastewater; there could be disperse releases throughout the product service, and products could also be discarded to the solid waste stream and deposited in landfills.

For the 28 phthalates under consideration, industry submissions provided under the Section 71 notice (Environment Canada 2014) indicate that 21 of these are in commerce, and seven of the substances — BCHP, DBzP, CHIBP, BIOP, DMCHP, DPrP and DnHP — are not in commerce in Canada above the reporting thresholds. As no environmental monitoring in Canada has been conducted for these seven substances, it is unknown whether they are present in Canadian water, sediment or soil; although, DBzP and DMCHP have been detected in Canadian house dust samples (Kubwabo et al. 2013).

Studies that have examined Canadian surface water samples for phthalates have involved analyses for 11 of the phthalates that are known to be in commerce, and all 11 of these substances have been detected in at least some samples.

The phthalates DMP, DEP, DIBP, DIHepP, DBP, BBP, DEHP, DnOP, DINP and DIDP have been detected in Canadian surface waters, sediment, and in various aquatic organisms (Makepeace et al. 1995; Data Interpretation Group 1999; McDowell and Metcalfe 2001; Garrett 2002; Morin 2003; Mackintosh et al. 2004; Alberta Environment 2005; Sosiak and Hebben 2005; Mackintosh et al. 2006; McConnell 2007; Blair et al. 2009; Aoki 2010; Keil et al. 2011; Alaee et al. 2013). DCHP has been detected in Canadian sediments (Alaee et al. 2013). No Canadian sampling studies for phthalates such as B84P, B79P, and DUP could be found in the literature. Current sampling being conducted by Environment Canada researchers may help to determine whether these substances are also occurring in the environment.

In addition to simply being found in the environment, in order for substances to be considered in a CRA, there must be reason to suspect that they also co-occur both spatially and temporally. There are various studies in which researchers have measured concentrations of multiple phthalates in samples of Canadian environment media, providing support for co-occurrence of these substances. Table 5-1 provides examples of studies that demonstrate co-occurrence of phthalates in surface waters in Canada.

**Table 5-1 Canadian monitoring studies demonstrating co-occurrence of phthalates in water samples**

| Location | Phthalates analyzed | Evidence of Co-occurrence | Reference |
|---|---|---|---|
| False Creek, Vancouver[a] | DMP, DEP, DIBP, DBP, BBP, DEHP, DIHepP, | Detection rates ranged from 17% of samples (for DIOP) to 100% (for DMP) | Mackintosh et al. 2006 |

| | | | |
|---|---|---|---|
| | DnOP, DIOP, DINP and DIDP[b] | | |
| Alberta, various locations downstream of wastewater treatment systems | DMP, DEP, DIBP, DBP, BBP, DEHP, DIHepP, DnOP, DIOP, DINP and DIDP[b] | DMP, DBP, DIBP and diisohexyl phthalate detected in three or four of the five sampling locations; other nine phthalates were detected at all locations | Sosiak and Hebben 2005 |
| Niagara River[c], at inflow from Lake Erie and at outlet to Lake Ontario | DMP, DEP, DBP, BBP, DEHP and DnOP | At inflow, DMP, DEP and DBP detected in all 38 samples; DnOP, BBP, and DEHP detected in 26, 9, and 4 of the 38 samples, respectively<br><br>At outlet, DMP, DEP and DBP detected in 45 of 46 samples; DnOP detected in 25 of 46 samples; BBP detected in 11 of 46 samples; DEHP not measured above detection limits in any samples | Data Interpretation Group 1999 |

[a]False Creek is an urban marine inlet in a formerly industrial area that receives inputs from sewer overflow system.
[b]The study also included two other phthalates not under consideration in this assessment: DnNP and diisohexyl phthalate.
[d]The Niagara River is an Area of Concern due to historical contamination from municipal and industrial discharges and waste disposal sites.

There is a slight possibility that co-occurrence could exist in some cases due to the degradation of longer-chain phthalates to shorter-chain phthalates. The majority of the literature indicates that degradation of diester phthalates occurs primarily through hydrolysis of the ester linkages to form monoester phthalates and phthalic acid. However, in one study using a single isolated strain of bacteria, researchers observed demethylation of the alkyl chains to degrade longer-chain phthalates to shorter-chain phthalates (Hashizume et al. 2002). It is generally thought that this would not be a significant degradation pathway in the natural environment.

In summary, given that many of the releases of phthalates in Canada end up passing through wastewater treatment systems, there is the potential for co-occurrence of phthalates originating from various sources and uses. The available monitoring data also confirms that all of the phthalates that have been analyzed are being detected in Canadian aquatic systems, to varying degrees. Therefore, there is support for the assumption that many of the phthalates under consideration are co-occurring in the Canadian environment.

## 5.3 Methods considered for cumulative ecological risk assessment of phthalates

For the ecological CRA of phthalates, it is proposed to follow a tiered approach, as outlined in the WHO/IPCS framework (Meek et al. 2011; Figure 2-1), in which simple assumptions are made in estimating effect and exposure levels at a lower tiered assessment, with refinements as needed and as the data allow, at higher tiers.

With a tiered approach, further refinement of the assessment is only carried out if the outcomes of lower tiers indicate a potential risk. This has the benefit of focusing efforts and resources, so that more labour- and data-intensive methods are not used if more simple approaches can already indicate that phthalates are unlikely to pose a concern.

The proposed methods for calculating cumulative risk at the first tier are based on concentration addition. Several authors have recommended using a concentration addition approach to assess chemical mixtures, at least initially, rather than an independent action approach, as any resulting error will be on the side of precaution, providing a worst-case scenario (Backhaus et al. 2003; Backhaus and Faust 2012). There are several approaches for determining the cumulative effects of a mixture or combination of substances in ecological systems that are based on the concept of concentration addition. These include the Toxic Unit Summation, Relative Potency Factor (e.g., Toxicity Equivalents), Hazard Index and Point of Departure Index methods, for example. Descriptions of several of these approaches, along with their advantages and disadvantages, were provided in Section 2 (Cumulative Risk Assessment Approaches), as well as in Kortenkamp et al. (2009).

The three approaches considered at Tier 1 are the PEC/PNEC method, the Toxic Unit Summation method, and the Sum of Internal Toxic Units method. Each of these methods is further discussed below.

### 5.3.1 PEC/PNEC Method

In this method, Predicted Environmental Concentrations (PECs) and Predicted No Effects Concentrations (PNECs) that are developed for the assessment of the individual substances are considered using a concentration addition approach. The PEC/PNEC method is a variation of the Hazard Index method (as described in Section 3.1). As in the HI approach, an exposure value (in this case, the PEC) is divided by an effect value (in this case the PNEC) for each substance in the assessment group. These ratios (i.e., the risk quotients, RQs) for all substances are summed to estimate the cumulative risk for the overall assessment group (i.e., the risk quotient $RQ_{PEC/PNEC}$):

$$RQ_{PEC/PNEC} = \sum_{i=1}^{n} RQ_i = \sum_{i=1}^{n} \frac{PEC_i}{PNEC_i}$$

The main difference from the HI method, as used when assessing cumulative risk to human health, is that because the PECs and PNECs refer to aqueous concentrations, all uptake pathways for aquatic organisms are inherently combined, so there is no need to calculate separate hazard quotients for different pathways of exposure. This approach provides a conservative estimate of the expected toxicity according to concentration addition (Backhaus and Faust 2012).

For some groups of substances, when conducting a CRA, PECs and PNECs would already be available from the assessment of the potential risk of each individual substance, such that very little additional work would be needed to calculate the cumulative risk quotient ($RQ_{PEC/PNEC}$). In the case of the Phthalates Substance Grouping, PECs and PNECs are available for some individual phthalate substances from the SOS reports (Environment Canada and Health Canada 2015a, b, c, d). However, there are also several phthalates for which aquatic PNECs could not be determined, and the SOS reports did not include PNECs and PECs for any of the additional phthalates that are being considered for the CRA.

It should be noted that PNECs should be based on apical endpoints related to survival, growth and development, and reproduction, rather than secondary endpoints at the biochemical, gene, cellular, or other sub-organismal level. PNECs can also only be determined for phthalates that cause adverse effects at concentrations at or below their water solubility limit. This means that some of the longer-chain phthalates could not be included in a cumulative assessment based on the PEC/PNEC method.

As there may be more than one aquatic PEC derived for a particular phthalate, the method for selection of the PECs for use in this approach are described further in Section 5.4.2. Backhaus and Faust (2012) note that, technically, this approach violates an assumption of concentration addition in that, by using PNECs, the toxicity data for each substance may not refer to the same biological endpoint and type of organism. The various PNECs may also be derived using different assessment factors[9], which can complicate interpretation of the resulting sum. Nonetheless, this simple calculation can give some indication as to whether there is a need to further refine the estimates of potential cumulative risk for the substances. If the cumulative risk quotient indicates potential concern, and it is known that the PECs used for this Tier 1 calculation were

[9] Assessment Factor (AF) – A factor applied to a critical toxicity value in order to derive a predicted no effect concentration (PNEC) for a substance. The AF is intended to: 1) extrapolate from short-term median effect concentrations to long-term low/no effect concentrations, and/or 2) account for interspecies variation in sensitivity to the substance.

based on very conservative assumptions, an effort should be made to refine the PECs to the extent possible and re-evaluate at this first tier.

If the $RQ_{PEC/PNEC}$ does not indicate a potential concern, then it would be concluded that there is no significant cumulative risk posed by the group of phthalates in the investigated exposure scenario.

### 5.3.2 Toxic Unit Summation

The Toxic Unit Summation approach basically involves a summation of toxic units[10] for each substance in the assessment group to obtain an overall toxic unit. A toxic unit represents the concentration of a substance scaled for its relative toxicity (Kortenkamp et al. 2009).

There are a number of assumptions associated with this approach. First, it is assumed that substances in the overall assessment group have the same mode of action and mechanism of action; in other words, they have similar adverse outcome pathways and will bind or interact with the same receptor or interact with the same tissue. In the case of the phthalates, the substances all appear to have a narcosis mode of action in aquatic organisms, at least for acute effects; therefore, the mechanism of action is presumably a non-specific interaction with cell membranes causing membrane disruption. It is also assumed that most chronic effects resulting from exposure to phthalates is also due to narcosis.

Second, the approach assumes that there are no interactions between substances, so combined effects will be additive and not antagonistic or synergistic. No information in the literature has been found to suggest that a mixture of phthalates would have antagonistic or synergistic effects. Chen et al. (2014) looked at the acute toxicity to zebrafish embryos of six phthalates (DBP, BBP, DEHP, DnOP, DINP, and DIDP) both individually and in a mixture of equal volumes. They found that the mixture was more toxic than any of the six phthalates alone and showed additive toxicity.

Third, all individual toxicity data are assumed to refer to the same type of organism (e.g., all fish, all invertebrates, or all algae) and the same biological endpoint (e.g., all median lethal concentrations). This assumption would be addressed through the selection of toxicity data for calculation of the sum of toxic units.

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[10] Toxic Unit (TU) – A dimensionless figure calculated as the ratio between the exposure level (e.g. a PEC) and a given acute or chronic endpoint (e.g. $EC_{50}$ or NOEC). The toxic units for a mixture (TUm) are calculated as the sum of individual TUs.

There are several requirements that must be observed when selecting ecotoxicological endpoint values for calculating the sum of toxic units. First, toxicity data must be available for the same type of species (i.e., algae, invertebrates, or fish) for each substance in the assessment group. Concentration addition requires that different taxonomic groups not be mixed together in the same calculation (Backhaus and Faust 2012). Second, the same type of endpoint, effect level, and exposure duration must be used for all toxicity data included in the calculation. The preference is to use all $EC_x$ values, as these are regression-based, rather than endpoints based on hypothesis testing such as No Observed Effect Concentrations (NOECs) or Lowest Observed Effect Concentrations (LOECs). Kortenkamp et al. (2009) argue against the use of NOECs with concentration addition because they may vary in their level of effects (a NOEC is defined as not being statistically different from controls, but it does not actually represent a 0% effect level). Therefore, the use of NOECs is discouraged, as the toxicity data for each individual substance would not necessarily refer to the same effect level. For those substances that do not have any empirical toxicity data, we are proposing to consider the use of analogues, read-across or modelled (e.g., ECOSAR 2012; Kipka & Di Toro 2009) ecotoxicity data. It is also noted that toxicity values should be based on apical endpoints that have population-level effects (e.g., survival, growth or reproduction), rather than endpoints based on effects at the sub-cellular level. Where there are multiple reliable $EC_x$ values (as determined through robust study summary evaluations) available for the same taxonomic group (e.g., algae, invertebrates, fish) for a particular substance, it is proposed to use the lowest (most sensitive value) in the toxic unit summation.

Given the assumptions of similar mode of action and additive effects, any substance in the assessment group should theoretically be interchangeable with another and the overall toxicity will remain the same, as long as the total toxic units remain constant.

The Sum of Toxic Units (STU) for a group of substances is calculated using the following equation (derived from Sprague 1970):

$$STU = \sum_{i=1}^{n} TU_i = \sum_{i=1}^{n} \frac{PEC_i}{EC_{x,i}}$$

Where:

STU = summation of the individual toxic units to give the TU for the group of substances

*n* = total number of individual substances in the group

$PEC_i$ = predicted environmental concentration of substance *i*

$EC_{x,i}$ = the ecotoxicological endpoint of substance *i* (e.g., $EC_{50}$ for inhibition of algal growth)

$TU_i$ = Toxic Unit of substance *i* in the group (rescales the concentration of each component in terms of its individual toxic potency, which in the case of phthalates is a function of their bioavailability and bioaccumulation capacity)

So essentially, a toxic unit is calculated for each substance in the group by dividing its predicted environmental concentration by its effect concentration. These toxic units are then summed for all substances in the assessment group. Typically, an $EC_{50}$ is used as the effect concentration (i.e., *x* = 50%), but it is also possible to calculate the STU for any other effect level (e.g., $EC_{10}$). If STU = 1, this suggests that the group of substances will have the total effect *x*; and if STU is smaller or larger than 1, the group of substances is predicted to have a smaller or larger effect, respectively.

Backhaus and Faust (2012) propose calculating separate Sums of Toxic Units (STUs) for each of three taxonomic groups: algae, daphnids, and fish. In the original toxic unit summation method proposed by Sprague (1970), it was suggested that sums of toxic units be calculated on an individual species basis. Consideration by taxonomic group instead is a pragmatic approach for considering species variability, recognizing that toxicity for the exact same species may not be available for all substances under consideration. STUs may also be calculated for more than one type of exposure scenario (e.g., using PECs for different sectors or exposure scenarios). The combination of taxonomic group and exposure scenario that is found to be most sensitive to the group of substances (i.e., the highest calculated STU) after application of an appropriate assessment factor, is selected. If the ecotoxicological endpoints used are acute (e.g., 96-hour $LC_{50}$s for fish) then it is proposed to use an assessment factor of 10 to extrapolate from short-term to long-term exposure. This is the same factor that would be used by Environment Canada in the assessment of a single substance. Given that three taxonomic groups are being considered, it is proposed that an extrapolation for inter-species variability is not needed. Therefore, if the ecotoxicological endpoints used are chronic (e.g., 28-day NOECs for invertebrates), it is proposed to use an assessment factor of 1. The resulting value is the risk quotient for the chemical group ($RQ_{STU}$), as described in the following equation:

$$RQ_{STU} = max\left(STU_{algae} \times AF, STU_{daphnid} \times AF, STU_{fish} \times AF\right)$$

$$= max\left[\sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,algae}} \times AF, \sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,daphnid}} \times AF, \sum_{i=1}^{n} \frac{PEC_i}{ECx_{i,fish}} \times AF\right]$$

Where:

$RQ_{STU}$ = risk quotient based on the sums of toxic units for various taxonomic groups

STU = sum of toxic units, for a particular taxonomic group

*n* = total number of individual substances in the assessment group

$PEC_i$ = predicted environmental concentration of substance *i* in the mixture

$ECx_i$ = the ecotoxicological endpoint (e.g., $EC_{50}$ or $LC_{50}$) for substance *i* in the mixture, for a particular taxonomic group

AF = Assessment Factor

In other words, for each substance in the cumulative assessment, a toxic unit is calculated for algae by dividing the predicted environmental concentration by the lowest effect concentration for algae, and these toxic units for all substances are added together to give a sum of toxic units for algae. This step is conducted simultaneously for invertebrates and fish to calculate toxic units for each of these taxonomic groups. The highest of these sums for the three taxonomic groups is selected and multiplied by an assessment factor to give the risk quotient based on the sums of toxic units ($RQ_{STU}$).

If the resulting $RQ_{STU}$ is lower than one, this suggests that the combined effects of the substances are unlikely to have an adverse effect on the environment. However, if the $RQ_{STU}$ is approaching or greater than one, then further consideration of the data, assumptions, and lines of evidence is needed to determine if there is a potential for risk to the ecosystem due to the combined effects of the chemicals. At this point, consideration should be given to the main sources of uncertainty in the assessment and whether any further refinements would be appropriate.

Conceptually, the main difference of this method from the PEC/PNEC method is the order in which the toxicity of the individual substances and the combined group of substances are estimated (Backhaus and Faust 2012b). With the $RQ_{PEC/PNEC}$, the toxicity of the individual substances to the aquatic ecosystem as a whole is determined first (through the calculation of PNECs), and then the toxicity of the combined group of substances is assessed (by summing the individual PEC/PNEC values). In calculating the $RQ_{STU}$, the toxicity of the combined group of substances is estimated first for each taxonomic group separately by summing the individual PEC/ECx values. Then the risk of the combined group of substances for the aquatic ecosystem as a whole is assessed using the standard approach for a single chemical, by selecting the most sensitive taxonomic group.

A limitation of the toxic unit summation method, similar to the PEC/PNEC method, is that phthalates that do not cause adverse effects at their limit of water solubility (such as the longer-chain phthalates), would need to be excluded from the calculation. This could potentially result in an underestimation of the cumulative ecological risk posed by phthalates.

### 5.3.3 Sum of Internal Toxic Units

The third Tier 1 approach considered is the Sum of Internal Toxic Units method. This approach is also based on concentration addition and assumes a common mode of

action among substances, but rather than summing toxic units based on external (i.e., water) exposure concentrations of substances, it sums the internal toxic units (i.e., based on concentrations in the tissues of the organism).

This is also referred to as a critical body residue approach. A Critical Body Residue (CBR) is the internal concentration of a chemical within an aquatic organism that corresponds to a particular measure of toxicity. For chemicals with the same mode of action, CBRs are expected to be relatively constant. McCarty and Mackay (1993) determined that CBRs associated with acutely lethal baseline neutral narcosis in small aquatic organisms typically range from about 2 to 8 mmol/kg, while those for chronic exposures range from 0.2 to 0.8 mmol/kg.

The advantage of this approach is that it takes into account the ability of the substance to be absorbed and delivered to a site of toxic action within the organism. This may be particularly relevant for the longer-chain phthalates, which have very low water solubility. Several papers have been published on summing critical body residues to look at cumulative risk (Dyer et al. 2000; Dyer et al. 2010; Escher et al. 2010).

The Sum of Internal Toxic Units (ITU) for a group of substances is calculated using the following equation (derived from Dyer et al. 2010):

$$ITU_{mix} = \sum_{i=1}^{n} ITU_i = \sum_{i=1}^{n} \frac{IC_i}{IEC_{x,i}} = \sum_{i=1}^{n} \frac{PEC_i \times BAF_i}{CBR}$$

Where:

$ITU_{mix}$ = summation of the individual internal toxic units to give the internal toxic unit for the group of substances
$ITU_i$ = internal Toxic Unit of the *i* substance in the group
n = total number of individual substances in the group
$IC_i$ = internal concentration of substance *i* in the group
$IEC_{x,i}$ = internal effect concentration of the substance *i* in the group
$PEC_i$ = predicted environmental concentration of substance *i* in the group (or could also be a measured environmental concentration)
$BAF_i$ = bioaccumulation factor (or bioconcentration factor)
CBR = critical body residue for chronic narcosis

In other words, for each substance in the assessment group, an internal toxic unit is calculated by dividing the internal concentration by the internal effect concentration. These toxic units are added together to give a sum of internal toxic units for the group of substances.

The internal concentration can be estimated by multiplying the concentration in the water (PEC, either predicted or measured) by the bioaccumulation factor for that substance (or the bioconcentration factor, if a BAF is not available).

The internal effect concentration is the critical body residue associated with baseline neutral narcosis and would be the same for all substances in the group. For the CRA of phthalates, the lower ends of the CBR ranges proposed for baseline narcotics by McCarty and Mackay (1993) would be used, i.e., 2 mmol/kg for acute lethality and 0.2 mmol/kg for chronic toxicity.

If the resulting $ITU_m$ is less than 1, this suggests that the combined effects of the substances in the group are unlikely to have an adverse effect. However, if the $ITU_m$ is approaching or greater than 1, then further consideration of the data, assumptions, and lines of evidence is needed to determine if there is a potential for risk to the ecosystem due to the combined effects of the chemical group.

## 5.4 Proposed approach for cumulative ecological risk assessment of phthalates

In considering the three methods described for Tier 1 assessment of cumulative ecological risk, it is proposed to use the Sum of Internal Toxic Units method. This is the only approach of the three that can accommodate the long-chain phthalates, given their lack of observed toxic effects at concentrations up to their water solubility limit. Inclusion of long-chain phthalates in the CRA is desirable because, although they are not particularly toxic, they are the phthalates that are present in Canadian commerce at the highest quantities.

Most of the data available for these substances focus on aquatic systems. Although many of the phthalates are expected to partition to sediments and may be found in soil as well (e.g., due to land application of biosolids containing phthalates), considering the very limited data available for these compartments, sediment and soil will not be considered in this approach. The minimal data that are available also indicate that there are unlikely to be concerns with phthalates in these media. The available toxicity data for sediment- and soil-dwelling organisms indicate that they are not particularly sensitive to individual phthalates, with no effects typically seen up to 1000 mg/kg or higher. In a study that measured concentrations of five phthalates in biosolids from several wastewater treatment systems in the Vancouver area, it was concluded that concentrations (all ≤ 11 mg/kg) were sufficiently low that there was no potential of exceeding the provincial soil quality standards for these phthalates, regardless of the amount of biosolids applied to soil (Bright and Healey 2003). Similarly, a review paper that evaluated several classes of substances in biosolids and their potential to cause adverse effects through land application of biosolids ranked phthalates as a low priority contaminant for research and monitoring in biosolids (Clarke and Smith 2011).

### 5.4.1 Selection of Substances

For the purposes of the phthalates assessment, it is proposed to consider the 28 phthalates described in Tables 1-1 to 1-3 as potential components in the cumulative ecological risk assessment of phthalates. It is recognized that this does not represent an assessment of the substance class, as there are several other phthalates that are known to be in commerce in Canada. However, it is assumed that this approach should give an indication of whether phthalates in the Canadian environment are likely to pose a concern. If the assessment based on these 28 phthalates indicates a risk quotient that is approaching 1, then further work could be considered to determine whether inclusion of other phthalates in the assessment group might result in a potential risk.

From the 28 phthalates in Tables 1-1 to 1-3, the list for inclusion in a cumulative assessment may be further pared down based on the potential for exposure and co-occurrence. There should be some evidence of presence in Canadian commerce, presence in environmental media in Canada, and evidence of the potential for co-occurrence of these phthalates. This information was described above in Section 5.2.2. A summary of these considerations for each of the 28 phthalates is provided in Table 5-2.

**Table 5-2 Exposure lines of evidence for inclusion of phthalate substances in ecological cumulative risk assessment**

| Substance | Manufacture, use, import in Canada[1] | Presence in environmental media in Canada[2] | Evidence of co-occurrence[3] | Inclusion in CRA |
|---|---|---|---|---|
| DMP | Yes | Yes | Yes | Yes |
| DEP | Yes | Yes | Yes | Yes |
| DPrP | No | NA | NA | TBD |
| DIBP | Yes | Yes | Yes | Yes |
| CHIBP | No | NA | NA | TBD |
| BCHP | No | NA | NA | TBD |
| DBP | Yes | Yes | Yes | Yes |
| BBP | Yes | Yes | Yes | Yes |
| DCHP | Yes | NA | NA | TBD |
| DMCHP | No | NA | NA | TBD |
| DIHepP | Yes | Yes | Yes | Yes |
| DIOP | Yes | NA | NA | TBD |
| BIOP | No | NA | NA | TBD |
| DEHP | Yes | Yes | Yes | Yes |
| DnHP | No | NA | NA | TBD |
| 79P | Yes | NA | NA | TBD |
| DINP1,2 | Yes | Yes | Yes | Yes |
| B79P | Yes | NA | NA | TBD |

| | | | | |
|---|---|---|---|---|
| B84P | Yes | NA | NA | TBD |
| DBzP | No | NA | NA | TBD |
| 610P | Yes | NA | NA | TBD |
| DIDP | Yes | Yes | Yes | Yes |
| DnOP | Yes | Yes | Yes | Yes |
| D911P | Yes | NA | NA | TBD |
| DUP | Yes | NA | NA | TBD |
| D911P-2 | Yes | NA | NA | TBD |
| DTDP | Yes | NA | NA | TBD |
| DIUP | Yes | NA | NA | TBD |

CRA: cumulative risk assessment; NA: data not available; TBD: to be determined
[1] As determined through S.71 survey results for the reporting year 2012 (Environment Canada 2014)
[2] Detection in monitoring studies of Canadian surface waters, sediment, and various aquatic biota
[3] Detection of the phthalate in Canadian environmental samples with other phthalates on this list

Of the 28 phthalates under consideration, results from the S.71 survey (Environment Canada 2014) indicate that 21 of these substances were in commerce in Canada for the year 2012, while seven substances do not appear to be in commerce in Canada at quantities above the reporting thresholds (i.e., manufacture or import of greater than 100 kg, or use of greater than 1000 kg, at a concentration equal to or above 0.001% by weight). It is expected that substances that were not reported under S.71 would have little to no contribution towards cumulative phthalate exposure. However, these substances would not automatically be excluded from the CRA, as they could still be in commerce at very low quantities, or could migrate to the environment from products that used the substances in the past. Their potential contribution to the CRA may be further informed by the analysis of Canadian environmental samples that is currently underway.

Studies that have examined Canadian surface water samples for phthalates have involved analyses for 11 of the phthalates, and all 11 of these substances have been detected in at least some samples (see references cited in section 5.2.2). There have been no efforts to date to monitor for the other 17 substances, so it is unknown whether they are present in Canadian waters or not. Again, a sampling campaign is currently underway to analyze for all 28 phthalates in environmental media at various Canadian locations. These data will be considered in the CRA and may give a better understanding of which substances are likely co-occurring.

Those substances that are not found to be co-occurring in the Canadian environment would have a contribution of zero to the cumulative ecological risk calculation.

### 5.4.2 Selection of Exposure Concentrations

In determining the predicted environmental concentrations (PECs) to include in the calculation of cumulative risk, there are several potential options. The different types of exposure estimates vary in complexity and in the required input data. Options include:

- Determine modelled PECs for several different generic scenarios (e.g., for different sectors), and calculate risk quotients for each separately
- Determine modelled PECs for specific local geographic location(s) that may have inputs from various sectors/sources (e.g., a wastewater treatment system discharge point), and calculate risk quotients for each separately
- Determine measured environmental concentrations for specific geographic location(s) based on available monitoring data

For risk assessments conducted under the European Water Framework Directive, it has been noted that combined exposures to multiple chemicals are determined through site-specific measurements and consideration of individual water bodies on a case-by-case basis (SCCS, SCHER, SCENIHR 2011).

It is proposed that for a first-tier assessment, the highest aquatic PEC available for each substance should be used, regardless of whether these are based on different scenarios, different sectors, or different locations. This simple and conservative approach would give an indication of whether there could be a potential for concern or not, and whether it would be worth investing further effort to refine the assessment. It is important with this approach to ensure that all potential sources of the phthalate have been considered and that we are confident that the selected PEC represents the highest concentrations that would be expected. If a potential for concern is indicated, then several $ITU_{mix}$ values could be calculated for individual sites, using measured environmental concentrations, to further evaluate the potential for concern at locations where higher phthalate concentrations would be expected.

The development of risk quotients based on cumulative effects from specific industrial facilities and/or commercial activities is not practical and not recommended. In many cases, phthalate uses can be quite specialized, so in most cases a particular facility or activity uses only one or two phthalate substances. Even where a facility or activity may have involvement with a larger number of phthalates, the use of batch processes in many cases would limit the potential for co-occurrence. It is also unlikely that releases from a particular sector to the environment would be occurring in isolation of other sources of phthalates. Information provided on Canadian facilities that manufacture or use phthalates indicates that all liquid effluents from those facilities are released to municipal sewers (Environment Canada 2014). Any given wastewater treatment system may also receive phthalates from facilities associated with a different industrial sector and would likely receive phthalates from non-industrial sources, such as consumer use of personal care products, so it would be unlikely to have combined exposures to multiple phthalates in the environment that originate from just a single facility or sector.

### 5.4.3 Selection of Bioaccumulation Factors

For the ITU method, internal exposures are estimated using a bioaccumulation factor (BAF) or bioconcentration factor (BCF). It is proposed that BAF values be used preferentially where available, to account for potential exposure via the diet in higher

organisms. BAFs (or BCFs) based on reliable experimental data (as evaluated using robust study summaries) would be used preferentially, with modelled BAFs used for substances that are lacking experimental data. Ideally, internal concentrations would be calculated separately for each taxonomic group (i.e., algae, invertebrates and fish). However, for many of the phthalates, bioaccumulation factors are only available for fish. For those few phthalates that do have BAF or BCF data available for algae and/or invertebrates as well, there are no obvious differences in the range of values from those of fish. Uptake of phthalates may be greater for fish and invertebrates due to exposure via the diet as well as through water, but on the other hand, transformation and elimination rates are also likely higher in the higher trophic levels. Therefore, for consistency, it is proposed to use the highest reliable fish BAF for each substance to calculate internal concentrations.

### 5.4.4 Reaching a Conclusion on the Cumulative Ecological Risk of Certain Phthalates

Once PECs and BAFs have been selected for each of the substances, a risk quotient based on concentration addition can be calculated using the Sum of Internal Toxic Units method. If this calculation indicates no concern for the environment (i.e., the risk quotient for the group of substances is well below 1), then it would be concluded that the phthalates under consideration are not posing a risk to the environment through their combined effects. However, if the $ITU_{mix}$ is approaching or greater than 1, then potential options for Tier 2 refinement would be considered.

There are several refinements at Tier 2 that could be considered, but those that would have the most impact are likely to be refinements of exposure estimates. These could include revisiting any conservative assumptions that were used in predicting exposures and seeing if more realistic assumptions can be made.

If concern is still indicated, and further refinement is required, then it is proposed to use PECs based on measured environmental concentrations for each substance in ambient Canadian surface waters, or in wastewater treatment system effluents (to which a dilution factor would be applied). PECs would be determined by taking the $95^{th}$ percentile of the available measured concentrations for a particular substance from reliable studies. Monitoring studies would be evaluated to ensure that appropriate sampling and analytical methods were used and that precautions were taken to minimize potential sample contamination from other sources. Contamination of analytical samples is a major problem with phthalate analyses, with potential sources for contamination at each stage of the process, including sampling, sample preparation, and chromatographic analysis (David et al. 2003). Ideally, measured concentrations would be considered for several representative locations in Canada, including those where higher concentrations of phthalates would be expected. A sampling campaign is currently being undertaken by Environment Canada researchers to obtain measured environmental concentrations of the 28 phthalates of interest at various targeted locations in Canada. Sampling locations have been selected to represent areas where

the greatest potential for industrial releases is expected. In addition, effluents from wastewater treatment systems that primarily receive inputs from domestic water use and landfill leachate (i.e., no industrial inputs) will also be analyzed to give an indication of potential environmental concentrations of phthalates resulting through releases from consumer products.

Another possible refinement is to remove substances that have low hazard and low exposure from the calculation of cumulative risk, if it is suspected that their inclusion may be exaggerating risks due to compounding of conservatism in exposure estimates. A second tier approach could also involve the use of probabilistic methods for estimating potential exposure levels using the full distribution of available monitoring data.

Following any Tier 2 refinements, if a potential concern is still indicated, then it would be concluded that the phthalates under consideration may pose a hazard to the environment through their combined effects (even if some of these substances do not pose a concern individually).

Cumulative assessment conclusions for the phthalates could be based on a number of lines of evidence and may consist of a combination of conclusions on individual substances and/or groups of phthalates.

If it is concluded that a group of phthalates, or any individual phthalates, may pose a risk to the environment, then further consideration would need to be given to what risk management measures should be taken to prevent or reduce releases. The results of the CRA will provide an indication of which phthalates are having the greatest contribution to the cumulative risk, which could help in focusing actions on the particular phthalates of greatest concern. It may also give an indication of how changes in use quantities or patterns might affect cumulative risk, to prevent the substitution of substances with equally hazardous alternative phthalates. Any proposed course of action would be published for public review and comment.

## 5.5 Uncertainties of the Ecological Approach

A fairly comprehensive list of potential uncertainties that may be expected in the risk assessment of a mixture or combination of multiple chemicals is provided by the three scientific committees of the European Commission (SCCS, SCHER, SCENIHR 2011). Specific examples of uncertainty that are applicable to this proposed approach for the phthalates assessment are described below.

In this approach, which is based on additivity of combined effects, we are assuming that all adverse effects caused by phthalates are due to narcosis and that this mode of action is the same for all types of organisms (algae, invertebrates, fish). However, it is known that certain phthalates can be estrogenic or can enhance estrogenic activity.

Therefore, it is possible that some of the reported toxicity data could be a result of modes of action other than narcosis and, therefore, may not be strictly additive.

The availability and adequacy of the database on bioaccumulation poses an uncertainty. Of the phthalates that have BAF and/or BCF values, in many cases these are available only for a few organisms and often not for each of the main taxonomic groups of fish, invertebrates and algae. Therefore, the BAF or BCF values may not reflect the full range of bioaccumulation potentials across taxonomic groups. Furthermore, for certain phthalates, empirical bioaccumulation data are not available; it has therefore been proposed in this approach to use read-across or modelled data for these substances. This introduces some uncertainty, as the read-across or modelled toxicity data may either over- or under-estimate the bioaccumulation potential of the phthalate of interest. Appendix C provides details and justification on analogues that are proposed for read-across of ecological endpoints.

Exposure scenarios being developed for these substances in many cases are based on default assumptions. In most cases, these assumptions are thought to be conservative, but it is not known how closely these compare to actual conditions. In cases where measured environmental concentrations are used, rather than predicted levels, there could be uncertainty as to whether the sampling data is representative of levels at other locations, or whether it is indicative of a realistic worst-case scenario.

The extent to which co-exposure of organisms to the different components in the assessment group is occurring is somewhat uncertain. This can be affected by many factors, such as persistence of the phthalates (which varies with alkyl chain length), and whether exposures are episodic or continuous (which varies with different uses of phthalates). This uncertainty would best be addressed through sampling at various locations to determine measured environmental concentrations for all phthalates in the assessment group. A sampling campaign is currently being conducted by Environment Canada researchers and should help to address this uncertainty.

In addition, the proposed approach focuses on the 28 phthalate diesters that were surveyed under Section 71 (i.e., 14 phthalates within the grouping, and 14 additional phthalates under consideration to inform the CRA). There are several other phthalates that are on Canada's DSL and that are known to be in commerce in Canada but that did not meet the categorization criteria. These other phthalates, which are not being considered in this approach, could co-occur with the phthalates that are currently under assessment and could also be contributing to cumulative effects in the environment. The relative contributions of these other phthalates present an uncertainty. By not including these other phthalates, the potential for harm to aquatic organisms could be underestimated.

It is also known that phthalate monoesters, as well as phthalic acid and alcohols, are produced as transformation products through both biotic and abiotic degradation of the diesters (Hashizume et al. 2002; Amir et al. 2005; Nalli et al. 2006). Various studies

indicate that the monoesters have relatively short half-lives (e.g., Scholz 2003). However, with continuous releases of phthalates, aquatic organisms may still experience chronic exposures to the transformation products. In a study that monitored phthalates in a Japanese river, it was observed that mono-ester phthalate concentrations of mono-n-butyl phthalate and mono-(2-ethylhexyl) phthalate were typically only slightly lower than concentrations of the corresponding diesters, and mono-methyl phthalate concentrations were typically higher than DMP concentrations (Suzuki et al. 2001). For three other diester phthalates that were detected in the river water (DEP, DIBP, BBP), the corresponding monoesters were not detected (Suzuki et al. 2001). Studies with various short-chain and medium-chain monoesters and phthalic acid have demonstrated that these degradation products are also considerably less toxic to aquatic organisms than the corresponding diesters (Scholz 2003; Jonsson and Baun 2003; Gartshore et al. 2003). In the case of the long-chain phthalates, while no aquatic effects tend to be seen with the diesters due to their very low water solubility, acute toxicity is observed for the long-chain monoesters in the mg/L range due to their higher water solubility and greater bioavailability (Scholz 2003; Staples et al. 2011). It is not known whether the monoester phthalates may also be contributing significantly to the overall combined effects of phthalates in aquatic environments. At this point, it is not proposed to quantitatively include additive effects of monoester phthalates that may be present in the water. However, this uncertainty may be considered as another line of evidence in the overall assessment of the cumulative ecological risk posed by phthalates. Additive effects of monoesters that are produced internally within an organism through biotransformation after uptake of the diester phthalates would implicitly be addressed through the Sum of Internal Toxic Units Method.

It should also be noted that this proposed approach only assesses the risk posed by a combination of phthalates, in isolation of other substances. Realistically though, numerous other types of chemicals, also acting through a narcotic mode of action, would typically be found in the environment and, therefore, could be exerting effects additively with phthalates. Consideration of the potential for cumulative effects due to complex mixtures consisting of phthalates and other types of substances is beyond the scope of this assessment.

# 6 Summary

## 6.1 Human Health Assessment

Phthalates are able to affect biological pathways in rats, leading to common adverse effects of the rat phthalate syndrome. The development of the proposed phthalate subgroups is derived from a SAR analysis using studies related to mechanistic events for phthalate-induced androgen insufficiency during male reproductive development in the rat and is proposed to be used to facilitate addressing data gaps.

Health Canada proposes that cumulative risk will be evaluated under the assumption that phthalates act via dose addition and that the risk will be estimated through the Hazard Index Approach with consideration of Relative Potency Factor, if the data

allows. The international CRAs to date support the application of the Hazard Index Approach and the use of an RPF, as illustrated in the recent CHAP report (US CPSC 2014). The WHO/IPCS Framework for Risk Assessment of Combined Exposures to Multiple Chemicals (Meek et al. 2001) will be observed for each hazard and exposure with refinement to higher tiers of assessment as required and practicable. Based on the information available at this time, a Tier 1 hazard characterization is achievable with refinements of the PODs through the derivation of BMD/BMDLs where the data allows. The exposure data that is currently available will allow for a Tier 2 exposure characterization with a combination of both deterministic and probabilistic estimates in addition to the incorporation of biomonitoring data, which will be estimated in parallel.

The key assumptions of the CRA are that the substances act via dose addition and that the substances act through a common mode of action with biological pathways leading to common effects of the RPS. Data gaps will be filled using quantitative read-across for the developmental endpoint based on the draft approach developed by Health Canada (2015). Those phthalates exhibiting effects within the RPS and found to be present or reasonably present in Canadian commerce or that show evidence of co-occurrence or co-exposure are proposed for inclusion in the CRA. Exposure estimates may not be limited to only those substances for which biomonitoring data is available, and only short-term, sub-chronic and chronic exposures will be assessed in the CRA. The uncertainties of the assessment include the determination of the most representative effect(s) within the RPS for derivation of the PODs due to the varying potency exhibited across effects. Exposure estimates have variability and uncertainty within the algorithms used to estimate exposure, which is compounded across substances in a cumulative context and may lead to overestimates of exposure. Moving forward, Health Canada will proceed with a tiered approach to the CRA of phthalates, refining where necessary and possible and using the information available.

## 6.2 Ecological Assessment

In aquatic organisms, phthalates with low or medium chain lengths can cause adverse effects through a non-specific narcotic mode of action. Long-chain phthalates are also thought to act through narcosis, but adverse effects in aquatic organisms are typically not seen at concentrations up to their water solubility limits. Given the common mode of action and evidence of co-occurrence in Canadian surface waters for at least some of the phthalates, it is proposed to consider the cumulative ecological risk of phthalates from all three subgroups collectively using a Sum of Internal Toxic Units method. This method, which is based on critical body residues, does not require the use of toxicity data based on external concentrations of phthalates in water and, therefore, can accommodate consideration of long-chain phthalates.

Collection and analysis of environmental samples from across Canada are currently being conducted for the 28 phthalates under consideration. These data will assist in confirming presence and co-occurrence of individual phthalates, as well as providing estimates of exposure levels.

Read-across using appropriate analogues (as described in Appendix C) will be used to fill data gaps where possible, and modelling will be used to address remaining data gaps as needed. Phthalates that are found to be present in the Canadian environment and co-occurring, as determined through Environment Canada sampling campaigns, would likely be included in the CRA. Uncertainties with the approach include assumptions used in predicting exposure levels in Canadian waters and whether these predictions are representative of all locations across the country. A lack of empirical data on bioaccumulation for some phthalates also presents some uncertainty in the estimates of internal exposure concentrations. Limiting the scope of the CRA to these 28 phthalates may also be underestimating the cumulative risk, as it is known that there are other phthalates on the DSL, and concentrations of monoester transformation products in the water column are not considered.

If the Tier 1 assessment indicates potential risk, further refinements may be made to the cumulative ecological risk assessment, data allowing.

## 6.3 Next Steps

Industry and other interested stakeholders are invited to submit comments on the content of this Proposed Approach for Cumulative Risk Assessment of Certain Phthalates. Comments received will be taken into consideration when finalizing the approach for the cumulative assessment of the Phthalate Substance Grouping. A draft screening assessment that incorporates consideration of cumulative risk, and which presents proposed conclusions on whether these substances meet the criteria under section 64 of CEPA 1999, is targeted for publication in 2016 for public comment.

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# 8 Appendices

## Appendix A. Summary of existing cumulative risk assessments of phthalates

| CRA Element | Australia | Danish EPA | CHAP |
|---|---|---|---|

| CRA Element | Australia | Danish EPA | CHAP |
|---|---|---|---|
| Substances Considered | DINP, DEHP, DEP<br>DBP, DINP, DEHP, DEP<br>DMP, DINP, DEP, DEHP, DBP<br>DMEP, DINP, DEP, DEHP | DEHP, BBP, DBP, DIBP | DBP, BBP, DINP, DIBP, DEHP |
| Assumptions and Approach Used | WHO/IPCS (Tier 1);<br>Dose Addition; Similar mode of action for each endpoint; Margin of Exposure method | Dose Addition; Risk Characteriza-tion Ratio (or Hazard Index method) | Dose Addition; Hazard Index method;<br>Case 1: Potency Estimates for Antiandrogenicity values from Kortenkamp and Faust (2010);<br>Case 2: Potency Estimates for Antiandrogenicity values from Hannas et al. 2011a; 2011b;<br>Case 3: Potency Estimates for Antiandrogenicity values from *de novo* analysis of individual phthalates by CHAP |
| Endpoints considered | Systemic, Fertility-Related, Develop-mental | Reproductive/ Develop-mental | Case 1: Antiandrogenicity *in vivo* data;<br>Case 2: Testosterone-modulated effects;<br>Case 3: Reproductive and developmental endpoints (specifically rat phthalate syndrome) |
| Exposures | 6-month-old infants<br><br>a) Co-occurance of phthalates in toys and childcare | 2-year-olds; 6/7-year-olds; adults<br><br>a) Co-occurance: | Biomonitoring data used to calculate daily intakes<br><br>Pregnant women |

| CRA Element | Australia | Danish EPA | CHAP |
|---|---|---|---|
| | articles<br><br>b) Co-Occurance of phthalates in toys and childcare articles and DEP in lotions for children | articles intended for use indoors and<br>articles that may come into direct contact with the skin or mucous membranes | Infants (2–36 months) |
| Outcome | Margins of exposure are adequate | Risk Characteriza-tion Ratio > 1 for 2 years of age; 6/7 years of age for high median exposures; and all age groups for worst case (95$^{th}$ or max); Proposal for restriction, subsequently withdrawn | Hazard Index exceeds 1.0 in about 10% of pregnant women in the US population for Case 1, 2, and 3<br><br>Hazard Index exceeds 1.0 in about 5% of infants for Case 1, 2, and 3 |

## Appendix B. Overview of cumulative risk assessment of phthalates by the Australian Department of Health

| Criteria | DINP | DBP | DMP | DMEP |
|---|---|---|---|---|
| Date | September 2012 | November 2013 | January 2014 | May 2014 |
| Chemicals in Cumulative Risk Assessment | DINP and DEHP, DEP | DBP and DINP, DEHP, DEP | DMP and DINP, DEHP, DBP, DEP | DMEP and DINP, DEHP, DEP |
| Method | Margin of Exposure Tier 1 | Margin of Exposure Tier 1 | Margin of Exposure Tier 1 | Margin of Exposure Tier 1 |
| Assumptions | Dose Addition | Dose Addition | Dose Addition | Dose Addition |
| Toxicity Endpoints | Systemic; Developmental; Fertility-related | Developmental; Fertility-related | Developmental; Fertility-related | Developmental; Fertility-related |
| Age groups | 6-month-old children | 6-month-old children | 6-month-old children | 6-month-old children |

| | | | | |
|---|---|---|---|---|
| Routes of Exposure | Oral: toys and childcare articles<br>Dermal: toys and childcare articles, cosmetics | Oral: toys and childcare articles<br>Dermal: toys and childcare articles, cosmetics | Oral: toys and childcare articles<br>Dermal: toys and childcare articles, cosmetics | Oral: toys and childcare articles<br>Dermal: toys and childcare articles, cosmetics |
| Exposure Scenarios | a) 1 plasticizer in toys and 1 in cosmetics<br>b) mix of 2 plasticizers in toys<br>c) mix of 2 plasticizers in toys and 1 in cosmetics | a) mix of 3 plasticizers in toys<br>b) mix of 3 plasticizers in toys and 1 in cosmetics | a) mix of 2 plasticizers in toys and 1 in cosmetics<br>b) mix of 3 plasticizers in toys and 1 in cosmetics<br>c) mix of 3 plasticizers in toys and 1 in cosmetics | a) mix of 2 plasticizers in toys and 1 in cosmetics<br>b) mix of 3 plasticizers in toys and 1 in cosmetics |
| Outcome | Adequate safety margin | Adequate safety margin | Adequate safety margin | Adequate safety margin |

a. Note, however, that 0.75% DEP and above is of concern. The maximum allowable concentration of DEP in body lotions is 0.5% in Australia.

## Appendix C. Ecological Category and Read-Across Approach for Phthalates

For the Phthalate Substance Grouping, a chemical category approach has been used as an assessment method for considering closely related chemicals together as a group. A read-across approach has also been used for the Grouping, in which data from other similar chemicals are used to predict properties or endpoints for substances that are lacking data. Guidance on both the formation of chemical categories and the use of read-across data is provided in the OECD Guidance on Grouping of Chemicals (OECD 2014). In the OECD guidance, recommendations are made on elements to consider in justifying the formation of a category and the read-across approach to fill data gaps. Justification for the approaches used in the ecological portions of the SOS reports and CRA approach for the Phthalates Substance Grouping are provided below.

### Grouping and Subgroup Justification

The 28 substances under consideration in the Phthalates Substance Grouping are all diesters of 1,2-benzenedicarboxylic acid, with no other substitutions on the benzene ring. The substances differ in the substructures attached to the ester linkages, which may consist of one of three combinations: two dialkyl chains, which may be linear

and/or branched; one alkyl chain and one phenyl or benzyl group; or two cyclic (phenyl and/or benzyl) groups (Figure C-1). The Grouping includes discrete substances, isomeric mixtures, which consist of phthalate molecules with varying alkyl chain lengths and branching but with a defined distribution, as well as UVCBs (Unknown or Variable Composition, Complex Reaction Products or Biological Materials), which consist of phthalate molecules with varying chain lengths and branching, but the composition and distributions of the alkyl chains are variable. The number of carbons in the ester side groups of the 28 phthalates ranges from one to 14.

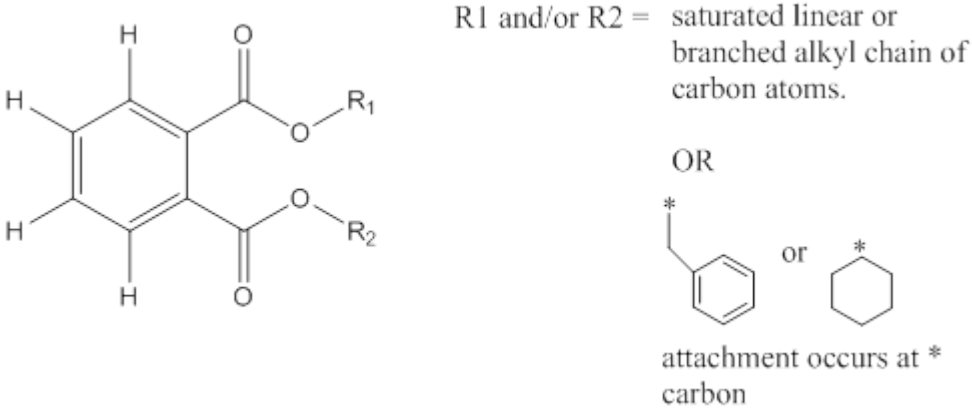



**Figure C-1. General structure of phthalates.**

Within the Phthalate Substance Grouping, the 28 substances have been divided into three subgroups based on their physical-chemical properties and described in terms of their alkyl side chain lengths, which correlate with these properties (see Table C-1).

The short-chain subgroup consists of phthalates with ester side chains containing one or two carbons, and molecular weights less than 225 g/mol. Log octanol-water partition coefficients (log $K_{ow}$) for substances in this subgroup are low (less than 3), and water solubility is moderate to high, at > 900 mg/L.

The medium-chain phthalates subgroup consists of substances that are characterized by ester side groups that mainly contain between three and seven carbons, and do not exceed nine carbons. Molecular weights of these substances range from 250 to 455 g/mol. The ester side groups, always in the *ortho*-position, occur in one of three side group combinations: as dialkyl phthalates, which are linear and/or branched alkyl chains; phenyl or benzyl phthalates that have both an alkyl chain and a cyclic group; or as dicyclic phthalates. Log $K_{ow}$ values for these substances are moderate to high, falling within the range of 3 to 8. Water solubility is low to moderate, spanning a wide range of approximately 0.003 to 108 mg/L.

The long-chain phthalates subgroup consists of phthalates with ester side chains that are primarily eight carbons or longer, with molecular weights ranging from 334 to 502 g/mol. Substances in this subgroup have high log $K_{ow}$ values (greater than 8), and low water solubility (less than 0.03 mg/L).

**Table C-1. Certain properties of substances in the three phthalates subgroups**

| **Subgroup** | **Log $K_{ow}$** | **Water Solubility (mg/L)** | **Molecular Weight (g/mol)** |
|---|---|---|---|
| Short-chain | < 3 | > 900 | < 225 |
| Medium-chain | 3 – 8 | 0.003 – 108 | 250 – 455 |
| Long-chain | > 8 | < 0.03 | 334 – 502 |

Tables C-2, C-3 and C-4 provide information on the substances in each of the short-chain, medium-chain and long-chain subgroups, respectively. More detailed information, including references, for the various physical-chemical properties are provided in the SOS reports for each subgroup. The main criterion for delineating the subgroups from an ecological perspective is the octanol-water partitioning coefficient (Log $K_{ow}$) (Figure C-2). Substances in the short-chain subgroup have log $K_{ow}$ values that are less than 3. Substances in the medium-chain subgroup have log $K_{ow}$ values that range from 3 to 8. And in the long-chain subgroup, substances have log $K_{ow}$ values greater than 8.

**Table C-2. Short-chain Phthalate Subgroup**

| Substance (CAS RN) | Substance Type and Branching Type | Ester Groups | # Carbons in Ester Groups | Molecular Weight (g/mol) | Log $K_{ow}$ | Water Solubility (mg/L) |
|---|---|---|---|---|---|---|
| DMP (131-11-3) | Discrete Linear | Methyl (x2) | 1 | 194.2 | 1.61 | 4000 |
| DEP (84-66-2) | Discrete Linear | Ethyl (x2) | 2 | 222.2 | 2.47 | 930 |

**Table C-3. Medium-chain Phthalate Subgroup**

| Substance (CAS RN) | Substance Type and Branching Type | Ester Groups | # Carbons in Ester Groups[a] | Molecular Weight (g/mol) | Log $K_{ow}$ | Water Solubility (mg/L) |
|---|---|---|---|---|---|---|
| DPrP (131-16-8) | Discrete Linear | Propyl (x2) | 3 | 250 | 3.27 | 108 |
| DIBP (84-69-5) | Discrete Branched | Isobutyl (x2) | 4 | 278.4 | 4.11 | 20.3 |
| CHIBP (5334-09-8) | Discrete Branched, Cyclic | Isobutyl, cyclo-hexyl | 4, (6) | 304.4 | 5.13 | 4.85 |
| BCHP (84-64-0) | Discrete Linear, Cyclic | n-butyl, cyclo-hexyl | 4, (6) | 304.4 | 5.22 | 3.67 |
| DBP (84-74-2) | Discrete Linear | n-butyl (x2) | 4 | 278 | 4.46 | 11.4 |
| BBP (85-68-7) | Discrete Linear, Benzyl | n-butyl, benzyl | 4, (7) | 312 | 4.91 | 2.69 |
| DCHP (84-61-7) | Discrete Cyclic | Cyclohexyl (x2) | (6) | 330.4 | 5.76 | 0.2 |
| DMCHP (27987-25-3) | Discrete Cyclic | Methyl cyclohexyl (x2) | (7) | 358.5 | 6.75 | 0.275 |
| DIHepP (71888-89-6) | Isomeric Mixture Branched | Isoheptyl (x2) | 6 – 8 | 362.5 | 6.15 | 0.017 |
| DIOP (27554-26-3) | Isomeric Mixture Branched | Dimethyl hexyl, methyl heptyl | 8 | 391 | 7.52 | 0.09 |
| BIOP (27215-22-1) | Isomeric Mixture Branched, Benzyl | Dimethyl hexyl; benzyl | 8, (7) | 368.5 | 6.71 | 0.1 |
| DEHP (117-81-7) | Discrete Branched | Ethyl hexyl (x2) | 8 | 391 | 7.14 | 0.003, 0.4 |
| DnHP (84-75-3) | Discrete Linear | n-hexyl (x2) | 6 | 334 | 6.82 | 0.03 |
| B79P (68515-40-2) | UVCB Linear and Branched, Benzyl | Linear and methyl branched heptyl | 7 – 9, (7) | 368.5 | 5.5 | 0.3 |

| Substance (CAS RN) | Substance Type and Branching Type | Ester Groups | # Carbons in Ester Groups[a] | Molecular Weight (g/mol) | Log $K_{ow}$ | Water Solubility (mg/L) |
|---|---|---|---|---|---|---|
| | | and nonyl, benzyl | | | | |
| B84P (16883-83-3) | Discrete Benzyl, Branched | Benzyl, Isooctyl-butyrate | (7), 12 | 454.6 | 6.76 | 0.81 |
| DBzP (523-31-9) | Discrete Benzyl | Benzyl (x2) | (7) | 346.4 | 5.09 | 0.51 |

[a] Carbon numbers listed within parentheses refer to cyclic groups.

**Table C-4. Long-chain Phthalate Subgroup**

| Substance (CAS RN) | Substance Type and Branching Type | Ester Groups | # Carbons in Ester Groups | Molecular Weight (g/mol) | Log $K_{ow}$ | Water Solubility (mg/L) |
|---|---|---|---|---|---|---|
| 79P (111381-89-6) | UVCB Linear and Branched | Heptyl and nonyl | 7 – 9 | 362 – 418 | 7.56 – 9.52 | 0.000017 – 0.0018 |
| DINP (68515-48-0; 28553-12-0) | Isomeric Mixture Branched | Branched Nonyls (x2) | 9 – 10 | 419 – 447 | 8.8 | 0.0006 |
| 610P (68648-93-1) | UVCB Linear | Mix of hexyl, octyl, decyl | 6, 8, 10 | 334 – 446 | 8.17 | 0.03 |
| DIDP (26761-40-0; 68515-49-1) | Isomeric Mixture Branched | Methyl branched heptyl, octyl and nonyl | 10 | 446 | 9.49 | 0.00017 |
| DnOP (117-84-0) | Discrete Linear | n-octyl (x2) | 8 | 391 | 8.10 | 0.00022 |
| D911P (68515-43-5) | UVCB Branched and Linear | Nonyl, decyl, undecyl | 9 – 11 | 418 – 475 | 8.3 | 0.00000016 – 0.000017 |
| DUP (3648-20- | Discrete Linear | Undecyl (x2) | 11 | 475 | 10.9 | 0.0000017 |

| Substance (CAS RN) | Substance Type and Branching Type | Ester Groups | # Carbons in Ester Groups | Molecular Weight (g/mol) | Log $K_{ow}$ | Water Solubility (mg/L) |
|---|---|---|---|---|---|---|
| 2) | | | | | | |
| D911P-2 (111381-91-0) | UVCB Linear | Nonyl, undecyl | 9 – 11 | 418 – 475 | 8.3 | 0.00000016 – 0.000017 |
| DIUP (85507-79-5) | UVCB Branched | Decyl, undecyl, dodecyl | 10 – 12 | 446 – 502 | 10.21 – 12.17 | $2.8 \times 10^{-8}$ – $3.0 \times 10^{-6}$ |
| DTDP (68515-47-9) | UVCB Branched | Undecyl, dodecyl, tridecyl, tetradecyl | 11 – 14 | 474 – 502 | 11.19 – 14.14 | $2.6 \times 10^{-10}$ – $3.3 \times 10^{-6}$ |

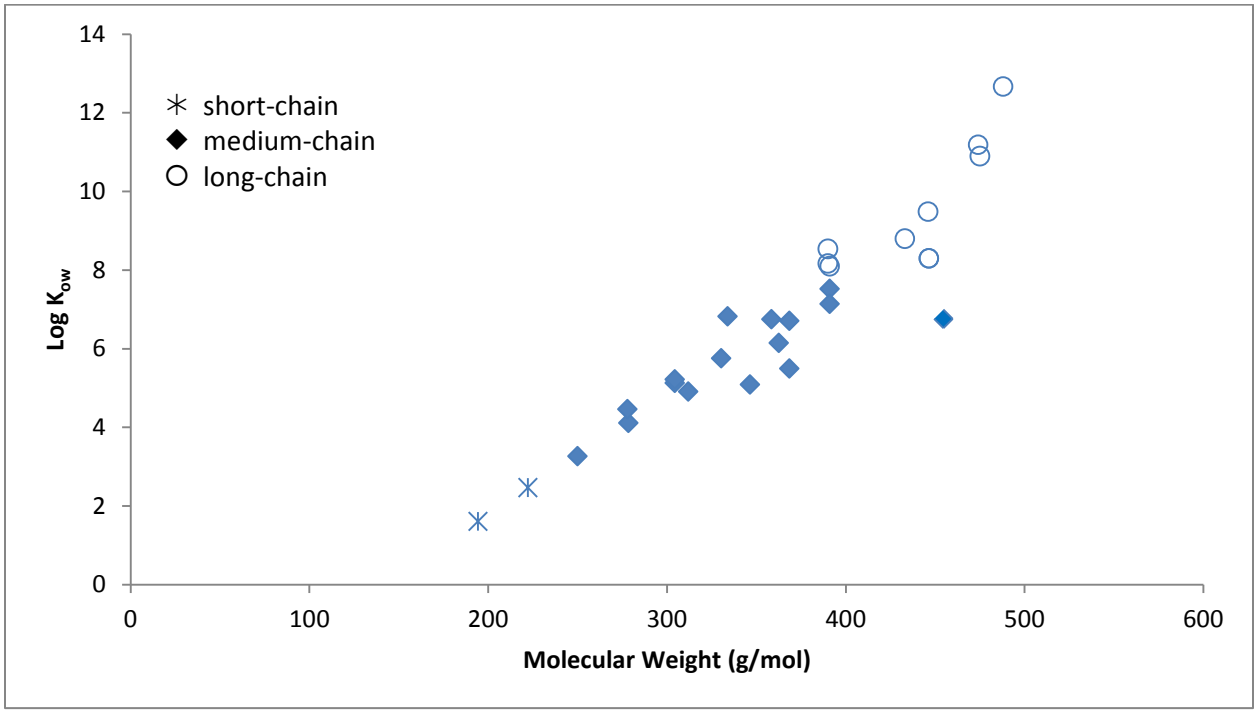



**Figure C-2. Distribution of Log $K_{ow}$ values across the Phthalate Substance Grouping**

Substances in the three subgroups are expected to show differences in their environmental fate and behaviour, including differences in bioavailability and ecotoxicity, due to these differences in log $K_{ow}$ ranges, as well as other physical-chemical properties, such as water solubility. This appears to be supported by both empirical and modelled data (see SOS reports for each subgroup). For example, with respect to aquatic ecotoxicity, the short-chain phthalates show acute median lethal effects ($LC_{50}$s) at concentrations in the low tens of mg/L; acute $LC_{50}$s for the medium-chain phthalates are typically in the tens to hundreds of µg/L, and the long-chain phthalates do not demonstrate acute toxicity to aquatic organisms at concentrations up to their water solubility limits.

**Analogue Approach Justification for Ecological Assessment**

Numerous substances in the Phthalate Substance Grouping have limited or no experimental data for key physical-chemical properties, fate, and ecotoxicological endpoints. Therefore, a read-across approach using analogue substances, as well as Quantitative Structure–Activity Relationships, i.e. (Q)SAR models, were used to fill the data gaps.

For the read-across approach, potential analogues were initially identified using the OECD QSAR Toolbox software (2012). The goal was to select substances that were both structurally and functionally similar to the phthalates being assessed. For a substance to be considered as a potential analogue, it needed to be a diester of 1,2-benzenedicarboxylic acid, with no other substitutions on the benzene ring (similar to all 28 phthalates considered in the grouping). A cut-off of 70% structural similarity, based on the Tanimoto Similarity Index (OECD QSAR Toolbox 2012), was also used as an initial cutoff point for identifying potential analogues. Further selection was based on the availability of data for the proposed analogues and the evaluation of similarity in other properties. The selected analogues were of similar molecular size and side groups, known to act through a similar mode of action — narcosis — and were characterized by comparable physical-chemical properties, particularly the water solubility and partition coefficients such as the $K_{ow}$, which influence the potential for environmental bioavailability. In many cases, data-rich substances within the same subgroup were used to read-across for similar substances with limited or no data.

Analogues identified for read-across to substances in each of the short-, medium-, and long-chain subgroups are described in Tables C-5, C-6, and C-7, respectively.

**Table C-5. Analogue identities for the short-chain phthalate subgroup**

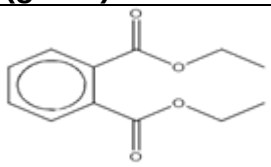
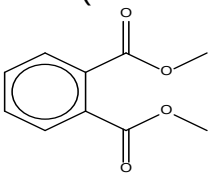
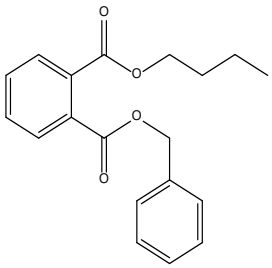
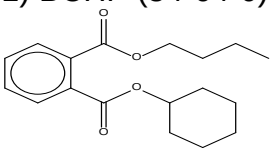
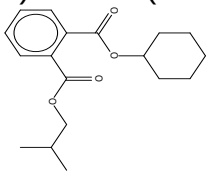
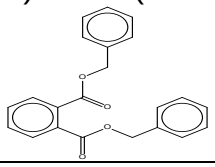
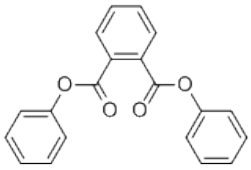
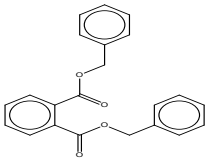
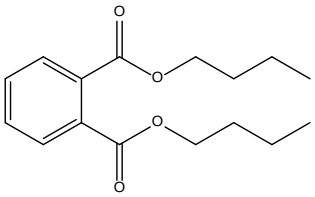
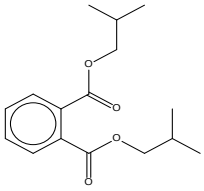
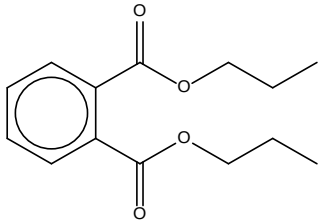
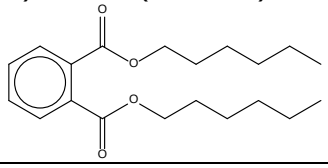
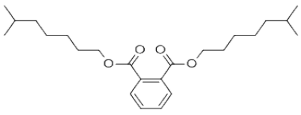
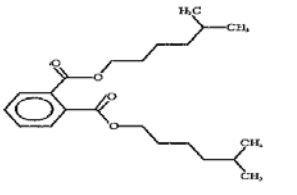
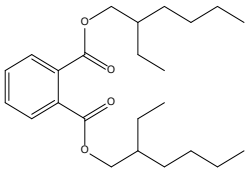
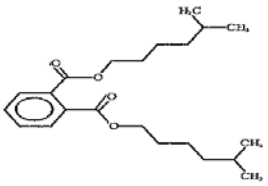
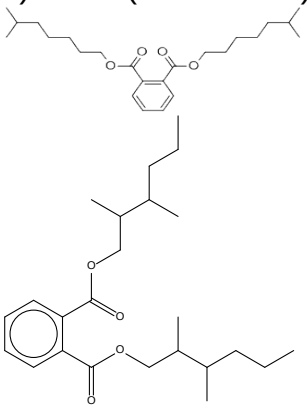
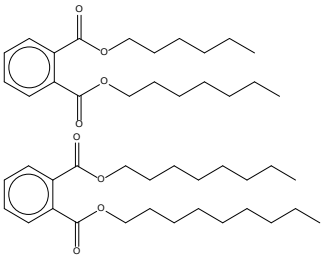
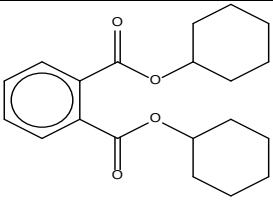
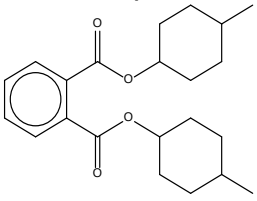
| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| Diethyl phthalate (DEP) (84-66-2) |  $C_{12}H_{14}O_4$ 222.24 | DMP (131-11-3)  | soil and sediment toxicity studies, inhalation toxicity in wildlife | 86.26 |

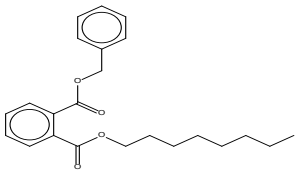
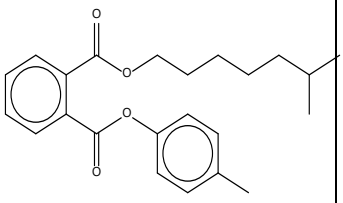
**Table C-6. Analogue identities for the medium-chain phthalate subgroup**

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| Butyl benzyl phthalate (BBP) (85-68-7) |  $C_{19}H_{20}O_4$ 312.35 | 1) BCHP (84-64-0)  2) CHIBP (5334-09-8)  3) DBzP (523-31-9)  | abiotic and biotic degradation studies; BCF, BAF, BSAF, BMF data; aquatic, soil and sediment toxicity studies; endocrine disrupting effects | 1) 86.63 2) 86.63 3) 79.06 |
| Diphenyl phthalate (DPhP) (84-62-8) |  $C_{20}H_{14}O_4$ 318.33 | DBzP (523-31-9)  | aquatic toxicity studies | 92.14 |

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| Dibutyl phthalate (DBP) (84-74-2) |  <br>$C_{16}H_{22}O_4$<br>278.34 | 1) DIBP (84-69-5)<br>  <br>2) DPrP (131-16-8)<br>  <br>3) DnHP (84-75-3)<br>  | abiotic and biotic degradation studies; aquatic, and sediment toxicity studies; BAF studies | 1) 85.80<br>2) 91.08<br>3) 84.86 |
| Diisooctyl phthalate (DIOP) (27554-26-3) |  <br>$C_{24}H_{38}O_4$<br>390.56 | DIHepP (71888-89-6)<br>  | biotic degradation; aquatic toxicity studies | 88.13; 93.43[a] |

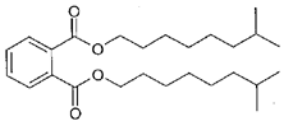
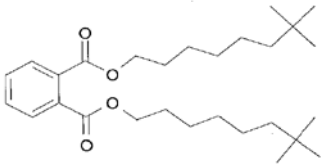
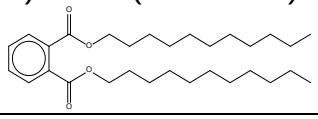
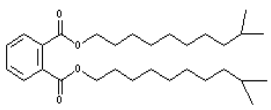
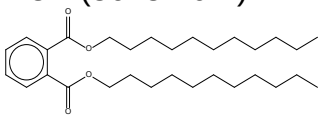
| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| Diethylhexyl phthalate (DEHP) (117-81-7) |  $C_{24}H_{38}O_4$ 390.56 | 1) DIHepP (71888-89-6)  2) DIOP (27554-26-3)  3) 79P (111381-89-6)  | abiotic and biotic degradation studies; BAF, BSAF data; aquatic and sediment toxicity studies | 1) 93.43<br>2) 89.33; 100[b]<br>3) 87.50; 86.64[c] |
| (DCHP) (84-61-7) |  $C_{20}H_{26}O_4$ 330.43 | DMCHP (27987-25-3)  | | 88.84 |

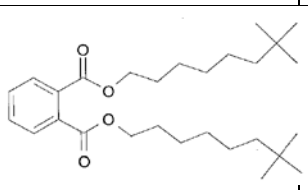
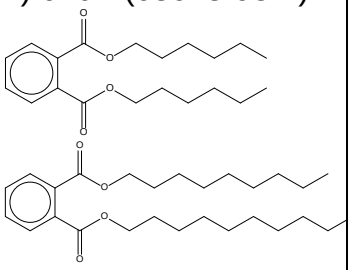
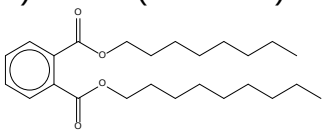
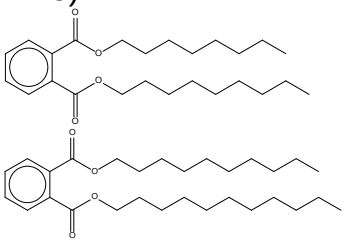
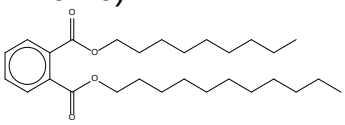
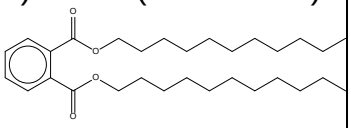
| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| (B79P) (68515-40-2) |  $C_{22}H_{28}O_4$ 368.48 | BIOP (27215-22-1)  | | 89.08; 87.03[d] |

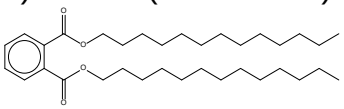
Abbreviations: CAS RN, Chemical Abstract Service Registry Number; BCF, bioconcentration factor; BAF, bioaccumulation factor; BSAF, biota-sediment accumulation factor; BMF, biomagnification factor; NA, data not available

[a] Similarity indices are given for comparison of DIHepP with two different isomers of DIOP.
[b] Similarity indices are given for comparison of DEHP with two different isomers of DIOP.
[c] Similarity indices are given for comparison of DEHP with two different components in 79P.
[d] Similarity indices are given for comparison of BIOP with two different components in B79P, one with 7 carbon alkyl chains, and one with 9 carbon alkyl chains, respectively.

**Table C-7. Analogue identities for the long-chain phthalate subgroup**

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| Diisononyl phthalate (DINP) (28553-12-0, 68515-48-0) |  $C_{26}H_{42}O_4$ 418.62 | 1) DIDP (26761-40-0, 68515-49-1)  2) DUP (3648-20-2)  | Anaerobic biodegradation; biodegradation and aquatic toxicity of primary degradation product | 1) 84.98 – 94.19[a] 2) 89.02 – 90.77[a] |
| Diisoundecyl phthalate (DIUP) (85507-79-5) |  | DUP (3648-20-2)  | Biomagnification factor | 80.52 |

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| | $C_{30}H_{50}O_4$<br>474.73 | | | |
| Diisodecyl phthalate (DIDP) (26761-40-0, 68515-49-1) |  <br>$C_{28}H_{46}O_4$<br>446.68 | 1) 610P (68648-93-1)<br>  <br>2) DnOP (117-84-0)<br>  <br>3) D911P (68515-43-5)<br>  <br>4) D911P-2 (111381-91-0)<br>  <br>5) DIUP (85507-79-5)<br>  | BCF studies | 1) 76.76 – 90.00[b]<br>2) 84.40; 88.93[c]<br>3) 83.83 – 88.93[d]<br>4) 86.10; 90.51[c]<br>5) 81.68; 85.77[c] |

| Systematic name of analogue (Acronym) (CAS RN) | Analogue chemical structure, molecular formula and molecular weight (g/mol) | Data-poor medium-chain subgroup substance | Endpoints for read-across | Tanimoto Similarity Index (%) |
|---|---|---|---|---|
| | | 6) DTDP (68515-47-9)  | | 6) 74.09; 77.63[c] |

[a] Range of similarity indices depending on which isomer of DINP was used for modelling.
[b] Range of similarity indices depending on which isomer of DIDP and which component in 610P was used for modelling.
[c] Similarity indices are given for comparison with two different isomers of DIDP.
[d] Range of similarity indices depending on which isomer of DIDP and which component of D911P was used for modelling.