Summary of Public Comments received on the proposed Cumulative Risk Assessment (CRA) approach for certain Phthalates

Comments on the proposed CRA approach for certain short, long, and medium chain Phthalates, to be addressed as part of the substance grouping initiative under Canada's Chemicals Management plan (CMP), were submitted by the following: American Chemistry Council (ACC), Canadian Consumer Specialty Products Association (CCSPA), Canadian Plastics Industry Association (CPIA), Imperial Oil, Industry Coordinating Group for CEPA (ICG), Japan Plasticizers Industry Association (JPIA), Canadian Environmental Law Association (CELA), and Environmental Defence.

A summary of comments and responses is included below, organized by topic:

Topic	Comment	Response
Data and information gaps	Clarify what information will be used to fill data gaps for data-poor substances.	The CMP screening assessments are based on considerations of the available data. New information can be submitted through several mechanisms defined under specific sections of Canadian Environmental Protection Act (CEPA) 1999 and other legislation. All CMP assessed substances are subject to future evaluation if new, significant information is provided that indicates a need for further consideration. The read-across approach for data-poor phthalates was applied using recent data from the most related data-rich phthalates, based on chemical structure, composition, metabolism, physical-chemical properties, and mechanism or mode of action (MOA).
	The considerations used in constructing the groups should be clearly described and documented. This is critical since the three groups of substances are anticipated to exhibit different hazard properties and modes of action (MOA).	The 28 phthalates are organized by subgroups in Table 1-1, Table 1-2, and Table 1-3 in the Proposed CRA Approach. This reflects the different MOA, and the environmental fate and behaviour of the various substances. This follows the Organisation for Economic Co-operation and Development (OECD) Task Force on Hazard Assessment's Guidance on Grouping of Chemicals.
	Table 4-3 includes three substances: 1,2-Benzenedicarboxylic acid, bis (methylcyclohexyl) ester (DMCHP); 1,2-Benzenedicarboxylic acid, dihexyl ester (DnHP); and 1,2-Benzenedicarboxylic acid, bis (phenylmethyl) ester (DBzP). These substances are not manufactured, used, or imported into Canada. Provide supporting evidence for their inclusion in the Proposed CRA Approach.	For these substances, scientific studies conducted in Canada indicate risks of exposure for Canadians, as outlined in Table 4-3 in the proposed CRA Approach.
	Include an exposure route for inhalation from building products such as those containing poly-vinyl chloride, including floor, wall and ceiling materials, which are associated with development of asthma.	The co-occurrence analysis of phthalates in the Canadian House Dust Study (2007 - 2010), is cited in table 4-3 of the proposed CRA Approach.
	There is a missing element in the proposed approach related to early immune system development.	Effects on the immune system were reported in "State of the Science Report – Part 1: Phthalate Substance Grouping, Medium Chain Phthalate Esters" (MCP SOS). Potential health effects were also evaluated in the Proposed CRA Approach.

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	Due to a rapidly changing marketplace, ensure that the draft screening assessment (dSAR) uses the most up-to-date phthalate exposure data to reflect current product usage, including exposures from cosmetics and personal care products.	The most recent and relevant exposure data provided by industry and additional relevant information from the public consultation on the dSAR will be considered in the final screening assessment.
	Indicate in the Proposed CRA Approach what are considered adverse effects, why these effects are considered adverse, and whether there are any qualifiers.	Adverse effects relative to male reproductive toxicity as described in the MCP SOS, were found to persist into adulthood. This is based on a conservative selection of endpoints.
	A list of acronyms would assist when reading the document.	A list of acronyms is included in the dSAR.
	The United States (U.S.) Consumer Product Safety Commission report by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives is cited incorrectly.	The correct citation is in the draft Screening Assessment Report.
	As outlined in the World Health Organization (WHO) 2002 State of the Science Report, "endocrine disruption is not considered a toxicological end point per se but a functional change that may lead to adverse effects." Provide clarity in the final screening assessment report (SAR) on which adverse effect(s) were selected and why they are considered adverse.	Noted.
	The hazard filter should be for the "adverse outcome." Figure 4-2 is a decision tree for application of the hazard and exposure filters.	Noted.
	In Table 4-4, state the confidence level for data that support migration from textiles onto the human skin, and further on to systemic circulation.	Noted.
	Consider the following recent U.S. Environmental Protection Agency reports:: · Christensen, K. L., Makris, S. L., & Lorber, M. (2014). Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment. *Regulatory Toxicology and Pharmacology*, 69(3), 380-389. · Gallagher, S. S., Rice, G. E., Scarano, L. J., Teuschler, L. K., Bollweg, G., & Martin, L. (2015). Cumulative risk assessment lessons learned: A review of case studies and issue papers. *Chemosphere*, 120, 697-705.	Noted.

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Risk assessment	Provide a sound rationale for expanding the group of phthalates in the Proposed CRA Approach (which includes additional phthalates not listed in the Chemicals Management Plan, Phase 2 grouping because they did not meet categorization criteria). Decisions previously made about these substances should be revisited. For example, some of these additional phthalates are already managed under the 2009 *Phthalates Regulations*.	These additional phthalates are considered in the Proposed CRA Approach because more than one type of phthalate may be present in the same environment, leading to cumulative effects on human and environmental health. Also, the 2009 *Phthalates Regulations* restrict the use of six phthalates in children's items. However, ecological concerns are not considered, and these substances may be used in other applications resulting in releases to the environment. Regulations will be updated if new information indicates a potential harm to the health of Canadians.
	In Table 4-2 of the Proposed CRA Approach, effects in rats with rat phthalate syndrome (RPS) for subgroup 2 MCP esters, diisononyl phthalate (DINP) is listed as being positive for reduced anogenital distance (AGD), nipple retention (NR), testicular pathology, and fertility parameters.	As described in the MCP SOS, the Government of Canada considered both significantly reduced AGD and NR in male rats after exposure to certain phthalates as valid indicators of androgen insufficiency during prenatal development. This may result in severe and irreversible effects on male reproductive systems and may, in turn, interfere with fertility. This approach is protective of any other potential effects observed at higher doses.
	There are species differences in adverse effects of diethylhexyl phthalate (DEHP) between rodents and primates and toxicity is more intensive in rodents. Since rodents are the most sensitive to antiandrogenic effects *in utero*, the MOA is not proper for the hazard characterization of humans in a dose addition method.	The processes involved in male rat reproductive development are similar to those in humans and there is no strong evidence to indicate that there are significant toxicokinetic/toxicodynamic differences between rodents and primates (see MCP SOS Appendix H). In the CRA for human health a default uncertainty factor of 100 was used in deriving hazard quotients for fetuses exposed to phthalates in utero to account for intra- and inter-species differences.
	The common MOA should not be antiandrogenic in nature. For example, can the shortening of AGD be linked to lower level of testosterone?	The proposed MOA was reviewed in the MCP SOS, and in "Phthalates and Cumulative Risk: The Tasks Ahead" (National Academy of Science, NAS 2008). The effects on the male reproductive systems are not clear. However, low levels of dihydrotestosterone (DHT) were also identified; and may cause shortened AGD in rats (Foster 2006), compromising reproductive capacity in adulthood.

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	It is essential that there be a clear understanding of the level of adverse effects. For example, shortening of AGD for male animals is mentioned in the proposal context. What is the degree of seriousness associated with the degree of shortening of AGD?	The OECD Guidance for mammalian reproductive toxicity testing and assessment calls for measurement of AGD and recommends measurement of NR. Several international regulatory agencies and scientific bodies use both measurements to identify potential effects of phthalates on the developing male reproductive system.
	A CRA should be based on adverse outcomes, and not pathways (or MOA), which lead to the adverse outcomes.	The Government of Canada considered a broader suite of effects related to male reproductive toxicity (see MCP SOS). Adverse effects on survival, growth or reproduction, regardless of pathway were also considered.
	Consider the principles of sound science and follow a weight of evidence approach when assessing the reliability and appropriateness of grouping or read-across strategies for assessing hazard and exposure information.	A weight of evidence approach is used in assessments conducted under the CMP. This approach weighs various sources of information to identify critical values used in the assessment, and it evaluates multiple lines of evidence in order to determine if a substance may pose a risk.
	For phthalates containing different ester groups, consider quantifying the relative amounts of each monoester metabolically produced to ensure that appropriate effect levels are used.	In the absence of available human data, a range of effect levels from the possible metabolite or parent phthalates were used for asymmetric phthalates where read-across was undertaken.
	Do not consider modulation of hormone levels to be adverse effects in the absence of clinical effects and gene expression changes.	Modulation of hormone levels in the absence of clinical effects and gene expression changes were considered as part of the overall interpretation of effects to support the MOA of RPS.
	Table 4-3 seems to be qualitative. Fully itemize and explain the information and assumptions underlying the exposure determination.	Table 4-3 (Proposed CRA Approach) is presented as qualitative. Two methods were used to quantify exposure: modelled estimates for daily intakes from monitoring data such as dust and food; and biomonitoring data from national surveys and other Canadian sources (see the dSAR).
	A quantitative cumulative assessment using relative potency may be problematic without detailed *in vivo* data on each of the phthalates in the assessment.	For these phthalates, quantifying the relative amount of each monoester produced *in vivo* would support read-across. However, the HI method was determined to be the most appropriate method for determining cumulative risks to human health at the lower tiered screening assessment level.

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	Overall, the cumulative approach outlined in the document for both human health and environmental assessment appears reasonable and is consistent with accepted methodology. We agree with the proposed tiered approach.	Noted.
	Potency comparisons across an early event do not necessarily translate to potency differences in later adverse outcomes.	Noted.
Human & ecological health	DINP is not a medium chain phthalate ester because it has a carbon backbone of C7. It should be included in the long chain group. Do not include it in the medium chain group, which demonstrate clear developmental/ reproductive toxicity.	From a human health perspective, DINP has been shown to adversely affect male offspring exposed *in utero* (Hannas et al. 2011, 2012); and contributes to other adverse anti-androgenic effects. Inclusion of DINP in the MCP subgroup is also supported by the United States Consumer Product Safety Commission Chronic Hazard Advisory Panel (US CHAP (2014).
	Critical body residues (CBRs) can only be made cumulative when a single MOA is in play. This assumption should be thoroughly substantiated. It is uncertain whether sufficient information is available to sustain this approach, since tissue residues are rarely available in concert with tests of apical endpoints.	Tissue residues for the individual phthalates were estimated and used in the ecological CRA calculations by comparing with a reference CBR associated with a narcotic MOA. The CRA is only one line of evidence in the dSAR. The potential for risk due to other specific MOAs was also considered as another line of evidence.
	Consider other theories that challenge the dose additivity concept at human exposure levels.	The Government of Canada follows the Framework for Risk Assessment of Combined Exposures to Multiple Chemicals (used by the WHO and the International Program on Chemical Safety).
	Summing HQs across pathways belies the concept of threshold, and there is no evidence that separate pathways generate dose additive effects. If the hazard for the most sensitive pathway is less than 1, it would be expected that the assessment is protective for any other pathways as well.	The CRA for human health used only the most sensitive effects of toxicity on the developing male reproductive system and was considered protective of other effects observed at higher doses (from other separate pathways).
	If an HI approach is used it must not replicate the methodological flaws of the US CHAP report.	The conservative lower tiered HI approach showed no concern for the potential cumulative risk of MCP for the general Canadian population, specifically for the more sensitive subpopulations (pregnant women, infants, and children).

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	The proposed approach to human health CRA focuses on adverse health outcomes as opposed to the pathways that lead to those adverse outcomes. We strongly support this approach. Consider all similar and even dissimilar chemicals that can contribute to adverse health outcomes.	Noted.
	High molecular weight phthalates (greater than six carbon alkyl chain length) do not accumulate in tissues to a degree sufficient to satisfy criteria for being bioaccumulative, nor do they biomagnify in aquatic ecosystems (they biodilute). Due to the low water solubility of high molecular weight phthalates, aquatic organisms also cannot achieve the internal body concentration needed to cause toxicity. Therefore, it is no appropriate to include high molecular weight phthalates in a cumulative ecological risk assessment.	The intent of the ecological CRA is to determine if the total internal concentrations of all the phthalates combined could cause adverse effects. Individual phthalates that do not cause adverse effects on their own, such as the high molecular weight phthalates, may still contribute to cumulative effects. This approach is supported by Mayer and Reichenberg (2006). Many of the phthalates being assessed, including some higher molecular weight phthalates, have been found in Canadian water, sediment and biota; this is evidence for co-occurrence of these higher molecular weight phthalates with other phthalates.
	Apply the CRA primarily to vulnerable populations, as indicated in the Proposed CRA Approach.	The screening assessments are based on consideration of the available data and include various conservative exposure scenarios that account for both the general population and for vulnerable populations in Canada. If information is available that suggests a specific sub-population would be particularly vulnerable, it will be considered in the assessment.
	The proposed methodology of using HI approach is appropriate for a screening level assessment to determine no risk, but would not be appropriate for a CRA for developing regulations. Any determination of risk would require further refinements.	Based on the available information on the common adverse effects (RPS) and the observed differences in potencies within the medium-chain phthalates, a lower tiered hazard characterization using the HI was considered to be the most appropriate approach. The HI method was selected because it is simple, flexible and allows for an indication of which substance(s) in the CRA, or which source and route, may be the predominant contributor(s) to the overall risk. Identification of the substances or sources and routes that are drivers of the CRA would be beneficial for informing risk management, if needed. If the HI was determined to be above 1 (indicating potential risk), then further investigation or refinement would be considered.

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Risk management	Publication of the *Phthalates Regulations* is supported, regulations that restricted the concentration of six specific phthalates in children's toys and child care articles that can be placed in the mouths of young children. Compliance with the Regulations should mean that exposure to these six substances has been reduced. This should be reflected in the risk assessments. All six of these substances are included in the CRA and SOS reports.	Exposure data used in the assessment (from biomonitoring, house dust, etc.) were obtained mainly after the *Phthalates Regulations* came into effect. They likely represent levels of exposure for these six phthalates at the time the samples were taken.
	Consider technical and economic feasibilities in any risk management proposals, and consult with stakeholders (i.e., manufacturers, importers and users of phthalates or phthalate-containing products).	Technical and economic feasibilities will be considered in the development of any regulations, instruments and/or tools respecting preventative or control actions. Based on the science in the risk assessment, the Government of Canada will select the most appropriate tool for risk management of these substances. This selection is made using a thorough, consistent and efficient approach that takes into consideration information received from both the assessment and other sources.
	Clarify the planned approach for moving forward if the potential for unacceptable risk is determined, and solicit public comments on next steps.	Consultation with stakeholders is an essential part of the risk management process, and the Government of Canada intends to consult extensively with all affected stakeholders when developing risk management measures.

References:

Hannas BR, Lambright CS, Furr J, Evans N, Foster PMD, Gray EL, Wilson VS. 2012. Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: a targeted RT-PCR array approach for defining relative potency. Toxicol Sci 125(2):544-557.

Hannas BR, Lambright CS, Furr J, Howdeshell KL, Wilson VS, Gray LE. 2011. Dose-response assessment of fetal testosterone production and gene expression levels in rat testes following in utero exposure to diethylhexyl phthalate, diisobutyl phthalate, diisoheptyl phthalate, and diisononyl phthalate. Toxicol Sci 123(1):206–216.

Mayer P, Reichenberg F. 2006. Can highly hydrophobic organic substances cause aquatic baseline toxicity and can they contribute to mixture toxicity? Environ Toxicol Chem 25(10): 2639-2644.

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