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Screening Assessment for

Substituted Diphenylamines

Environment and Climate Change Canada

Health Canada

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Canada

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Synopsis

Pursuant to section 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment on fourteen substituted diphenylamines (SDPAs). The SDPAs were identified as priorities for action as they met the categorization criteria under subsection 73(1) of CEPA or were considered a priority based on other human health concerns or on their potential use as alternatives for each other. One of these fourteen SDPAs is benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene, known as BNST, which had previously been assessed during the Challenge initiative of the Chemicals Management Plan, and which is re-assessed based on new information obtained after the original assessment.

The Chemical Abstracts Service Registry Number[1] (CAS RN) and Domestic Substances List (DSL) names of the fourteen SDPAs are listed below. These include seven discrete substances and seven substances that are UVCBs (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials). They are all diphenylamines with various degrees of phenyl or alkyl substitution and similar physical-chemical properties. The seven substances that are UVCBs also contain chemical structures that are the same or analogous to the discrete SDPAs in this assessment.

Identity for substances in the SDPAs assessment

CAS RN	DSL Name	Chemical Structure(s) used in the Ecological Assessment
101-67-7	Benzenamine, 4-octyl-N-(4-octylphenyl)-	Dioctyl DPA
4175-37-5	Benzenamine, 4-octyl-N-phenyl-	Monooctyl DPA
10081-67-1	Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]-	Dimethyl distyrenated DPA
15721-78-5	Benzenamine, 4-(1,1,3,3-tetramethylbutyl)-N-[4-(1,1,3,3-tetramethylbutyl)phenyl]-	Dioctyl DPA
24925-59-5	Benzenamine, 4-nonyl-N-(4-nonylphenyl)-	Dinonyl DPA

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

26603-23-6	Benzenamine, ar-octyl-N-(octylphenyl)-	Dioctyl DPA
27177-41-9	Benzenamine, ar-nonyl-N-phenyl-	Monononyl DPA
36878-20-3	Benzenamine, ar-nonyl-N-(nonylphenyl)-	Monononyl DPA[a] Dinonyl DPA[a]
68411-46-1	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene	Monobutyl monooctyl DPA[a] Monooctyl DPA[a] Dioctyl DPA[a]
68442-68-2	Benzenamine, N-phenyl-, styrenated	Monostyrenated DPA[a] Distyrenated DPA[a]
68608-77-5	Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivs.	Diethyl monononyl DPA[a] Diethyl dinonyl DPA[a]
68608-79-7	Benzenamine, N-phenyl-, (tripropenyl) derivs.	Monononyl DPA[a] Dinonyl DPA[a]
68921-45-9[b]	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene (BNST)	Monooctyl DPA[a] Dioctyl DPA[a] Monostyrenated DPA[a] Monooctyl monostyrenated DPA[a]
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-Trimethylpentene	Monooctyl DPA[a] Monobutyl monooctyl DPA[a] Dioctyl DPA[a] Dibutyl DPA[a] Monobutyl DPA[a]

[a] Representative structures selected for this UVCB for the purposes of this assessment
[b] Substance previously assessed in the Challenge and re-assessed based on new information obtained after the original assessment and structural similarity to other SDPAs

SDPAs do not occur naturally in the environment. Based on the results of the mandatory and voluntary surveys for years 2006, 2011, 2012, and the Domestic Substances List (DSL) Inventory Update for 2008, they are used in high quantities in Canada. In 2011, between 1 000 000 and 10 000 000 kg of SDPAs were imported into Canada, either as individual substances or as part of specialty chemical additive packages, according to the results of the CEPA section 71 survey. In the same year, over 10 000 000 kg of SDPAs were also manufactured in Canada, the majority (over 90%) of which was exported. CAS RN 68921-45-9 (BNST) was not surveyed in 2011. For BNST, between 100 000 and 1 000 000 kg of this SDPA was imported into Canada in 2006, and between 1 000 000 and 10 000 000 kg was manufactured in 2006 according to the results of the CEPA section 71 survey. The major uses of SDPAs in Canada are as antioxidants in automotive and industrial lubricants. SDPAs are also used as antioxidants/antidegradants in the manufacturing of plastics or polyurethane foams and rubber products, and are imported in polymers or polyols.

Ecological Assessment

Environmental exposure to SDPAs was examined in multiple scenarios representing industrial activities and overall uses of SDPAs in Canada. The key activities examined were the manufacturing of SDPAs and the blending of lubricants, which are the major anticipated sources of release to the environment. Additional activities were examined, including SDPA uses in the plastics and rubber sectors, automotive and powertrain assembly lines, disposal of lubricants, and biosolids amendment to agricultural land. These scenarios focused on the total representative SDPA structures, given that SDPAs are potential replacements for each other, and changes in product formulations could occur with the total SDPA usage remaining relatively constant.

SDPAs are characterized by low water solubilities, low vapour pressures and high to very high octanol-water partition coefficients. Among the SDPA structures, those with the log K_{ow} of less than 9 (i.e., monooctyl DPA, dimethyl distyrenated DPA, mononononyl DPA, monostyrenated DPA, distyrenated DPA, dibuty DPA, monobutyl DPA, monobutyl monooctyl DPA and monooctyl monostyrenated DPA) are considered to be bioavailable, while those with the log K_{ow} exceeding 9 (i.e., dioctyl DPA, dinonyl DPA, diethyl mononononyl DPA and diethyl dinonyl DPA) are not easily absorbed from the exposure medium or diet and thus are considered to have very low bioavailability and have limited bioaccumulation potential. Due to their lack of bioavailability, dioctyl DPA, dinonyl DPA, diethyl mononononyl DPA, and diethyl dinonyl DPA are considered to have a lower ecological hazard potential.

Due to their hydrophobic nature, SDPAs in the environment are primarily associated with sediments, suspended particulate matter and soil. They are considered to be persistent in the environment but are not expected to undergo long-range transport in water or air. As such, long-term exposures are expected to be near discharge areas and closer to emission sources.

Analyses revealed that the potential for adverse effects from SDPAs in the environment, including benthic species, aquatic species (fish), piscivorous mammals, and soil-dwelling organisms, is low.The determination of SDPA toxicity in aquatic species is affected by their low water solubilities, where effects are observed at exposure concentrations that surpass substance solubility limits. Low toxicity to soil- and sediment-dwelling organisms was also observed in SDPA exposure studies using the earthworm and freshwater midge as test species, respectively. Toxicity to the representative piscivorous mammal species was evaluated using a read-across approach with rodent data, resulting in a toxicity reference value indicating potential for adverse effects (<10 mg/kg bw/day). To evaluate ecological effects of SDPAs, critical body burden (CBR) calculations were conducted for representative benthic species, aquatic species (fish), piscivorous mammals, and soil-dwelling organisms, and compared to the internal threshold levels causing death for narcotic chemicals. The CBR values

were found to be below the threshold levels for both acute and chronic exposures, indicating minimal potential risk from exposure to SDPAs.

Considering all the lines of evidence presented in this screening assessment, there is currently low risk of harm to organisms and the broader integrity of the environment from the fourteen SDPAs considered in this assessment. It is concluded that the fourteen SDPAs considered in this assessment do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Human Health Assessment

The human health assessment considers all available lines of evidence on the fourteen SDPA substances. For the human health assessment, exposure of the general population to SDPAs from environmental media is expected to be low, given the physical-chemical properties and use pattern of these substances. Exposure from food is not expected. Exposure to the general population from the use of products available to consumers results primarily from foam cushioning and automotive lubricants via oral and dermal routes, respectively.

Available empirical data for 8 of the 14 substances in this grouping indicates that these substances are not likely genotoxic. Based on the empirical data available for this substance grouping, health effects following short-term oral exposure in animal studies include the liver and haematological and/or clinical chemistry parameters. The kidney is a target organ at higher levels.

Comparisons of estimates of exposure to the general population to SDPAs from levels in environmental media and from use ofproducts available to consumers with levels associated with adverse health effects are considered to be adequate to account for uncertainties in the health effects and exposure databases.

Based on the information presented in this screening assessment, it is concluded that the fourteen SDPAs considered in this assessment do not meet the criteria under paragraph 64(*c*) of CEPA, as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Overall Conclusion

It is concluded that the fourteen SDPAs considered in this assessment do not meet any of the criteria set out in section 64 of CEPA. This conclusion also applies to BNST, one of the fourteen substances assessed; this substance had previously been found to meet the criteria set out in section 64 of CEPA in a

2009 screening assessment conducted during the Challenge initiative of the Chemicals Management Plan.

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Tables and Figures

1. Introduction

Pursuant to section 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of Environment and the Minister of Health have conducted a screening assessment of fourteen substituted diphenylamine (SDPA) substances to determine whether these substances present or may present a risk to the environment or to human health.

The original Substituted Diphenylamines Substance Grouping under the Chemicals Management Plan included thirteen substances that were identified as priorities for action as they met the categorization criteria under section 73(1) of CEPA or were considered a priority based on other human health concerns, or on their potential use as alternatives for each other. Based on common chemical structures (components) and similar physical-chemical properties, an additional SDPA, benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene, CAS RN 68921-45-9, known as BNST, was included in this assessment. BNST had previously been assessed during the Challenge initiative of the CMP (ECCC, HC 2009). Recent measured environmental concentrations for SDPAs considered in this assessment, suggest that they have a lower potential to accumulate in aquatic and terrestrial organisms than previously available information had indicated. From a human health perspective, this recent environmental data together with current information on use of BNST in products suggests that there is little concern for human exposure to BNST. Therefore, the substance BNST was included and re-assessed in the SDPA grouping.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including information submitted by stakeholders. Relevant data for the ecological assessment were identified up to November 2016. Relevant data for the human health assessment were identified up to September 2015. Empirical data from key studies as well as modelled results were used to reach the conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review and/or consultation. Comments on the technical portions relevant to human health were received from Dr. Bernard Gadagbui, Toxicology Excellence for Risk Assessment; Dr. Louis Scarano, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency (EPA); Dr. Paul J. Lioy, Robert Wood Johnson Medical School, Rutgers University; and Dr. Raghuraman Venkatapathy, Environmental Computational Chemist and Technical Manager for Pegasus Technical Services. Comments relevant to the ecological assessment were received from technical experts including Dr. James Armitage, University of

Toronto and Dr. Leonard Sweet, Lubrizol Corporation. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution[2]. The screening assessment presents the critical information and considerations upon which the conclusion is made.

[2]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and products available to consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

2. Substance Identity

This screening assessment examines a group of related substances known as substituted diphenylamines (SDPAs).

The general structure of SDPAs is presented in Figure 2-1. The amine group acts as an electron donating group and therefore the preferred electrophilic aromatic substitution by alkenes of DPA will occur at the para or ortho position to the amine. SDPAs in this assessment have 1-4 substituents on the diphenylamine.

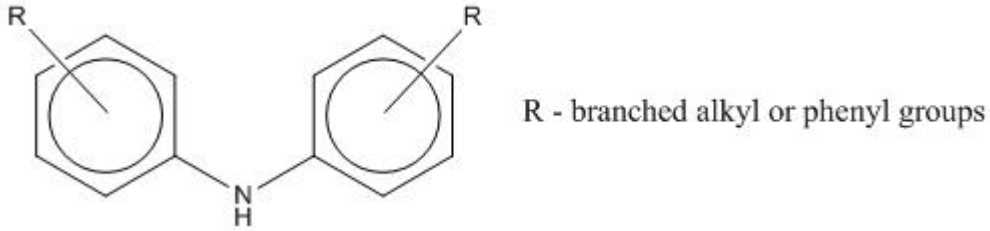
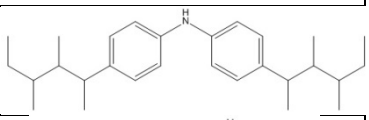
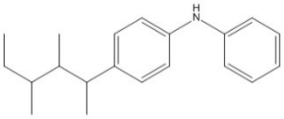
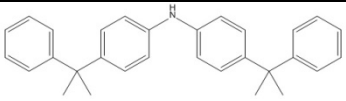
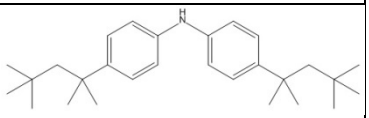
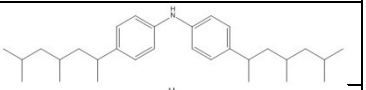
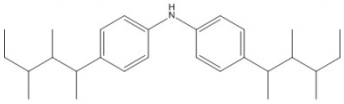
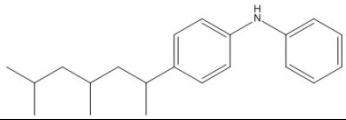


Figure 2-1 General structure common to SDPAs

This screening assessment focuses on fourteen SDPA substances. These include five discrete substances, two isomeric mixtures (considered discrete substances for the purpose of this assessment) and seven substances considered as UVCBs (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials). UVCBs are mixtures that contain a number of chemical structures in varying concentrations. The representative chemical structures for the SDPAs in this group are presented in Tables 2-1 and Table 2-2. All representative chemical structures were identified from Environment and Climate Change Canada's chemical analysis of standards and information submitted by industry consistent with expected products for the chemical reactions stated in the substance names (ChemBioDraw Ultra 2010, Smith and March 2001).

Table 2-1 Substance identity for discrete SDPAs

CAS RN	DSL Name[a]	Chemical Name and Formula[b]	Chemical Structure
101-67-7	Benzenamine, 4-octyl-N-(4-octylphenyl)-	Dioctyl DPA $C_{28}H_{43}N$	
4175-37-5	Benzenamine, 4-octyl-N-phenyl-	Monooctyl DPA $C_{20}H_{27}N$	
10081-67-1	Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-	Dimethyl distyrenated DPA	

CAS RN	DSL Name[a]	Chemical Name and Formula[b]	Chemical Structure
	phenylethyl)phenyl]-	$C_{30}H_{31}N$	
15721-78-5	Benzenamine, 4-(1,1,3,3-tetramethylbutyl)-N-[4-(1,1,3,3-tetramethylbutyl)phenyl]-	Dioctyl DPA $C_{28}H_{43}N$	
24925-59-5	Benzenamine, 4-nonyl-N-(4-nonylphenyl)-	Dinonyl DPA $C_{30}H_{47}N$	
26603-23-6[c]	Benzenamine, ar-octyl-N-(octylphenyl)-	Dioctyl DPA $C_{28}H_{43}N$	
27177-41-9[c]	Benzenamine, ar-nonyl-N-phenyl-	Monononyl DPA $C_{21}H_{29}N$	

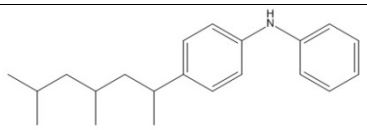
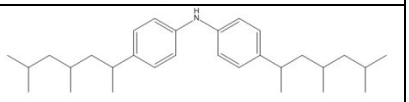
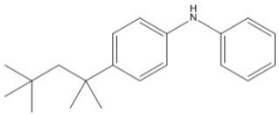
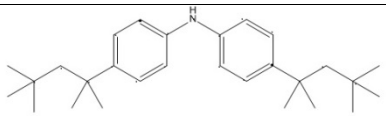
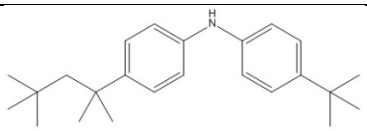
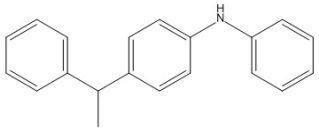
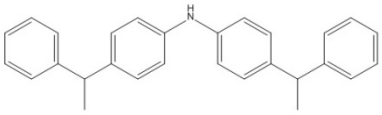
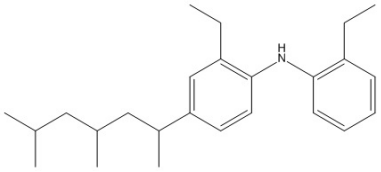
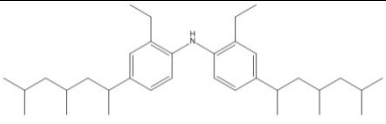
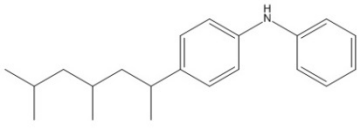
[a]DSL – Domestic Substances List
[b] Chemical Formula of Chemical Structure
[c]Multi-constituent substance of various *ortho/para* substituted isomers

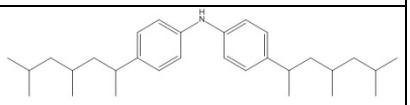
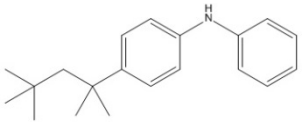
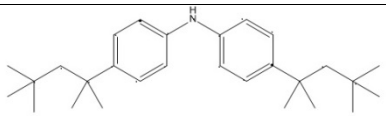
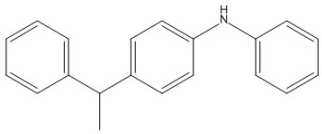
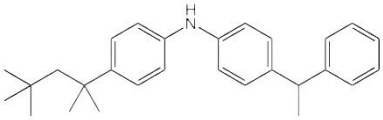
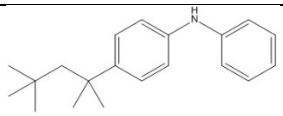
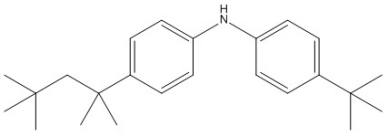
UVCB mixtures contain a number of different chemical structures in varying concentrations as the alkylation of diphenylamine by various olefins can produce various substitution patterns and variable branching patterns. Where information was available, chemical structures representing the larger proportions of the UVCB and spanning the range of bioavailability potential were selected. The following criteria were used in determining a representative chemical structure/branching pattern:

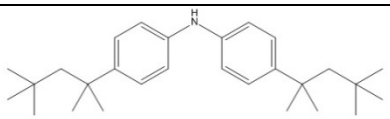
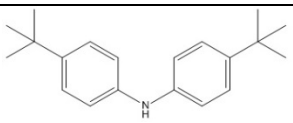
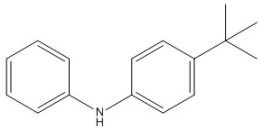
- The aniline nitrogen will be ortho/para directing; however, preference is given to para-substitution due to steric effects of the *N*-phenyl group;
- The reaction proceeds through the most stable carbocation intermediate ("Markovnikov type") to determine the point of attachment; and
- When the olefin is named in the name of the substance, then that olefin is used in deriving the representative chemical structure.

Table 2-2 indicates the chemical structures deemed to be most representative and which comprise the major proportions within the UVCB. The range of components and the corresponding percent composition of each component within the corresponding SDPA was taken into consideration when selecting the representative structures included in the assessment. In this assessment, the terms "butyl", "octyl" and "nonyl" are used to refer to the number of carbon atoms and represent branched alkyl chains.

Table 2-2 Substance identity for SDPAs identified as UVCBs

CAS RN	DSL Name[a]	Representative Chemical Name and Formula[b]	Representative Chemical Structure
36878-20-3	Benzenamine, ar-nonyl-N-(nonylphenyl)-	Monononyl DPA $C_{21}H_{29}N$	
36878-20-3	Benzenamine, ar-nonyl-N-(nonylphenyl)-	Dinonyl DPA $C_{30}H_{47}N$	
68411-46-1	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene	Monooctyl DPA $C_{20}H_{27}N$	
68411-46-1	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene	Dioctyl DPA $C_{28}H_{43}N$	
68411-46-1	Benzenamine, N-phenyl-, reaction products with 2,4,4-trimethylpentene	Monobutyl monooctyl DPA[c] $C_{24}H_{35}N$	
68442-68-2	Benzenamine, N-phenyl-, styrenated	Monostyrenated DPA $C_{20}H_{19}N$	
68442-68-2	Benzenamine, N-phenyl-, styrenated	Distyrenated DPA $C_{28}H_{27}N$	
68608-77-5	Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivs.	Diethyl mononoyl DPA $C_{25}H_{37}N$	
68608-77-5	Benzenamine, 2-ethyl-N-(2-ethylphenyl)-, (tripropenyl) derivs.	Diethyl dinonyl DPA $C_{34}H_{55}N$	
68608-79-7	Benzenamine, N-phenyl-, (tripropenyl)	Mononoyl DPA: $C_{21}H_{19}N$	

CAS RN	DSL Name[a]	Representative Chemical Name and Formula[b]	Representative Chemical Structure
	derivs.		
68608-79-7	Benzenamine, N-phenyl-, (tripropenyl) derivs.	Dinonyl DPA $C_{30}H_{47}N$	
68921-45-9	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene	Monooctyl DPA $C_{20}H_{27}N$	
68921-45-9	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene	Dioctyl DPA $C_{28}H_{43}N$	
68921-45-9	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene	Monostyrenated DPA $C_{20}H_{19}N$	
68921-45-9	Benzenamine, N-phenyl-, reaction products with styrene and 2,4,4-trimethylpentene	Monooctyl-monostyrenated DPA $C_{28}H_{35}N$	
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-trimethylpentene	Monooctyl DPA $C_{20}H_{27}N$	
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-trimethylpentene	Monobutyl monooctyl DPA $C_{24}H_{35}N$	

CAS RN	DSL Name[a]	Representative Chemical Name and Formula[b]	Representative Chemical Structure
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-trimethylpentene	Dioctyl DPA $C_{28}H_{43}N$	
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-trimethylpentene	Dibutyl DPA $C_{20}H_{27}N$	
184378-08-3	Benzenamine, N-phenyl-, reaction products with isobutylene and 2,4,4-trimethylpentene	Monobutyl DPA $C_{16}H_{19}N$	

[a] DSL – Domestic Substances List
[b] Chemical Formula of Representative Chemical Structure
[c] As per industry submission

In Tables 2-1 and 2-2, SDPAs have been described based on their chemical structure. Given that some SDPAs in this assessment share analogous structures, Table 2-3 provides the cross-reference between structures and the CAS RN for all the SPDAs in this assessment. This representative chemical structure nomenclature will be used for the ecological assessment.

Table 2-3 Common chemical structures found in the SDPA assessment

Chemical Structure	Found in the Discrete Substance	Found in the UVCB
Monobutyl DPA	None	CAS RN 184378-08-3
Dibutyl DPA	None	CAS RN 184378-08-3
Monooctyl DPA	CAS RN 4175-37-5	CAS RN 68411-46-1 CAS RN 184378-08-3 CAS RN 68921-45-9
Dioctyl DPA	CAS RN 15721-78-5 CAS RN 26603-23-6 CAS RN 101-67-7	CAS RN 68411-46-1 CAS RN 184378-08-3 CAS RN 68921-45-9
Monononyl DPA	CAS RN 27177-41-9	CAS RN 36878-20-3 CAS RN 68608-79-7
Dinonyl DPA	CAS RN 24925-59-5	CAS RN 36878-20-3 CAS RN 68608-79-7

Monobutyl monooctyl DPA	None	CAS RN 184378-08-3 CAS RN 68411-46-1
Monooctyl monostyrenated DPA	None	CAS RN 68921-45-9
Monostyrenated DPA	None	CAS RN 68442-68-2 CAS RN 68921-45-9
Distyrenated DPA	None	CAS RN 68442-68-2
Dimethyl distyrenated DPA	CAS RN 10081-67-1	-
Diethyl monononyl DPA	None	CAS RN 68608-77-5
Diethyl dinonyl DPA	None	CAS RN 68608-77-5

3. Physical and Chemical Properties

Relevant physical and chemical properties for the SDPAs and the values selected for use in the modelling of persistence, bioaccumulation and toxicity are located in Appendix A. Empirically-derived values reported as unbounded (i.e., values with > or <) and those values originating from studies that could not be obtained to determine their robustness (i.e., those cited in US EPA 2009) were not considered applicable for use in this assessment.

Available empirical data for the SDPA representative structures indicate that these structures have low water solubility (i.e., < 0.1 to 2 mg/L) (SafePharm 2002a,b, BASF SE 2010a), low vapour pressure (<1 to $9x10^{-5}$ Pa) (Intertek Pharmaceuticals 2013, SafePharm 2002a, BASF SE 2010a, b; US EPA 2009) and high log K_{ow} values (4.64 to 8.8) (Intertek Pharmaceuticals 2013, Safepharm Laboratories 2002a, c).

Monobutyl DPA has modelled water solubility that is two orders of magnitude greater than that of any of the other SDPA structures in this assessment. This high modelled water solubility is attributed to the monobutyl component with the least branching and lowest number of carbon atoms in the assessment. While the Experimental Value Adjustment (EVA) method provides semi-empirical values for this assessment, it is acknowledged that there remains some uncertainty in these particular values because an extrapolation process is used.

Empirical data for the representative structures suggest that volatilization from water and moist soil is low to moderate based on the vapour pressure and the Henry's Law Constants. The modelled log K_{oc} values (3.75 – 8.17) suggest low to moderate mobility in soil and the modelled water solubility suggest that the representative structures are sparingly soluble. Empirical data for some physical-chemical properties for the SDPAs identified as UVCBs were obtained from commercial product data. The commercial product usually contained approximately 95-100 % of the UVCB based on information provided in the Material Safety Data Sheets. This was considered sufficient purity to attribute the physical-chemical property value to the UVCB as a whole. It should be noted, that, although the commercial product data are attributed to the whole UVCB, the actual chemical structures could differ from the representative structures presented in this assessment. As such, the commercial product data for the UVCB may differ from the modelled values presented in this assessment. The commercial product data for the UVCBs suggest low solubility (< 0.005 – 2 mg/L).

SDPAs contain an ionizable functional group (amine, organic base) and can exist in both the neutral and ionized forms in the environment. The estimated dissociation constant (pKa, 0.8±0.4) of the conjugate acid indicate that the neutral form will strongly dominate in aqueous environments across the environmentally relevant range of pH 6-9. Accordingly, the modelled physical-chemical property values found in Appendix A are for the neutral forms only.

The OECD Toolbox (OECD 2012) was employed to identify any potential analogues with measured data for physical and chemical properties. The identified analogues with empirical data were not considered sufficiently structurally similar to the members of the SDPAs assessment. Rather, the identified analogues exhibited structural, physical, and chemical properties (e.g., water solubility, vapour pressure and log K_{ow}) more similar to their starting material, diphenylamine. These differences were deemed too large to take into account using quantitative methods or qualitative methods.

However, if there are slight to moderate differences in structure, adjustments to property estimates can be accounted for by using the EVA method in the EPISuite model (EPISuite 2000-2010). Therefore, the empirical water solubility and log K_{ow} data from mononononyl DPA and the empirical Henry's Law Constant data for diphenylamine (CAS RN 122-39-4) were used as read-across and subjected to the EVA method to estimate the same physical-chemical property values for other SDPAs in the assessment.

EVA modelled values were selected to ensure physical-chemical parameter consistency amongst the structures. There is one discrepancy in water solubility (monobutyl DPA) and one discrepancy for Henry Law's Constant (diethyl dinonyl DPA). Diethyl dinonyl DPA has the highest modelled log K_{ow} (13.58) but also the lowest water solubility (4.8×10^{-7} mg/L) amongst the SDPAs in this assessment. A physical-chemical parameter consistency check was performed and considered reasonably acceptable for the log K_{ow} values for all the SDPAs, but the log K_{ow} value for diethyl dinonyl DPA is still considered to be high.

4. Sources

SDPAs do not occur naturally in the environment. According to the results of a DSL Inventory Update conducted for the year 2008, four SDPAs were not in commerce (CAS RN 4175-37-5, 15721-78-5, 26603-23-6, and 184378-08-3) at reporting thresholds of 100 kg/year (ECCC 2013a) and three substances were not surveyed (CAS RN 24925-59-5, 68608-79-7 and 68921-45-9). The results for the other SDPAs indicated that, in 2008, more than 10 000 000 kg of SDPAs were manufactured and 1 000 000 – 10 000 000 kg were imported into Canada. In a separate survey for the year 2006, results showed that 100 000 – 1 000 000 kg of the SDPA CAS RN 68921-45-9 (BNST) were imported into Canada and 1 000 000 – 10 000 000 kg were manufactured (ECCC 2009b); however, quantities of BNST in commerce are known to now be considerably lower.

In 2011 and 2012, voluntary questionnaires were issued to Canadian and international producers of SDPAs and the automotive manufacturing sector to obtain information on their production of SDPAs and use of SDPAs in lubricants, respectively (ECCC 2011b, 2012a, 2012b). A notice issued under section 71 of CEPA (ECCC 2012a) for the reporting year 2011, indicated that between 1 000 000 and 10 000 000 kg of SDPAs were imported into Canada and more than 10 000 000 kg of SDPAs were manufactured and sold as part of speciality chemical additive packages[3] or as individual substances by approximately forty companies in Canada. The majority of SDPAs produced in Canada are exported (more than 90%). BNST was not surveyed in 2011 but based on industry submissions, the following SDPAs were reported to be manufactured or imported into Canada in 2011 above the reporting threshold of 100 kg/year: CAS RN 101-67-7, 10081-67-1, 15721-78-5, 27177-41-9, 36878-20-3, 68411-46-1, 68442-68-2, 68608-77-5, 68608-79-7 and 184378-08-3. Other SDPAs surveyed in 2011 (CAS RNs 4175-37-5, 24925-59-5 and 26603-23-6) may be present as representative structures within SDPAs which are UVCBs in this group or may be analogous to these representative structures (ECCC 2012a; Study Submission 2014a).

[4]Additive packages include a mixture of additives (specialty chemicals) based on the function and properties of the substances used and specifications of the end-product to which it will be added during product formulation (e.g., in lubricants, plastic, foam, rubber and miscellaneous products).

5. Uses

SDPAs are a subclass of amine antioxidants. Amine antioxidants are used to prevent the degradation of the materials (e.g., lubricants, foams) into which they are added. SDPAs perform as primary antioxidants and function by destroying free radicals as they form, thereby preventing degradation of the base organic compounds (Hadjuk et al. 2012). Antioxidants are added in polyols imported for the production of polyurethane foams, resulting in concentrations of <0.1% SDPAs in the finished foam products (US EPA 2009).

Two common types of antioxidants used in lubricants are chemically known as hindered phenols and substituted (or alkylated) diphenylamines. For mild lubricant applications, phenolic antioxidants are often used because they tend to be less costly. SDPAs are commonly used in more demanding applications, such as engine oils, compressor oils, turbine oils, and aviation oils. It is also common to use a combination of phenolic and SDPA antioxidants in a formulation as they are known to have a synergistic effect (ECCC 2009c).

In Canada, SDPAs are primarily used as antioxidants in the blending of lubricants. Lesser quantities of SDPAs are used in the manufacturing of plastic, polyurethane foam, rubber, and miscellaneous products. SDPAs are also added to adhesive mixtures in the manufacturing of hot melt adhesives and other industrial adhesives not intended for commercial or consumer use (ECCC 2012a). Some SPDAs are approved for use in adhesives used in food packaging materials intended for consumer use (February 2013 email from Food Directorate, to Risk Management Bureau, Health Canada; unreferenced).

SDPAs may be imported or sold as part of a speciality chemical additive package (ECCC 2012b). These packages are not produced in Canada but are imported from the United States and Europe (ECCC 2012b). SDPAs are also imported into Canada in polymers or polyols for use in the manufacturing of plastics or foams. SDPA concentrations in the final plastic and flexible/rigid polyurethane foam products are typically less than 0.1% (ECCC 2012a). Between 10 000 – 100 000 kg of SDPAs were reported to be used as antioxidants in the manufacturing of plastic and flexible/rigid polyurethane foam products. CAS RN 68921-45-9 (BNST) was not surveyed in 2011 or 2012.

SDPAs are also added to the rubber mixture in the manufacturing stage of the rubber compound or rubber sheets and then sold to rubber product manufacturing facilities. Between 10 000 and 100 000 kg of SDPAs were reported to be used in the rubber sector as antioxidants and anti-degradants in the manufacturing of rubber products (e.g., tires, belts and bushings) (ECCC 2012b). CAS RN 68921-45-9 (BNST) was not surveyed in 2011 or 2012.

SDPAs are used in the United States as anti-degradants in rubber, foamed polymers and high-temperature fluids, such as lubricants, gear oils and hydraulic

fluids (US EPA 2009). SDPAs are reported to be used in the European Union in lubricants, greases, polyurethanes, hydraulic fluids, metalworking fluids and rubber and plastic products (ECHA 2013a,b,c).

The SDPAs considered in this assessment are not listed as approved food additives in Canada in the *Lists of Permitted Food Additives* which have been incorporated by reference in Marketing Authorization under the authority of the *Food and Drugs Act* (Health Canada 2013). SDPAs included in this group are not listed in the internal Drug Product Database (DPD 2013), , the Natural Health Products Ingredients Database (NHPID 2013) or the Licensed Natural Health Products Database (LNHPD 2013) as medicinal or non-medicinal ingredients present in disinfectant, human or veterinary drug products in Canada (March 2013 e-mail from Therapeutic Products Directorate, Natural Health Products Directorate and Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

6. Measured Concentrations

SDPAs were measured in environmental media (i.e. water, sediments and biota) as well as in wastewater and biosolids from relevant locations across Canada. No other measured environmental concentrations were identified worldwide. Environment and Climate Change Canada and a manufacturer of SDPAs were each involved independently with sampling near a known manufacturing site in Canada. These measured concentrations are specific to that manufacturing site and its receiving waterbody. Environment and Climate Change Canada was also involved with sampling activities near industrial and urban areas in Ontario and other locations at or near wastewater treatment systems (WWTS)[4] in Canada in an attempt to have representation from other SDPA industrial, commercial and consumer activities. Additional information on measured concentrations is compiled in ECCC (2017a).

6.1 Site-specific measured concentrations submitted by industry

SDPA concentrations measured using liquid chromatography – mass spectroscopy (LC-MS) in water and sediment (Study Submission 2014a, Study Submission 2014b, Study Submission 2014c) were provided by industry for selected SDPAs near a Canadian manufacturing site.

The sediment concentration data on SDPAs (i.e. monooctyl, dioctyl, mononoyl and dinonyl DPA components were reported) from Study Submission 2014a was critically reviewed by Environment and Climate Change Canada and a number of limitations were identified. These included poor recovery due to insufficient extraction of SDPAs through the utilization of a mechanical shaker with isopropanol; insufficient details on the sampling and storage protocols; poor detection using full scan for the mass spectrometer analysis (i.e. use of a full scan decreases the probability of detecting SDPAs by raising the detection limit); and quality control/quality assurance measures not being reported. Some of these deficiencies may have resulted in an underestimation of SDPA levels in sediments and thus, the results were not reported in this assessment.

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

The industrial wastewater and surface water data on SPDAs (i.e. monononyl and dinonyl DPA components were reported) from Study Submission 2014b and Study Submission 2014c were also critically reviewed by Environment and Climate Change Canada. The industrial wastewater was sampled on four separate occasions to characterize SDPA levels as a snapshot in time. Similar to the sediment data, limitations in methodology may have resulted in an under-estimation of SDPA concentrations in both the industrial wastewater and surface water samples. Based on the review, analytical deficiencies identified included accuracy of the calibration curve calculations; matrix suppression as the water samples were directly injected without dilution with solvent; and absence of spike and recovery information. Due to these deficiencies, the values from Study Submission 2014a, 2014b, 2014c were not considered further in this screening assessment.

Tables 6-1- 6-3 below presents biological, sediment and water data from Study Submission 2015a. This data was collected by industry in 2014-2015 for SDPA analysis near the same Canadian manufacturing site. Concentrations of SDPAs were measured in biota from various trophic levels (i.e., aquatic plants, fish and invertebrates) to help inform understanding of bioaccumulation behaviour of SDPAs. SDPAs were not measured above the method detection limits (i.e. < 0.02 – < 0.2 µg/g whole fish) in any fish tissue residues for any of the SDPAs analyzed (i.e, mononononyl DPA, dinonyl DPA, monooctyl DPA, dioctyl DPA, monobutyl DPA, dibutyl DPA, monobutyl monooctyl DPA, and dimethyl distyrenated DPA). Water and sediment samples were also analysed for SDPAs using LC-MS. The depth of the sediment cores ranged between 40 and 60 cm. SDPA levels in surface water were not detected above the method detection limits (< 0.017 – < 0.406 µg/L). Environment and Climate Change Canada critically reviewed the data from Study Submission 2015a. The review found a number of deficiencies, as follows:

- Sediment core sampling did not allow for historical observations (i.e. no protection applied to avoid vertical mixing and sections were not dated); however, the sediment core samples can be viewed as grab samples for sediment concentrations near an industrial area.
- The analytical methods for water and biota were not supported with sufficient quality assurance and quality control information and are likely to under-report due to high method detection limits.
- In the bioaccumulation/trophic magnification study, there was insufficient sampling at the lower trophic levels (e.g., sediment-dwelling macroinvertebrate species) given the expected presence of SDPAs in the sediment. Sediment-dwelling macro-invertebrate species are a core part of a bentho-pelagic foodweb in direct contact with sediments; in addition, the study did not specify how trophic position was calculated without a primary consumer. For example, there is uncertainty regarding the trophic position and feeding relationship of the species sampled and whether they represent the best species to represent a bentho-pelagic foodweb in this creek. Sediment macro-invertebrates, the base trophic position in the

foodweb, were not sampled yet it is expected that these species would have the highest exposure to SDPAs. Five fish species (central stoneroller, creek chub, common shiner, white sucker, and pumpkinseed) were sampled from the local waterbody. There is some uncertainty regarding the feeding relationships of the species selected as most species had feeding preferences for aquatic/terrestrial insects, algae, and other fish. Only the white sucker and the pumpkinseed had comparatively preferential feeding for benthic species. As such, tissue residue concentrations were not used quantitatively to determine bioaccumulation factors. The tissue residues therefore represent site-specific exposure conditions and may not necessarily reflect the intrinsic ability of SDPAs to bioaccumulate given the different controlling factors for exposure in different environments across Canada.

Inspite of the study uncertainties and limitations, SDPAs were not measured above the method detection limits (< 0.02 – < 0.2 µg/g whole fish,<0.017 – <0.406 µg/L in surface water). The sediment core data cannot be used to determine historical deposition, but it can be used simply as sediment concentrations along with the surface sediment concentrations in the SDPA manufacturing exposure scenarios. Average total SDPAs (of the components listed in Table 6-1 – 6-3) in sediments ranged from 10 to 5 500 ng/g dw.

Table 6-1 Summary of core and surface sediment concentrations for some SDPAs upstream of a Canadian manufacturing site (Study Submission 2015a)

Component	Sampling Location[b]	Range of Concentration for Sediment Cores (µg/kg dw[c])	Range of Concentration for Surface Sediment (µg/kg dw) (upper 2 cm)
Monononyl DPA	Upstream of manufacturing operations	NS[a]	< 3
Dinonyl DPA	Upstream of manufacturing operations	NS[a]	< 6
Monooctyl DPA	Upstream of manufacturing operations	NS[a]	< 2
Dioctyl DPA	Upstream of manufacturing operations	NS[a]	< 3
Monobutyl DPA	Upstream of manufacturing operations	NS[a]	< 3

Component	Sampling Location[b]	Range of Concentration for Sediment Cores (µg/kg dw[c])	Range of Concentration for Surface Sediment (µg/kg dw) (upper 2 cm)
Dibutyl DPA	Upstream of manufacturing operations	NS[a]	< 4
Monobutyl monooctyl DPA	Upstream of manufacturing operations	NS[a]	< 3
Dimethyl distyrenated DPA	Upstream of manufacturing operations	NS[a]	20

Table 6-2 Summary of core and surface sediment concentrations for some SDPAs within a Canadian manufacturing site (Study Submission 2015a)

Component	Sampling Location[b]	Range of Concentration for Sediment Cores (µg/kg dw[c])	Range of Concentration for Surface Sediment (µg/kg dw) (upper 2 cm)
Monononyl DPA	Within manufacturing site property boundaries	167 – 4444	8 – 266
Dinonyl DPA	Within maufacturing site property boundaries	402 – 3298	55 – 396
Monooctyl DPA	Within manufacturing site property boundaries	6 - 2072	4 – 390
Dioctyl DPA	Within manufacturing site property boundaries	23 – 21 184	10 – 2263
Monobutyl DPA	Within manufacturing site property boundaries	< 2 - 582	< 2 – 5
Dibutyl DPA	Within	3 – 778	< 3 – 11

	manufacturing site property boundaries		
Monobutyl monooctyl DPA	Within manufacturing site property boundaries	7 - 1881	< 4 – 137
Dimethyl distyrenated DPA	Within manufacturing site property boundaries	175 – 25 266	341 – 4611

Table 6-3 Summary of core and surface sediment concentrations for some SDPAs downstream of a Canadian manufacturing site (Study Submission 2015a)

Component	**Sampling Location[b]**	**Range of Concentration for Sediment Cores (µg/kg dw[c])**	**Range of Concentration for Surface Sediment (µg/kg dw) (upper 2 cm)**
Monononyl DPA	Downstream of manufacturing operations	NS[a]	53
Dinonyl DPA	Downstream of manufacturing operations	NS[a]	308
Monooctyl DPA	Downstream of manufacturing perations	NS[a]	19
Dioctyl DPA	Downstream of manufacturing operations	NS[a]	417
Monobutyl DPA	Downstream of manufacturing operations	NS[a]	<2
Dibutyl DPA	Downstream of manufacturing operations	NS[a]	7
Monobutyl monooctyl DPA	Downstream of manufacturing operations	NS[a]	18
Dimethyl distyrenated DPA	Downstream of manufacturing operations	NS[a]	2292

[a] not sampled
[b] both upstream and downstream sampling locations consisted of a single grab sample
[c] dry weight

6.2 Measured concentrations generated by Environment and Climate Change Canada

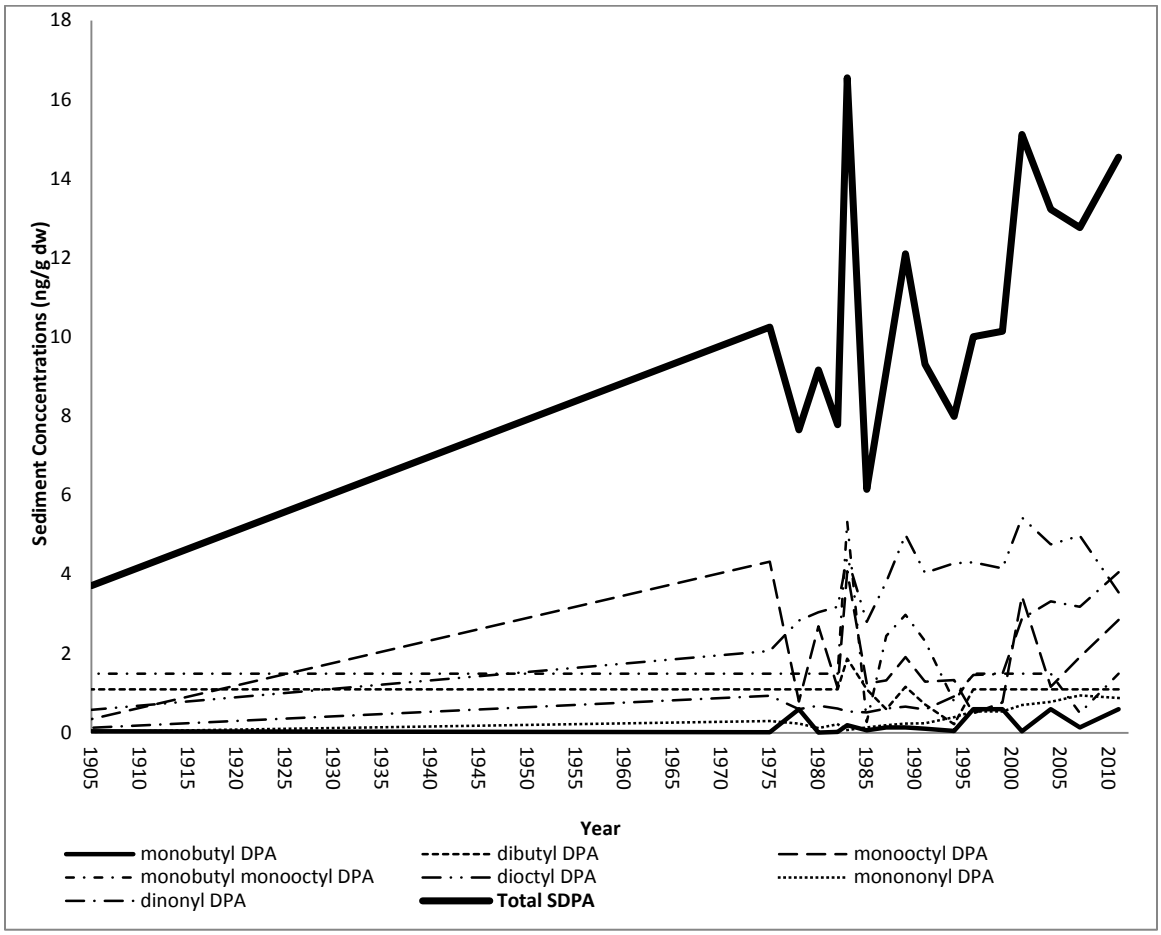
Environment and Climate Change Canada conducted sampling and analyses of SDPAs in surface water, sediments (surface and cores) and biota near the same Canadian SDPA manufacturing site identified in section 6.1 and across Ontario. Sampling and analyses were also conducted of wastewater (influent and effluent) and biosolids from WWTSs across Canada, including the WWTS which receives treated industrial wastewater from the afore-mentioned SDPA manufacturing site and from other contributing sources (see Tables 6-4 - 6-10). Sampling for the various media took place between 2012 and 2015. All analytes were detected using LC-MS.

6.2.1 Sediment and Surface Water

Analytical methods developed by Environment and Climate Change Canada for SDPAs were validated using instrument detection. Accuracy[5] and method detection limits[6] were verified using spiked sample and recovery experiments, matrix effects by spiking extracts, and linear dynamic range of calibration curves. The extraction efficiency for SDPAs from sediment had recoveries close to 60% on average. Reasonable extraction efficiencies were observed for the extraction of SDPAs from aqueous media with recoveries of 77 to 79% for surface water. The extraction efficiency for butyl DPAs was close to 40% in surface water, possibly representative of its higher degree of water solubility. Reliability of the sediment and surface water sampling is considered acceptable and is considered further in the exposure scenarios for this assessment.

[5] Concentration yielding an instrument response with signal to noise ratio of 5
[6] Standard deviation of at least 5 method blanks times three with matrix effect applied

Figure 6-1 Historical trend of some SDPA concentrations in sediment (ng/g dw) in Lake Ontario (1905 – 2011) (ECCC 2017a)



Long description:

Figure 6-1 shows the historical profile of some SDPA concentrations in sediment cores from Lake Ontario from 1905 – 2011. Although it is possible that bioturbation and other types of mixing may have obscured past historical trends, Figure 6-1 does indicate that individual SDPA concentrations generally remained below 6 ng/g dw with dioctyl DPA, monobutyl monooctyl DPA, and monooctyl DPA showing the greatest presence in sediment over the years. Also, monooctyl DPA, dinonyl DPA, monobutyl monooctyl DPA, and monobutyl DPA show a slight increasing trend since 2005.

Table 6-4 presents the range of concentrations in core sediment for SDPAs in Lake Ontario. Sediment core depth ranged from 0.5 to 16 cm. Table 6-5 shows the range of concentrations in surface sediment across sites in Ontario and at a Candian SDPA manufacturing site. Tables 6-6 and 6-7 show the surface water concentrations for some SDPAs across Ontario and at a Canadian SDPA manufacturing site.

Table 6-4 Summary of sediment core concentrations for some SDPAs in Lake Ontario (ECCC 2017a)

Component	Range of concentration in sediment cores from Lake Ontario (ng/g dw)
Monobutyl DPA	0.013 – < 0.60
Dibutyl DPA	0.22 – 1.9
Monooctyl DPA	<0.35 – 4.3
Monobutyl monooctyl DPA	0.28 – 5.3
Diooctyl DPA	< 0.58 – 5.4
Monononyl DPA	0.023 – 0.95
Dinonyl DPA	< 0.13 – 4.1
Dimethyl distyrenated DPA	0.064 – 2.9
Diethyl monononyl DPA	NS[a]

[a] not sampled

Table 6-5 Summary of surface sediment concentrations (ng/g dw) for some SDPAs in Ontario and in a waterbody near a manufacturing site (ECCC 2017a)

Component	Cootes Paradise	Lake Ontario	Detroit River	St.Clair River	Etobicoke Creek	Waterbody near manufacturing site
Monobutyl DPA	0.014 – 0.10	0.032 – 0.67	0.10 - 0.77	< 0.11 – 0.35	< 0.14 – 1.8	0.019 – 0.24
Monooctyl DPA	0.98 – 9.1	2.5 - 35	7.0 – 16	0.92 – 7.1	0.5 – 6.5	0.36 – 9.6
Dibutyl DPA	0.061 - < 0.2	< 0.2	< 0.2 – 2.3	< 0.032 – 0.33	1.4 – 7.7	< 0.33 – 4.7
Monobutyl monooctyl DPA	0.097 – 0.30	0.03 – 0.91	0.027 – 6.5	0.047 - 0.66	4.0 - 33	0.034 – 34
Dioctyl DPA	0.26 – 1.3	< 0.068 – 4.8	< 0.031 – 7.0	0.11 – 1.0	3.5 - 22	0.051 – 57
Monononyl DPA	0.74 – 1.9	<0.073 – 1.6	0.4 – 12	0.48 – 0.89	8.1 - 31	0.17 – 19
Dinonyl DPA	1.5 – 3.9	0.25 – 16	< 1 - 21	1.6 – 3.1	26 -88	0.36 – 76
Dimethyl distyrenated DPA	0.19 – 0.47	< 0.032 – 1.1	< 0.043 - 11	< 0.050 – 0.079	0.97 - 39	0.22 – 190
Diethyl monononyl DPA	< 0.2	< 0.	< 0.2 – 0.23	< 0.2	< 0.2	n/a

n/a: not available

Table 6-6 Summary of unfiltered surface water concentrations (ng/L) for some SDPAs in Lake Ontario and in a waterbody near a manufacturing site (ECCC 2017a)

Component	Range of concentration in surface water from Lake Ontario (ng/L)	Range of concentration in surface water from a waterbody near the manufacturing site (ng/L)
Monobutyl DPA	0.035 - <0.7	< 0.17 – 0.52
Dibutyl DPA	< 0.13 - <0.54	< 0.13 – <0.55
Monooctyl DPA	0.0095 <1.4	0.0080 < 1.3
Monobutyl monooctyl DPA	0.045 - < 2.4	0.090 – <3.5
Dioctyl DPA	< 0.36 – 5.4	0.26 – <0.88
Monononyl DPA	0.014 – 0.33	0.16 – 0.56
Dinonyl DPA	0.19 - < 0.60	0.29 – 33
Dimethyl distyrenated DPA	0.29 – 5.0	< 0.48 – 99
Diethyl monononyl DPA	0.048 – 0.12	<0.1

Table 6-7 Summary of unfiltered surface water concentrations (ng/L) for some SDPAs in other sites in Ontario (ECCC 2017a)

Component	Detroit River	Etobicoke Creek	Lake Erie	St. Clair River
Monobutyl DPA	0.041	< 0.28	< 0.7	0.013 - < 0.7
Monooctyl DPA	0.076	< 0.72	< 1.4	< 0.0.047 – 1.4
Dibutyl DPA	0.14	< 0.25	0.081	0.0073 - < 0.13
Monobutyl monooctyl DPA	1.0	< 1.8	0.38	0.082 - < 2.4
Dioctyl DPA	2.2	4.7 – 5.9	1.4	<0.36 - < 0.49
Monononyl DPA	0.60	0.20 – 0.46	0.38	0.077 - < 0.22
Dinonyl DPA	3.2	0.86 – 2.0	1.4	0.30 – 0.63
Dimethyl distyrenated DPA	3.0	3.1 – 4.3	1.4	< 0.48
Diethyl monononyl DPA	< 0.1	0.031 - 0.32	<0.1	< 0.1

Zhang et al. (2016) developed and tested an analytical method for the determination of components of two SDPAs (CAS RNs 68442-68-2 and 68411-46-1) in sediment, wastewater, and biosolids. The method was based on gas

chromatography-tandem mass spectrometry (GC-MS/MS). The methodology was tested using nine sediment samples collected in Ontario in 2012. The determined concentrations were comparable to the results from ECCC (2017a) except for dioctyl DPA with concentrations an order of magnitude greater, 765 ng/g (dry weight dw)). The median concentrations ranged from below the detection limit for monostyrenated DPA (0.08 ng/g dw) to 9.78 ng/g dw for dioctyl DPA.

6.2.2. Wastewater

Wastewater influents and effluents were sampled from 9 WWTSs across Canada, including the WWTS receiving industrial wastewater from a Canadian SDPA manufacturing site, and analyzed for SDPAs using LC-MS. Samples were collected using composite sampling techniques: 200 mL of water every fifteen minutes for 24 hours in a refrigerated sampling device using pre-cleaned stainless steel containers. Composite sampling was repeated for three consecutive days at each WWTS during both warm and cold seasons. Wastewater treatment types included facultative and aerated lagoons, chemically assisted primary treatment, secondary aerobic biological treatment, and advanced biological nutrient removal treatment. Grab samples of biosolids were also collected from each WWTS for three consecutive days during both warm and cold seasons. All sampling was conducted by Environment and Climate Change Canada in the manner as described in Guerra et al. (2015). Reliability of the wastewater sampling is considered acceptable and the determined concentrations are used in the exposure scenarios for this assessment. Reasonable efficiencies were observed for the extraction of SDPAs with 77% to 79% for influent and effluent. For liquid samples, the method detection limit was highest for influent, followed by effluent and then surface water.

Environment and Climate Change Canada's wastewater sampling (Table 6-8) showed that WWTSs across Canada had SDPAs in their effluent but at significantly lower concentrations compared to influent. The major SDPA components detected in wastewater influent were monooctyl DPA, monobutyl monooctyl DPA, dioctyl DPA, monononyl DPA and dinonyl DPA, with highest concentrations corresponding to dinonyl DPA (median of 159, maximum of 2779 ng/L). Influent and effluent concentrations' detection frequency ranged between 70.6 – 100% with diethyl mononononyl DPA detected the least at 15 - 38%. The remaining SDPAs had detection frequencies above 70%. All SDPAs were detected in wastewater effluent with concentrations ranging from 8.8 ng/L (monobutyl DPA) to 125 ng/L (dinonyl DPA). The median concentrations of SDPA components ranged from 3.36 ng/L (dimethyl distyrenated DPA) to 159 ng/L (dinonyl DPA) in influent and 0.48 ng/L (dimethyl distyrenated DPA) to 13.0 ng/L (dinonyl DPA) in effluent.

Biosolids generated by WWTSs (Table 6-8) appear to contain a sizeable fraction of SDPAs with concentrations as high as 13 760 ng/g dw for dinonyl DPA. Total SDPAs (of the components listed in Table 6-8) in the biosolids from these plants

ranged from 172 to 31 297 ng/g dw. Biosolids treatment included dewatering only, aerobic digestion and/or anaerobic digestion. Biosolids detection frequency for SDPAs was predominately 100% with only monobutyl DPA detected at the lesser frequency of 95%.

Table 6–8 Summary of influent, effluent and biosolids concentrations for some SDPAs at WWTSs across Canada (ECCC 2017a)

Component	Range of concentration for influent (ng/L)	Range of concentration for effluent (ng/L)	Range of concentration in biosolids (ng/g dw)
Monobutyl DPA	0.12 – 43	0.031 – 8.8	< 0.044 – 57812
Monooctyl DPA	0.14 – 290	0.016 – 38	7.3 – 2640
Dibutyl DPA	< 0.54 – 98	0.016 – 26	1.6 – 594
Monobutyl monooctyl DPA	0.78 – 654	0.025 – 79	8.8 – 2444
Dioctyl DPA	2.4 – 375	0.0085 – 45	33 – 3220
Monononyl DPA	0.83 – 1422	< 0.030 – 65	7.5 – 7580
Dinonyl DPA	5.6 – 2779	0.080 – 125	109 – 13760
Dimethyl distyrenated DPA	0.041 – 49	0.090 – < 9.1	4.7 – 462
Diethyl monononyl DPA	0.030 – 3.6	0.016 – 0.24	< 0.22 – 19

Zhang et al. (2016) analyzed 5 biosolids concentrations from wastewater treatment systems across Canada in July 2013. Biosolids concentrations of 0.59 to 4.52 ng/g dw for monostyrenated DPA and 48.22 to to 513.86 ng/g dw for diooctyl DPA.

6.2.3Biota

White Sucker fish (*Catostomus commersonii*) were sampled upstream and downstream of a WWTS receiving wastewater from a Canadian SDPA manufacturing site (ECCC 2017a, b). Tissues were analyzed by liquid chromoatography tandem mass spectrometry (LC-MS/MS) in 2014. Method blanks spike and recovery and matrix effects were determined for the nine SDPAs in Table 6-9. Samples were quantified for SDPAs using standards of SDPAs for monobutyl DPA, dibutyl DPA, monooctyl DPA, dioctyl DPA, monobutyl monooctyl DPA, monononyl DPA, dinonyl DPA, dimethyl distyrenated DPA and monooctyl monostyrenated DPA. Although an attempt was made to sample comparable fish both upstream and downstream of the manufacturing site, white sucker upstream fish were larger compared to downstream fish. A mean body mass of 223 ±48 g was measured for upstream samples compared to 91 ±35 g for downstream fish. Wet weight concentrations were statistically higher downstream than upstream of the site for monobutyl DPA ($p = 0.025$), monononyl DPA ($p = 0.021$), dimethyl distyrenated DPA (0.0044), and monooctyl

monostyrenated DPA (p = 0.046) in white sucker. In general, the median concentrations for the other SDPAs were also higher in the downstream population; however, the difference was not statistically significant.

Table 6-9 Summary of White Sucker concentrations for some SDPAs upstream and downstream of a WWTS receiving wastewater from a Canadian SDPA manufacturing site (ECCC 2017a, b)

Component	Wet weight concentrations (ng/g ww)	Lipid weight concentrations (ng/g lw)	Detection limits (ng/g dw)
Monobutyl DPA Upstream	<LOD – 0.13	<LOD – 5.2	0.004
Monobutyl DPA Downstream	<LOD – 0.013	0.02 – 0.60	0.004
Monooctyl DPA Upstream	0.007 – 0.48	0.42 – 19	0.002
Monooctyl DPA Downstream	0.007 – 0.26	0.27 - 16	0.002
Dibutyl DPA Upstream	<LOD – 0.24	< LOD – 18	0.004
Dibutyl DPA Downstream	0.038 – 0.71	1.6 - 28	0.004
Monobutyl monooctyl DPA Upstream	<LOD – 0.64	<LOD – 50	0.005
Monobutyl monooctyl DPA Downstream	0.03 – 1.4	1.2 - 127	0.005
Dioctyl DPA Upstream	<LOD – 0.29	< LOD – 11	0.001
Dioctyl DPA Downstream	0.00 – 0.52	0.06 - 48	0.001
Monononyl DPA Upstream	0.005 – 0.046	0.36 – 3.2	0.005
Monononyl DPA Downstream	0.04 – 0.44	2.3 - 37	0.005
Dinonyl DPA Upstream	<LOD – 0.087	<LOD – 3.3	0.008
Dinonyl DPA Downstream	<LOD – 0.086	<LOD – 5.1	0.008
Dimethyl distyrenated DPA Upstream	<LOD– 0.29	<LOD – 14	0.001
Dimethyl distyrenated DPA Downstream	0.37 – 5.5	15 - 235	0.001

Monooctyl monostyrenated DPA Upstream	<LOD – 0.073	<LOD – 5.2	0.011 – 0.55
Monooctyl monostyrenated DPA Downstream	0.018 – 0.14	1.4 – 5.7	0.011 – 0.55
Monostyrenated DPA Upstream	<LOD – 20.82	<LOD - 1890	0.025 - 0.14
Monostyrenated DPA Downstream	<LOD – 0.76	<LOD - 37	0.025 - 0.14

LOD: limit of detection

In another sampling effort, Lu et al. (2016a) sampled crayfish (*Orconectes* spp), hornyhead chub (*Nocomis biguttatus*), and common shiner (*Luxilus cornutus*) in an urban creek in Canada. Sampling was undertaken in the urbanized area of a creek, and upstream of the urban area in a rural/agricultural area in 2014 (Table 6-8). Analyses were performed using an ultra performance liquid chromatography tandem mass spectrometer (UPLC-MS/MS) for monobutyl DPA, dibutyl DPA, monooctyl DPA, monobutyl monooctyl DPA, dioctyl DPA, monononyl DPA, dinonyl DPA, and dimethyl distyrenated DPA (Table 6-8). Overall, the highest concentrations were determined for crayfish tissues. Lipid weight levels for the highest measured components in crayfish included dioctyl DPA, dinonyl DPA and dimethyl distyrenated DPA, with concentrations ranging up to 3389 ng/g (lw) in a downstream sample. Generally, however, concentrations in biota were higher downstream in comparison to upstream for all biota sampled.

Table 6-10 Summary of crayfish, chub and shiner concentrations for some SDPAs in an urbanized area and upstream of the urbanized area (Lu et al. 2016a)

Component	Crayfish (lw) concentrations (ng/g)	Chub (lw) concentrations (ng/g)	Shiner (lw) concentrations (ng/g)
Monobutyl DPA Upstream	<0.003 – (0.03)	<0.004 – 0.11	<0.004
Monobutyl DPA Downstream	<0.003 – 0.71	<0.004 – 0.07	<0.004 – 0.21
Monooctyl DPA Upstream	<0.05 – 4.86	0.55 – 4.80	<0.01 – 0.47
Monooctyl DPA Downstream	0.05 – 136	0.60 – 5.87	0.59 – 4.35

Dibutyl DPA Upstream	<0.004 – 18.8	<0.005	<0.005 – 0.26
Dibutyl DPA Downstream	0.50 - 135	<0.005 – 5.40	0.70 – 4.99
Monobutyl monooctyl DPA Upstream	<0.04 – 18.5	<0.01 – 1.23	1.02 – 1.50
Monobutyl monooctyl DPA Downstream	0.39 - 301	<0.01 – 72.7	0.42 – 16.8
Dioctyl DPA Upstream	<0.34	0.12 – 3.51	<0.005 – 0.28
Dioctyl DPA Downstream	<0.34 - 2067	0.02 – 67.3	0.19 – 4.14
Monononyl DPA Upstream	<0.02 – 4.67	<0.002	<0.002 – 0.96
Monononyl DPA Downstream	6.80 - 232	<0.002 – 4.75	1.06 – 37.3
Dinonyl DPA Upstream	<0.035 – 20.9	0.28 – 2.69	0.65 – 3.08
Dinonyl DPA Downstream	11.3 - 1838	<0.001 – 11.6	0.33 – 31.1
Dimethyl distyrenated DPA Upstream	<0.15	0.40 – 1.61	1.60 – 15.9
Dimethyl distyrenated DPA Downstream	<0.15 - 3389	0.29 – 96.0	1.70 – 83.9
Monooctyl monostyrenated DPA Upstream	<0.03 – 13.9	<0.03 – 9.97	<0.001 – <0.03
Monooctyl monostyrenated DPA Downstream	<0.01 – 25.0	<0.01 – 5.2	<0.01 – 2.56
Monostyrenated DPA Upstream	<0.008	<0.001 – 0.52	1.06 – 2.16
Monostyrenated DPA Downstream	<0.001 – 1.20	<0.001 – 0.22	<0.001 – 0.82

l.w.: lipid weight concentration

LOD: limit of detection

Lu et al. (2016b) also sampled for SDPAs in bottlenose dophins (*Tursiops truncatus*) (blood plasma) from Florida in 2014, northern pike (*Esox lucius*) (blood plasma) from the St. Lawrence River in 2011 and white sucker fish (*Catostomus commersonii*) (homogenate) from an urban creek in Ontario in 2014. For dolphin blood plasma, monooctyl DPA was detected in all samples with concentrations ranging from 0.05-0.07 ng/g (wet weight or ww). Two other SDPAs were detected in dolphin blood plasma, including dimethyl distyrenated DPA and monobutyl monooctyl DPA with concentrations up to 0.052 ng/g (ww). Higher detection frequencies and concentrations for all SDPAs except dimethyl distyrenate DPA were observed in northern pike blood plasma, up to 4.17ng/g (ww), compared to that from the dolphin, up to 0.072 ng/g (ww). For white sucker homogenates, monooctyl DPA, dibutyl DPA, monononyl DPA, monobutyl monooctyl DPA, dioctyl DPA and dimethyl distyrenated DPA were frequently detected and levels ranged from <0.000001 - 1.51 ng/g (w.w).

Sühring et al. (2016) reported that four SDPA components (monostyrenated DPA, monooctyl DPA, monooctyl monostryenated DPA, and dioctyl DPA) were the primary contaminants in European eels (*Anguilla anguilla*) from the German river Ems. All samples were analyzed with ultra high-resolution mass spectrometry and multidimensional gas chromatography; however, due to standard impurities and the lack of isotope-labelled reference standards, it was only possible to determine the relative order of magnitude of the SDPAs in the samples. Highest levels were detected in gonads of artificially matured female eels with concentrations in the µg/g ww range for dioctyl DPA and monooctyl DPA. Dioctyl DPA and monooctyl DPA concentrations were in the ng/g ww range, with highest levels in the gonads, followed by muscle tissue and eggs. The results of this study show that SDPAs are found in muscle tissues of eels, and may be maternally transferred into gonads and eggs.

7. Environmental Fate

The results of Level III fugacity modelling (New EQC 2011, Table 7-1) indicate that SDPAs are expected to predominantly partition to soil or sediment, depending on the environmental compartment of release. Five SDPAs representative structures were selected for modelling to represent a range of Log K_{ow} values.

Table 7-1 Percentage of selected SDPA representative structures partitioning into each compartment

Representative Structure	Percentage to media	Air	Water	Soil	Sediment
Monooctyl DPA	Air (100%)	11.7	1.43	45.2	41.7
Monooctyl DPA	Water (100%)	Negligible	3.31	Negligible	96.7
Monooctyl DPA	Soil (100%)	Negligible	Negligible	99.7	Negligible
Distyrenated DPA	Air (100%)	Negligible	Negligible	85.4	14.2
Distyrenated DPA	Water (100%)	Negligible	1.28	Negligible	98.7
Distyrenated DPA	Soil (100%)	Negligible	Negligible	99.8	Negligible
Diethyl dinonyl DPA	Air (100%)	Negligible	Negligible	94.5	5.38
Diethyl dinonyl DPA	Water (100%)	Negligible	Negligible	Negligible	99.1
Diethyl dinonyl DPA	Soil (100%)	Negligible	Negligible	Negligible	99.1
Monobutyl DPA	Air (100%)	5.29	Negligible	40.8	53.2
Monobutyl DPA	Water (100%)	Negligible	1.37	Negligible	98.6
Monobutyl DPA	Soil (100%)	Negligible	Negligible	99.8	Negligible
Monooctyl monostyrenated DPA	Air (100%)	Negligible	Negligible	78.3	20.4
Monooctyl monostyrened DPA	Water (100%)	Negligible	2.12	Negligible	97.7
Monooctyl monostyrened DPA	Soil (100%)	Negligible	Negligible	99.0	Negligible

When released to water, SDPAs are predominantly expected to adsorb to sediment (96.7- >99%). If SDPAs are released to soil, the structures are expected to have low mobility in soil based on their high log Koc values, and thus, almost exclusively adsorb to soils (>99%).

When released to air, less than 12% SDPAs remain in air. However, based on the sources of SDPAs, no releases are expected to air. Additionally, vapour pressures and Henry's Law constants indicate that volatilization from water and moist soil will be low. Therefore, releases to air will not be considered further in this assessment.

7.1 Persistence

Based on the Level III fugacity modelling results in conjunction with the physical-chemical properties of the SDPAs, soil and sediment are the key environmental reservoirs for SDPAs. However, as SDPAs are primarily released to the water compartment through industrial or consumer use, the degradation potential in water is relevant and is also examined. Empirical and modelled data for SDPAs were considered in order to provide the best possible weight of evidence for the persistence of the SDPAs.

Most of the biodegradation models suggest that there may be some primary degradation for monononyl DPA, monooctyl DPA, monostyrenated DPA, and diethyl monononyl DPA. However, dinonyl DPA, dioctyl DPA, distyrenated DPA, monooctyl monostyrenated DPA and diethyl dinonyl DPA generally do not undergo primary degradation. Nevertheless, biodegradation (i.e., ultimate) to complete mineralization is very slow for all chemical structures. In addition, the available UVCB product data for CAS RN 36878-20-3, 68411-46-1, 68442-68-2, 68608-79-7, and 184378-08-3 confirms that these substances are persistent. Read-across results from an analogous substance (CAS RN 36878-20-3) conducted to OECD guidelines and accordance with GLP, concluded that CAS RN 68921-45-9 is not readily biodegradable (ECHA 2014).

The multiple branched alkyl chains are known to degrade slowly and sterically impede the degradation of the diphenylamine core. Although some transformation is expected to occur in the water-soluble fractions, the biodegradation rate is expected to be minimal (BASF SE 2010a). In addition, most SDPAs contain structural features that are not easily biodegradable (e.g., C=C bonds). Therefore, considering the model and empirical results as well as the structural features, there is sufficient evidence to indicate that the biodegradation mineralization half-life of most SDPAs is ≥ 182 days in water. Using an extrapolation ratio of 1:1:4 for water:soil:sediment biodegradation half-life (Boethling et al. 1995), the half-life in soil is also ≥182 days and the half-life in sediments is ≥ 365 days. This indicates that SDPAs persist in soil and sediment. This is substantiated by the fugacity modelling which indicated that the majority of SDPAs would not remain long in water or air due to their low water solubility

and low vapour pressure. As such, the greatest exposure potential to organisms will likely be through sediment and soil (through consumption of organic matter and direct contact). This long residence time in soil or sediment can contribute to continuous and cumulative exposure to organisms.

7.1.1 Empirical Data for Persistence

7.1.1.1 Sediment

Thompson et al. (2006) performed a large-scale *in situ* experiment near the Bailey Peninsula area (Casey Station, East Antarctica) with synthetic lubricant products containing a complex chemical mixture that included several alkyl diphenylamines, di-*t*-butyl diphenylamines, di-*t*-octyl diphenylamines and *t*-butyl diphenylamines. The objective of the study was to monitor the natural degradation of synthetic lubricants in marine sediments. All alkylated diphenylamines, with the exception of *t*-butyl-diphenylamine, were resistant to degradation in all of the synthetic lubricants. The *t*-butyl-diphenylamine was reduced significantly over 5 weeks but then no further reduction was observed after 51 weeks.

7.1.1.2 Water

The photolytical half-life of diphenylamine in water during solar irradiation is 2-33 hours depending on the season, diphenylamine being transformed into carbazoles (Drzyzga 2003). Drzyzga (2003) also concluded that wastewater sludge should be able to transform diphenylamine and its derivatives to aniline, as the main product of anaerobically and microbially mediated degradation of diphenylamine. Available empirical biodegradation data for some SDPAs show a range of 0-9 percent biodegradation over 4–56 days indicating that the half-life in water and/or sludge is likely to be longer than 182 days (6 months) (see Table 7-2). Using the OECD-Guideline for Testing of Chemicals No.: 301 B (May 1981), Ciba-Geigy Ltd (1988a) showed that an emulsifier (nonylphenol) was added to increase the homogeneity due to the poor solubility of CAS RN 68411-46-1 in water. However, ready biodegradation was still not observed.It should be noted that the full studies were not available publicly for the following references in Table 7-2: ECHA (2013c), CHRIP (c2002-2012a, b) and the European Commission (2006b). As such, the robustness of the values cited in these studies could not be determined.

Table 7-2 Available empirical data for the degradation of SDPAs

	Medium	Degradation endpoint/unit	Degradation value (%)	Reference
27177-41-9 (94 -96 % purity)	Water	96 hours/%	0	Study Submission 2011
101-67-7	Sludge	28-day biodegradation	2	CHRIP c2002-2012a

	Medium	Degradation endpoint/unit	Degradation value (%)	Reference
		/%		
10081-67-1	Sludge	28-day biodegradation /%	1	CHRIP c2002-2012b
27177-41-9 (94 -96 % purity)	Activated sludge[a]	56 days/%	0	SafePharm 2002d
36878-20-3	Activated sludge	28-day biodegradation /%	8	European Commission 2006a
68411-46-1	Activated domestic sludge	28-day biodegradation /%	0 % for 10.6 mg substance 1 % for 20.1 mg substance	Ciba-Geigy Ltd 1988a
68442-68-2	Domestic wastewater	28-day, biodegradation /%	9	European Commission 2006b

[a] Identified as “activated sewage sludge” in SafePharm 2000d

7.1.2 Modelled Data for Persistence

Since few empirical data on the degradation of SDPAs are available, a (Q)SAR-based weight-of-evidence approach was applied using the degradation models shown in Appendix B. Physical and chemical properties of the SDPAs are amenable to model prediction and are within the “model domain of applicability” (e.g., structural and/or property parameter domains).

As well, SDPAs do not contain functional groups expected to undergo hydrolysis. Therefore, other fate processes in water (e.g. microbial degradation) are considered to determine overall persistence in water.

7.2 Bioaccumulation

This discussion on the potential for bioaccumulation examines several parameters, including intrinsic properties of the substance (i.e., log K_{ow}, log K_{oa}), bioconcentration factor (BCF) and bioaccumulation factor (BAF). The derivation and role of metabolism rate constants in determining bioaccumulation potential are also examined. To provide the best possible weight of evidence for the bioaccumulation potential of SDPAs, both empirical and modelled data for SDPAs are considered.

The empirical and modelled log K_{ow} and modelled log K_{oa} values for SDPAs suggest that some of these structures have a high intrinsic potential to bioaccumulate in biota. The high log K_{oc}s exhibited by SDPAs indicate additional

hydrophobic interactions and are likely to result in decreased bioavailability. SDPAs with log Kow values of approximately 9.0 or less were considered to represent the most bioavailable forms and are regarded as realistic worst-cases for bioaccumulation. Based on lines of evidence that include log K_{ow}, and modeled BAF data, the following structures are suggested to be potentially bioavailable: monooctyl DPA, dimethyl distyrenated DPA, mononononyl DPA, monostyrenated DPA, distyrenated DPA, dibutyl DPA, monobutyl DPA, monobutyl monooctyl DPA and monooctyl monostyrenated DPA. Detection of SDPAs in biota near the manufacturing site confirms a potential for bioaccumulation for some SDPAs.

7.2.1 Role of Intrinsic Chemical Properties on Bioaccumulation Potential

Empirical and modelled log K_{ow} values of 4.45 to 13.58 for SDPAs suggest that some of these structures have a high intrinsic potential to bioaccumulate in biota. The combination of high log K_{ow} and modelled log K_{oa} values of 9.16 to 15.6 suggests, that given a terrestrial dietary exposure without considering metabolism potential (given the lack of data on metabolism rates for wildlife), SDPAs will have the potential to biomagnify in terrestrial food webs as suggested by Gobas et al. (2003) and Kelly et al. (2007). However, the use of log K_{ow} and log K_{oa} are not necessarily sufficient evidence, by themselves, to determine bioaccumulation potential as these are simply partition coefficients that do not account for physiological parameters such as metabolism. The high log K_{oc}s exhibited by SDPAs indicate additional hydrophobic interactions and likely contribute to decreased bioavailability. SDPAs are regarded as non-ionizing substances that are expected to undergo a hydrophobic/lipophilic driven passive diffusion mechanism of bioaccumulation based on equilibrium partitioning, which is predicted by log K_{ow}. In this sense, they match mechanistic bioaccumulation model domains and the use of log K_{ow} and log K_{oa} become very sensitive input parameters in bioaccumulation modelling.

The measurement of log K_{ow} values above 8 becomes increasingly uncertain due to the difficulty of measuring partitioning properties accurately for superhydrophobic compounds. Minimal BCF testing has been conducted beyond this limit (i.e. substances with log K_{ow} above 8) and studies often use solubilizing agents which reduces the tests' strength of inference. Arnot and Gobas (2006) critically evaluated available bioaccumulation data (BCF and BAF) for fish and other organisms and created an empirical database of quality BCF and BAF values that the Government of Canada has used for the categorization of the DSL and is now using for screening assessments. In the BCF/BAF databases from Environment and Climate Change Canada (Arnot and Gobas 2003b) and in Arnot and Gobas (2006), the empirical distribution of "acceptable" fish BCF and BAF data shows that there are practically no recorded values for substances with log K_{ow} values above approximately 8.2 (except for one or two highly halogenated biphenyls with much slower rates of biotransformation than SDPAs).

This assessment considers log K_{ow} values of 1.0-~8.2 to be the empirical "log K_{ow} domain" for model results based on Kelly et al. (2004) and Arnot and Gobas (2003a, 2003b, 2006). SDPAs that have a log K_{ow} value greater than 8.2 are considered out of the model domain for the mass-balance three trophic level BCFBAF model (Arnot and Gobas 2003b) and the (Q)SAR-based Dimitrov et al. (2005) model. Importantly, the lack of empirical BCF and BAF data for chemicals with log K_{ow} values greater than 8.2 does not allow for benchmarking of predicted results. Consequently, SDPAs with log K_{ow} values greater than 8.2 were not further modelled in this assessment. Kelly et al. (2004) summarized the relationship between dietary absorption efficiency and substance log $K_{ow.}$ Kelly et al. (2004) demonstrated that the absorption of ingested chemical in fish (and other wildlife) decreases with increasing log $K_{ow.}$ Starting with log K_{ow} values of ~ 7 - 7.5, the diffusion of hydrophobic substances, such as the SDPAs, across an unstirred water layer to the luminal membrane (i.e. gastrointestinal tract) of an organism is rate-limiting for very high log K_{ow} substances with very low solubility in the water layers (i.e., slow in = slow out). Although Arnot and Gobas (2003a, 2003b, 2006) do state that the log K_{ow} domain of the model ranges from 1-9, there is insufficient empirical field evidence (i.e., BAF) to support model estimates based on log K_{ow} values beyond 8.2.

SDPAs with log K_{ow} values of 8.2 or less represent the most bioavailable forms and can be considered as a realistic worst-case for bioaccumulation and toxicity potential for SDPAs. This domain consideration pertains to modelling only and does not mean that SDPAs with log K_{ow} values greater than 8.2 will not bioaccumulate at all. For log K_{ow} values as high as 9, a low to moderate degree of laboratory bioconcentration has been observed for some long-chain phthalate esters and cyclic siloxanes, albeit using solvents during testing. SDPAs in this range of log K_{ow} values will not be modelled due to a high degree of uncertainty. As a precautionary measure, they will be assessed on a qualitative basis as there is some evidence of laboratory bioconcentration. SDPAs with log K_{ow} values greater than 9 are considered strongly adsorbed to solid particles under natural conditions and will not present sufficient bioavailability for uptake by aquatic or terrestrial organisms.

Dioctyl DPA, dinonyl DPA, diethyl mononononyl DPA, diethyl dinonyl DPA have log K_{ow} greater than 9 and are therefore out of the model domain. There is also insufficient field evidence for any significant bioaccumulation for structures within this range of log $K_{ow.}$ Given the low water solubility and the high log K_{ow} values, it is considered that the bioaccumulation potential for these structures in aquatic organisms is very low or negligible. Based on these lines of evidence, these SDPAs will not be discussed further in section 7.2. Empirical and modelled data for bioaccumulation for the other SDPAs are presented below.

7.2.2 Empirical Data for Bioaccumulation

Empirical laboratory-derived data were available for a few SDPAs identified as discrete substances (CAS RN 101-67-7, 10081-67-1, and 27177-41-9) (Table 7-3). The empirical data for CAS RN 101-67-7 and 10081-67-1 were obtained from the National Institute of Technology and Evaluation (NITE) CHIRP database. This database provides basic chemical substance information on laws, regulations, and hazard and risk assessment in Japan. However, the actual full studies are not available publicly for any of the values cited. As such, the robustness of these particular values could not be determined.

Table 7-3 Available empirical BCF for SDPAs

CAS RN	Test organism	Kinetic and/or steady-state BCF value (L/kg)[a]	Reference
101-67-7	Common carp *(Cyprinus carpio)*	0.8 – 1.3 (at 0.1 mg/L) 3 – 5.5 (at 0.01 mg/L)	CHIRP c2002-2012a
10081-67-1	Common carp *(Cyprinus carpio)*	12 – 57 (at 100 µg/L) 53 – 124 (at 10 µg/L)	CHIRP c2002-2012b
27177-41-9 (purity 94 -96 %)	Common carp *(Cyprinus carpio)*	110 – 476 (at 0.1 mg/L) 395 – 1870 (at 0.01 mg/L)	Mitsubishi Chemical Safety Institute Ltd. 2000

[a] Values in parentheses represent the test concentrations at which the BCFs were derived

A stakeholder provided a carp bioconcentration study for a purified compound (94 -96 % purity) described by the company as CAS RN 27177-41-9 (Mitsubishi Chemical Safety Institute Ltd. 2000).The study was conducted according to the testing method prescribed for testing new chemical substances as required by the Chemical Substances Control Law of Japan. A solubilizer was used (i.e., 2-methoxyethanol) at 0.4 mg/L for the low exposure level of 0.01 mg/L and at 4 mg/L for the high exposure level of 0.1 mg/L, thus facilitating the uptake of the substance but creating a condition of uncertain environmental relevance. One-year-old carp weighing about 5 g each were used in the test. The exposure period was for 42 days with periodic measurements of the test substance. The concentration of the test substance in the fish ranged from 10.7 to 48.1 µg/g at the high exposure level and from 3.95 to 17.7 µg/g at the low exposure level. The BCF was 110-476 for the high exposure level and 395-1870 for the low exposure level. Since the range of BCF was within 20% from day 28 to day 42 of exposure, it was indicated that the bioconcentration had reached steady state. The steady state BCF was 411 for high exposure level and 1730 for low exposure level.

Lu et al. (2016a) and Tetreault et al. (2016) calculated field-based bioaccumulation factors for shiner, chub and crayfish using samples taken from an urban creek in Canada as reported in section 6.2.3. However, a review of

these estimates revealed a high degree of uncertainty. First, total water concentrations (water and suspended sediments) were used in the ratio method as opposed to the dissolved (considered bioavailable) phase. BAFs and BCFs are usually calculated as the ratio of the chemical concentration in water and organism tissue (whole body or lipid fraction) and are very sensitive to the concentration of chemical in the dissolved phase in water. The BAFs were also estimated based on “not detected” water concentrations, or concentrations just above detection limit. Thus, it cannot be assumed that dissolved-phase SDPAs were available for uptake. As noted in Section 7.2.3, there is uncertainty surrounding the “true” bioaccumulation potential for superhydrophobic substances like SDPAs with high log K_{ow}s, due to the very low or non-existent (i.e., below or non detectable) bioavailable fraction in the dissolved phase. A second uncertainty is that the water sampling was conducted in 2012, while the biota sampling occurred in 2014 in different seasons, and thus, it is not known what environmental concentrations resulted in the determined levels in tissues. There is also uncertainty respecting exposure due to potential organism mobility.

Due to the uncertainties in the field-BAFs estimated by Lu et al. (2016a) and Tetreault et al. (2016), they are not considered further in this assessment.

Lu et al. (2016a) also evaluated the bioaccumulation from sediment using BSAF for three species (crayfish, chub and shiner) based on samples taken in a creek in an urbanized area, and upstream. BSAFs for the SDPAs ranged from 0.09 – 2.68 for crayfish, 0.002 to 0.59 for shiner and 0.005 to 0.44 for chub. The BSAF results indicated very low accumulation for all SDPAs for all species. The BSAF results are <1 for all substances except for monobutyl monooctyl DPA (BSAF of 2.68) for crayfish (upstream) and dibutyl DPA (BSAF of 1.52) for crayfish (downstream). The BSAF results indicate that for substances with the highest sediment concentrations (dimethyl distyrenated DPA, and monooctyl DPA , concentrations ranging from 0.31- 3.4 ng/g dw), there was zero to low accumulation. However, these BSAF results are highly uncertain as the tissue and sediment sampling were conducted two years apart and in different seasons. There is also uncertainty respecting exposure due to potential organism mobility.

No empirical biomagnification (BMF) or trophic magnification (TMF) values were available for SDPAs. Due to technical issues with an empirical TMF study (Study Submission 2015a), including missing critical species from the food web, inadequate sampling at the lower trophic levels and elevated detection limits, a TMF could not be calculated.

7.2.3 Modelled Data for Bioaccumulation

Bioaccumulation factors (BAF) are measured under field conditions as the ratio of the whole body burden of a chemical taken up from all exposures to that of the ambient water concentrations. Measures of BAF are a preferred metric for assessing the bioaccumulation potential for substances with log K_{ow} > ~4.0 because it accounts for all chemical exposures including the diet, which

predominates for substances at high log K_{ow} values (Arnot and Gobas 2003a). BAF can provide a more realistic measure of total transfer of a chemical from exposure media than individual bioaccumulation metrics such as BCF or BMF. Metabolism corrected kinetic mass-balance modelling was used to fill this data gap as no empirical BAF values were available for SDPAs. The discussion regarding the modelled data for bioaccumulation focuses on the derivation of an overall metabolic rate constant (k_M) for SDPAs and modelling of BCF.
The metabolic rate constant is a very sensitive input parameter for bioaccumulation modelling. Due to the structural similarity within the SDPA assessment, it is reasonable to consider the derivation of a single metabolic rate constant for all SDPAs given that a Phase I reaction (aliphatic carbon oxidation) and a Phase II reaction (N-glucuronide oxidation) are predicted to be responsible for any transformation of the SDPA structure. K_M is known to be a highly variable parameter (Arnot et al. 2008a, Arnot et al. 2008b) and thus, an average k_M can best represent a value of central tendency to account for this variation and better represent the k_M for SDPAs that are UVCBs.

There are two approaches to estimate the metabolic rate constants either by using empirical BCF data or using (Q)SARs: In the first approach, the average semi-empirical k_M for SDPAs was first estimated using available empirical BCF data (see Table 7-3). Kinetic rate constants were normalized to the weight, temperature and lipid content of the fish in Mitsubishi Chemical Safety Institute Ltd (2000). This was performed using the approach outlined in Arnot et al. (2008a) when the BCF or the depuration rate constant is known. In this method, k_M is derived according to either one of the following equations, although equation 2 is preferred:

$$k_M = (k_1 \varphi / BCF) - (k_2 + k_E + k_G) \quad (1)$$

$$k_M = k_T - (k_2 + k_E + k_G) \quad (2)$$

where:

k_M = the metabolic rate constant ($days^{-1}$)
k_1 = the uptake rate constant (Arnot and Gobas 2003a)
φ = fraction of freely dissolved chemical in water (Arnot and Gobas 2003a)
BCF = the available empirical bioconcentration factor
k_2 = the respiratory elimination rate constant (Arnot and Gobas 2003a)
k_E = fecal egestion rate constant (Arnot and Gobas 2003a)
k_G = growth rate constant (Arnot and Gobas 2003a)
k_T = the total elimination or depuration rate constant (from the empirical study)

The purpose of the above equation is to fit the kinetic model with the observed BCF data, thus providing reasonable estimations of the rate constants. The empirically observed elimination half-life of 15 days equals a k_M of ~0.05 d^{-1} given that all of the elimination is due to metabolism (Mitsubishi Chemical Safety

Institute Ltd 2000)). The metabolic competency of an organism can be related to body weight and temperature (e.g., Hu and Layton 2001; Nichols et al. 2009). Accordingly, the k_M was normalized to the conditions of a middle trophic level fish representative of Canadian waters (fish weight =184 g, lipid content = 6.8%, temperature = 10˚C) according to the procedures outlined in Arnot et al. (2008b) as follows:

$$k_{M,N} = k_{M,i}(W_N/W_i)^{-0.25} \exp(0.01(T_N - T_i))$$

where:

W_N = the normalized mass of the organism (0.184 kg)
W_i = the original study-specific mass of the organism (kg)
T_N = the normalized water temperature (10ºC)
T_i = the original study-specific water temperature (ºC)

After the above normalization routines are applied, the resulting average k_M is 0.05 d^{-1} for a fish weighing 184 g. This is consistent with the observed half-life in Mitsubishi Chemical Safety Institute Ltd (2000).

In the second approach, the median metabolic rate constant for SDPAs was estimated using the k_M (Q)SAR sub-model in BCFBAF model v3.0 in EPIWIN v4.0 (based on Arnot et al. 2009) as the BCFBAF model v3.0 did not contain empirically derived k_M values for the SDPAs. The average k_M from this method, which relies on structural fragment comparison, is also 0.05 d^{-1} for a 184g fish (0.10 for a 10g fish). The metabolic rate constant for all SDPAs with log K_{ow} less than 9 was also estimated using the Dimitrov et al. (2005) BCF_{Max} model with Mitigating Factors. In this approach, the probability of metabolic transformation is used to estimate the rate of transformation. The average k_M from the BCF_{Max} model is 0.02 d^{-1} (with rounding).

As seen from the above calculations, there is consistency between semi-empirical k_M values derived using available BCF data and those predicted using (Q)SAR models. When all of the empirical and modelled sources of k_M are considered, the grand average k_M for all SDPAs is 0.04 d^{-1} for a 184 g fish or ~0.08 d^{-1} for a 10g fish. This rate is regarded as a slow rate of metabolism (less than 0.1 d^{-1})(Arnot and Gobas 2006; Nichols et al. 2009). The grand average k_M value was then used to model the BCF and BAF of a middle trophic level fish using a three trophic level modification of the fish bioaccumulation mass-balance model from Arnot and Gobas (2003a).

A summary of the results for SDPAs that have a log K_{ow} values less than 8.2 are presented in Table 7-4. Predicted BCF and BAF values are reported for a middle trophic level fish representative of Canadian waters based on a modification of the mass-balance model from Arnot and Gobas (2003b) (v.1.11).

Table 7-4 Summary of modelled data for bioaccumulation for SDPA structures with log K_{ow} values < 8.2 in fish

Log K_{ow}	k_M (d^{-1}) 184g fish	Model and model basis	Endpoint	Value wet weight (L/kg)	Reference
4.5 – 7.3	NA[c]	BCFBAF Sub-model 1 (linear regression)	BCF	401 – 13 400	BCFBAF 2000-2010
4.5 – 7.3	0.04	BCFBAF Sub-model 2 (mass balance)	BCF[a]	891-1349	Modified three trophic level model v1.11(Arnot and Gobas 2003a)
4.5 – 7.31	0.04	BCFBAF Sub-model 3(mass balance)	BAF[a]	1550 – 61366	Modified three trophic level model v1.11(Arnot and Gobas 2003a)
4.5 – 7.31	NA[c]	BCF_{Max} with mitigating factors	BCF[b]	39 – 1403	Dimitrov et al. 2005
6.8 – 8.2	NA	BCFBAF Sub-model 1 (linear regression)	BCF	3360 – 13 400	BCFBAF 2000-2010
6.8 – 8.2	0.04	BCFBAF Sub-model 2(mass balance)	BCF[a]	135 – 2089	Modified three trophic level model v1.11(Arnot and Gobas 2003a)
6.8 – 8.2	0.04	BCFBAF Sub-model 3(mass balance)	BAF[a]	22 121 – 50 049	Modified three trophic level model v1.11(Arnot and Gobas 2003a)
6.8 – 8.2	NA[c]	BCF_{max} with mitigating factors	BCF[b]	229 – 2393	Dimitrov et al. 2005

Abbreviations: log K_{ow}, octanol-water partition coefficient; k_M, metabolic rate constant, BCF, bioconcentration factor; BAF, bioaccumulation factor; NA., not applicable.
[a]Results generated using weight, lipid and temperature for a middle trophic level fish.
[b]Possible mitigating factors include ionization, molecular size, metabolism and water solubility.
[c]Model cannot be adjusted to include grand average k_M

It is noted that BAFs, either field measured or modeled, like BCFs, are very sensitive to the concentration of chemical in the dissolved phase in water. This is because BAF and BCF are typically calculated as the ratio of the chemical concentration in water (water and diet and water, respectively) and organism tissue (whole body or lipid fraction). Water-based bioaccumulation metrics can therefore present significant uncertainty regarding "true" bioaccumulation potential for superhydrophobic substances like some SDPAs because of the very low or non-existent (i.e., below or non detectable) bioavailable fraction in the dissolved phase. For example, at log K_{ow} 9.0, the dissolved fraction of a neutral organic chemical in water is ~0.5%.[7] Because field samples are often based on total water concentrations (particulate and dissolved phase), it is therefore impossible to determine if superhydrophobic SDPAs have been detected in the bioavailable dissolved phase. This is a dominant reason to use the tissue residue concentrations from field studies for exposure and risk analysis.

7.2.3.1 Bioavailability of SDPAs

The bioavailability of a chemical is governed by various chemical and physical factors that control the chemical activity and accessibility or availability of a chemical to an organism. The bioavailability is often a limiting factor to predicting the rate of bioaccumulation from various environmental matrices (e.g. air, water, and sediment) and thus, may be used as a relative metric to compare the accumulation potential of various chemicals..

Based on the lines of evidence presented in Section 7.2.3, including log K_{ow} values, predicted rates of metabolism and modelled BAF data, the following structures are considered to be potentially bioavailable: monooctyl DPA, dimethyl distyrenated DPA, monononyl DPA, monostyrenated DPA, distyrenated DPA, dibutyl DPA, monobutyl DPA, monobutyl monooctyl DPA and monooctyl monostyrenated..

Monobutyl DPA has a lower log K_{ow} value (4.45) compared to the other SDPAs in this assessment. The resulting predicted BAF (i.e., 1550) still indicates some level of bioavailability and the relatively higher modelled water solubility (4.79 mg/L) also shows greater bioavailability due to exposure via the gills.

A BAF for monobutyl monooctyl DPA and monooctyl monostyrenated DPA with log K_{ow} values of 8.67 and 8.69, respectively, could not be reliably predicted. However, it is considered that these chemical structure presents some degree of bioavailability potential given that their log K_{ow} value are not significantly greater than the approximate limit of bioavailability (log K_{ow} value ~9.0).

[7] Assuming a dissolved and particulate organic carbon concentration of 5.0E-07 kg/L

7.2.4 Measured Concentrations for Bioaccumulation and Critical Body Residue (CBR)

Aquatic biota (fish and crayfish) were sampled near a manufacturing site in Canada and their tissues analysed for SDPAs (Study Submission 2015a). The intent of this work was to assess the bioaccumulation potential of SDPAs over a range of trophic levels (i.e., aquatic plants, fish, and invertebrates) in a local waterbody near the manufacturing site mentioned in section 6.0. As the fish sampling is specific to the site and its receiving waterbody, the results may not be representative of the various types of waterbodies or fish species across Canada. Analyses were conducted for mononononyl DPA, dinonyl DPA, dimethyl distyrenated DPA, monooctyl DPA, dioctyl DPA, monobutyl DPA, dibutyl DPA and monobutyl monooctyl DPA.

As noted in Section 6.1, there were a number of deficiencies that restricted the use of the fish Study Submission (2015a) tissue residue data in this screening assessment; therefore, these data were not used to determine the bioaccumulation factors as they represent a snapshot of food web accumulation under site-specific exposure conditions. The data does not necessarily reflect the intrinsic ability of the substance to bioaccumulate given the different controlling factors for exposure in different environments. While uncertainties and limitations were identified with respect to the study design, and analytical and sampling methods, the data does show that SDPAs were not measured above the method detection limits (< 0.02 – < 0.2 µg/g) in any fish tissue residues.

Additional fish sampling of all eight components of SDPAs conducted at the same location as Study Submission (2015a) confirmed low concentrations of SDPAs in white sucker fish (ECCC 2017a). Levels of SDPAs in fish were orders of magnitudes lower than the detection limits in the Study Submission (2015a) data (< 0.02 – < 0.2 µg/g) and are summarized in Section 6.2.3.

Fish sampling of seven SDPA substances carried out in an urban creek also confirmed low levels in white sucker fish, shiner, chub, crayfish and northern pike (Lu et al. 2016ab; Tetreault et al. 2016). Concentrations of the SDPAs were orders of magnitude (<0.000001 - 0.034 µg/g) below the detection limits in the Study Submission (2015a) data (<0.02 - <0.2 µg/g).

Therefore, the method detection limits from Study Submission (2015a) can be utilized as a default upper bound in the exposure scenarios and critical body residue approach (McCarty et al. 1992).

7.2.5 SDPAs in Benthic Organisms

Predicting tissue residues in benthic organisms based on the concentration in sediment employs the use of sediment bioaccumulation factors also known as biota-sediment application factors (BSAFs). The BSAF is an empirical ratio, defined as the chemical concentration in tissue (on a lipid-normalized basis) over the chemical concentration in sediment (normalized to the organic carbon levels

in the sediment) (National Research Council of the National Academies 2003). Simply, the BSAF is a partitioning factor designed to account for the propensity of an organic chemical to partition between the organic carbon matter contained in the sediment versus the lipids in tissue (US EPA 2009).

$BSAF = (C_t/F_l) / (C_s/F_{oc})$

where:

C_t = contaminant concentration in the benthic organism
F_l = the lipid fraction in the tissue
C_s = contaminant concentration in the sediment
F_{oc} = the organic carbon fraction in the sediment

Depending upon the affinities of the non-polar organic chemical for lipid and sediment organic carbon, the BSAF, under these specific conditions, should be in the range of 1 to 2 (US EPA 2009). However, variation in BSAF is observed for individual species as well as individual contaminants and the application of a BSAF from one location to another location is limited due to site variabilities. BSAF values are dependent on the physical-chemical properties of both the organic contaminant and sediment as well as the lipid content of the organism. Taking all these variabilities in species and site differences into account, a BSAF of 3 is considered reasonably conservative for the SDPAs in this risk assessment (Morrison et al. 1996; Van Geest et al. 2011). For the direct ingestion pathway, BSAF can be used as a screening device, i.e., the concentration measured in the sediment is simply multiplied by the BSAF to determine the amount in the organism that is then compared to critical body residue thresholds. McCarty (1986, 1987a, 1987b, 1990), McCarty and Mackay (1993), McCarty et al. (1985, 1991), Van Hoogen and Opperhuizen (1988), and McCarty et al. (2013) have shown that internal concentrations of neutral narcotic chemicals causing death are fairly constant at about 2-8 mmol/kg for acute exposures and 0.2-0.8 mmol/kg for chronic exposures.

The total internal SDPA concentration in benthic organisms and potential risk is calculated in Section 8.2.2.1.2

8. Potential to Cause Ecological Harm

8.1 Ecological Effects Assessment

The water, soil and sediment compartments are the media of interest for the SDPAs based on sources of release and environmental partitioning. In order to provide the best possible weight of evidence for assessing the ecological effects of SDPAs, empirical and modelled data were considered, where appropriate, notably for the sediment and soil compartments. There are a few empirical data available for toxicity from soil and sediment.

8.1.1 Mode of Action

SDPAs share the slightly hydrophilic functional group, diphenylamine, which is chemically reactive (BASF SE 2010a); however, its effect is hindered by substitution in SPDAs making them overall baseline narcotic chemicals.

8.1.2 Modelled Data for Aquatic Toxicity

A range of aquatic toxicity values were obtained from the various (Q)SAR models for those SDPAs that have log K_{ow} < 8.2 (Tables 8-1 and 8-2). These include monobutyl DPA, dibutyl DPA, monooctyl DPA, monononyl DPA, monostyrenated DPA, and distyrenated DPA.

The structural classes of SDPAs (i.e., as diphenylamines with varying degrees of phenyl or alkyl group substitution) are amenable to model predictions as they are considered to be in the model domain of applicability for neutral organic SARs (e.g., within the structural and/or property parameter domains of the model database). Therefore, the application of most (Q)SAR models to SDPAs is considered appropriate with some exceptions as described below.
In the Canadian Persistent Organic Pollutants Profiler model (CPOPs 2012), some model predictions indicated both that the structural class of diphenylamine is outside the model domain of applicability and that the substance may not be soluble enough to measure the predicted effect. Therefore, results are not presented for this model.

A number of values from the ECOSAR model (2012) for neutral organics contained in the EPISuite (2000-2010) model were considered to provide unreliable toxicity estimates for some SDPAs. Modelled acute or chronic toxicity values identified some predictions as “chemical may not be soluble enough to measure this predicted effect” and/or “out of domain of the model”. These predictions are annotated in Table 8-2.

The suggested log K_{ow} model domain limits for acute predictions is ~5.0 indicating that there are no neutral organics in the model training set above this cut-off. There are no acute values below 0.001 mg/L in the ECOSAR (2012) training set for most neutral organic SARs. As such, most modelled acute toxicity results were not applicable given that the log K_{ow} values range from 5.15 to 7.31.

The exception is monobutyl DPA which has a log K_{ow} of 4.45 and a water solubility of 4.79 mg/L; acute toxicity model predictions for monobutyl DPA are provided in Table 8-1 and indicate high to moderate toxicity. However, read-across was not used because the physical-chemical values for monobutyl DPA are different from the other SDPAs.

The suggested log K_{ow} domain limit for chronic toxicity is ~8.0 indicating that there are no neutral organics in the model training set above this cut-off. Predicted chronic toxicity concentrations in the sub microgram per litre range are inherently uncertain due to difficulties with water-based testing for such superhydrophobic compounds like SDPAs. While the chronic toxicity predictions for the SDPAs are generally below their water solubility, chronic toxicity predictions are generated based on log K_{ow} correlations which are often beyond practical toxicity testing methodologies. Thus, the modelled chronic aquatic toxicity values are considered highly uncertain and unreliable as they do not address the primary route of exposure for SDPAs, which is likely through the food chain from benthic organisms, fish and their mammalian predators. Table 8-2 provides the chronic toxicity modelling results for SDPAs with a log K_{ow} less than 8.2.

Modelled aquatic toxicity data indicate that acute and chronic effects are expected at concentrations at or below water solubility. The results of Level III fugacity modelling confirm that SDPAs are expected to predominantly reside in soil and sediment, depending on the compartment of release. CTVs were not derived from the modelled data (due to the uncertainties described above) for any of the SDPAs in this assessment and subsequent predicted-no-effect-concentrations (PNECs) in water were not calculated.

Table 8-1 Summary of modelled data for aquatic toxicity for monobutyl DPA with log K_{ow} 4.45 and water solubility 4.79 mg/L

Test organism	Type of test (exposure time)	End-point	Toxicity Value (mg/L)	Reference
Fish	Acute (96 hours)	LC_{50}	1.167	ECOSAR 2012
Daphnia magna	Acute (48 hours)	LC_{50}	0.826	ECOSAR 2012
Algae[a]	Acute (96 hours)	EC_{50}	0.924	ECOSAR 2012
Fish	Chronic (30 days)	ChV	0.149	ECOSAR 2012
Daphnia magna	Chronic (16 days)	ChV	0.152	ECOSAR 2012
Algae[a]	Chronic	ChV	0.683	ECOSAR 2012

Test organism	Type of test (exposure time)	End-point	Toxicity Value (mg/L)	Reference
	(96 hours)			
Fish	Acute (96 hours)	LC_{50}	0.265	EPISuite 2000-2010
Daphnia magna	Acute (48 hours)	LC_{50}	0.240	EPISuite 2000-2010
Algae	Acute (96 hours)	EC_{50}	0.457	EPISuite 2000-2010
Fish	Chronic (30 days)	ChV	0.034	EPISuite 2000-2010
Daphnia magna	Chronic (16 days)	ChV	0.046	EPISuite 2000-2010
Algae[a]	Chronic (96 hours)	ChV	0.298	EPISuite 2000-2010

Abbreviations: ChV, chronic toxicity value, : EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms

[a]Algal 96hr test can be considered chronic test as it is multiple generation test

Table 8-2 Summary of modelled data for aquatic toxicity for SDPAs with a log K_{ow} less than 8.2[c]

Range of Log K_{ow}[c]	Water Solubility (mg/L)	Test organism	Type of test	End-point	Toxicity Value (mg/L)	Reference
5.15 - 7.31	1.14E-06 - 0.047	Fish	Chronic (30 days)	ChV	0.0008 – 0.046	ECOSAR 2012
5.15 - 7.31	1.14E-06 - 0.047	*Daphnia magna*	Chronic (16 days)	ChV	0.0016 – 0.055	ECOSAR 2012
5.15 - 7.31	1.14E-06 - 0.047	Algae[b]	Chronic (96 hours)	ChV	0.018[a] – 0.314	ECOSAR 2012
5.15 - 7.31	1.14E-06 - 0.047	Fish	Chronic (30 days)	ChV	0.0005 –0.026	EPISuite 2000-2010
5.15 - 7.31	1.14E-06 - 0.047	*Daphnia magna*	Chronic (16 days)	ChV	0.0011 –0.037	EPISuite 2000-2010
5.15 - 7.31	1.14E-06 - 0.047	Algae[b]	Chronic (96 hours)	ChV	0.02 – 0.263[a]	EPISuite 2000-2010

Abbreviations: ChV, chronic toxicity value

[a] Model warning that chemical may not be soluble enough to measure this predicted effect
[b] Algal 96hr test can be considered chronic test as it is multiple generation test
[c] These include dibutyl DPA, monooctyl DPA, mononononyl DPA, monostyrenated DPA, and distyrenated DPA

8.1.3 Empirical Data for Aquatic Toxicity

In the High Production Volume (HPV) Challenge Program of the United States Environmental Protection Agency (US EPA), producers and importers of the HPV program voluntarily sponsored chemicals. This resulted in new toxicity studies if adequate data did not already exist. As a result, empirical studies were conducted for CAS RN 101-67-7, 36878-20-3, 68442-68-2, and 68921-45-9. The results of these studies were submitted by industry to the European Commission or to ECHA under the REACH program. However, the actual study reports were not available publicly for any of the data submitted to the US EPA (2009), the European Commission (2006a and 2006b), or ECHA (2013b, 2013c and 2014). As such, the robustness of the study values could not be determined.

Studies for CAS RN 36878-20-3, 68442-68-2, 68411-46-1, and 68921-45-9 did not report the use of solvents/dispersants. However, the results are questionable as most study results are orders of magnitude above their water solubility limits which leads to difficulties in interpretation (e.g., US EPA 2009, European Commission 2006a and 2006b, ECHA 2013b, ECHA 2013c, ECHA 2014, Ciba-Geigy 1988b, Ciba-Geigy 1988d, Ciba-Geigy 1988c, Harlan Laboratories 2013a, Harlan Laboratories 2013b and RCC Ltd. 2004). For example, the US EPA (2009) chose to use the water solubility limit as the no observable effect concentration (NOEC) and conclude “no effects at saturation” for most studies. ECHA (2014) reported aquatic toxicity results for CAS RN 68921-45-9 that were an order of magnitude greater than the reported water solubility. It may be considered that in aquatic tests where solvents/dispersants were not applied and where the toxicity values were far above the water solubility of the substances, the results can only be interpreted as “no effect at saturation”. Test concentrations far above the water solubility of the substance can contain soluble impurities whose effects might also confuse the interpretation of the substance toxicity. Weyman et al. 2012 indicated that if a solvent is used but the test substance is not completely dissolved, then the un-dissolved material present in the test media has the potential to exert adverse (physical) effects on the test organisms. These effects include blocking of fish gill membranes, encapsulation/entrapment of daphnids, or the reduction of light intensity in algal tests. While these effects may be environmentally relevant, they may confound interpretation of toxicity studies. This may be the case for some of the studies described in US EPA (2009) where some physical effects were observed for CAS RN 101-67-7 and 36878-20-3. Additionally, the results for most of these studies should have been reported as loading rates as opposed to concentrations (whether it be measured or nominal). In these studies, the term “nominal concentration” may have been used as a synonym for “loading rate” which is not always correct. Study Submission (2005) reported a 48-hour immobilisation study with Daphnia magna for CAS RN 68921-45-9. The effects in this study are

related to the loading rate. Potential analytical determination problems were noted at the reported loading rates which prevented the inclusion of this study.

According to the US EPA (1996), the nominal test level, for aquatic tests, is the concentration that would exist if all test material added to the test solution was completely dissolved and did not dissipate in any way. Consequently, in studies where the “nominal” concentrations exponentially exceeded the water solubility limits, the endpoints should have been reported more appropriately, as EL50 (loading rate causing adverse effect in 50% of exposed organisms) or LL50 (loading rate causing mortality of 50% of exposed organisms) instead of the reported EC50 and LC50.

Solvents and dispersants were used for aquatic toxicity studies on CAS RN 68411-46-1, 101-67-7, and 27177-41-9 (e.g., US EPA 2009, Study Submission 2011g, SafePharm Laboratories 2003a, SafePharm Laboratories 2003b, SafePharm Laboratories 2003c, SafePharm Laboratories 2003d and SafePharm Laboratories 2003e) to enhance the apparent water solubility above the maximum thermodynamic equilibrium solubility in water. However, it should be emphasized that reaching such high concentrations (in molecular form) of SDPAs is not likely realistic in the Canadian environment. It is acknowledged that in the aquatic environment and in the laboratory studies, the water solubility values will rarely be identical. Indeed, laboratory tests are conducted under conditions that do not take into account the various co-solvents that exist in the environment that may ultimately affect the solubility and bioavailability of a substance. Temperature, pressure, and surfactants (which may be present in the aquatic environment) are other important factors which may affect solubility of the chemicals in the real world. At the same time, water solubility enhancement in the environment will not be as high as 4-5 orders of magnitude over solubility in the laboratory conditions. Accordingly, studies without strong solvents and dispersants have greater strength of inference as they are more likely to be environmentally relevant.

The available empirical aquatic toxicity data indicate that acute effects are not expected within the solubility limits for SDPAs. Critical Toxicity Values (CTVs) were not derived from the empirical data (due to the uncertainties described above) for any of the SDPAs in this assessment and subsequent predicted-no-effect-concentrations (PNECs) in water were not calculated.

8.1.4 Empirical Data for Soil and Sediment Toxicity

Soil and sediment toxicity studies were submitted for one commercial product containing a mixture of CAS RN 27177-41-9 and CAS RN 36878-20-3 (Study Submission 2015b, Study Submission 2015c, and Study Submission 2015d). The components of the commercial product mixture were identified as mainly monononyl DPA and dinonyl DPA. As these studies were based on the commercial product, results are usually attributed to the commercial product as a

mixture and not necessarily the individual component(s) within the commercial product.

Three empirical studies were assessed for their reliability and acceptability: one acute and one reproductive toxicity study with earthworms (*Eisenia fetida*) and one prolonged toxicity study with the freshwater midge (*Chironomus riparius*). All studies showed low organism toxicity to the commercial product (see Table 8-3).

Table 8-3 Summary of empirical data for sediment and soil toxicity for a commercial product containing a mixture of CAS RN 27177-41-9 and CAS RN 36878-20-3

Test organism	Type of test	End-point	Toxicity Value (mg/kg)	Reference
Freshwater Midge (*Chironomus riparius*)	Benthic	Chronic 28-day	NOEC[a]> 100	Study Submission 2015b
Earthworm (*Eisenia fetida*)	Terrestrial	Acute 14-day LC_{50}	NOEC > 1000	Study Submission 2015c
Earthworm (*Eisenia fetida*)	Terrestrial	Chronic, 28-day reproduction	NOEC > 1000	Study Submission 2015d

[a] No Observed Effect Concentration

For the sediment-freshwater midge toxicity study (Study Submission 2015b) factors considered to impact the reliability and acceptability are as follows:

- Monononyl DPA and dinonyl DPA are poorly water-soluble. Only nominal concentrations are reported with no verification of the actual concentrations of the test substance in the test system. Verification of the stability and homogeneity of the test substance in the sediment were not determined.
- Insufficient test concentrations and replicates to ensure adequate statistical power to detect 20% difference from the control at the 5% level of significance. The study reported three treatment concentrations (1, 10, and 100 mg/kg) and two replicates per treatment. In order to ensure adequate statistical power, the OECD 218 Test Guideline (OECD 1984) recommends, at least five concentrations and three replicates per concentration to estimate an EC_{50} and five test concentrations with four replicates to estimate an NOEC.
- The volume of acetone used for solubilizing the test substance is not reported. It is not known whether the proportion of acetone to test substance was high or low.
- Insufficient time for stabilization of spiked sediment/overlying water was provided. Although, the recommended time is 48 hours (OECD 1984),

only 20 hours was allowed in the study and the test concentration was not measured at the end of the equilibration period.
- Study was not conducted under Good Laboratory Practices (GLP)[8].
- Two of the four test validity criteria for the OECD 218 Test Guideline (OECD 1984) are reported to be met, i.e., emergence of the controls are at least 70% at the end of the test and *C. riparius* emerged from the control vessels between 12 and 23 days. The two test validity criteria not met were the absence of measurements for pH (pH should be between 6-6), dissolved oxygen (should be at least 60%), and water temperature (should not differ by more than 1.0˚ Celsius).

For the acute soil-earthworm toxicity study factors considered to impact the reliability and acceptability are as follows:

- Monononyl DPA and dinonyl DPA are poorly water soluble.Only nominal concentrations are reported with no verification of the actual concentrations of the test substance in the test system. Verification of the stability and homogeneity of the test substance in the soil were not determined.
- Periodic analyses of water and soil for potential contaminants were not performed according to GLP but were performed using certified laboratory and standard US EPA analytical methods. However, the use of standard methods may be insufficient given the inherent difficulties of sampling and analyzing SDPAs in any given media. Stability of the test substance under storage conditions at the test site was not determined in accordance with GLP.

For the soil-earthworm reproductive toxicity study factors considered to impact the reliability and acceptability are as follows:

- Loss of test substance over the test duration - an explanation is not given.
- Reference toxicant test to verify that the response of the earthworms in the test system are responding within normal levels last occurred in 2006 when it would be good laboratory practice to conduct a reference toxicant test at the same time as the study.

[8] Good Laboratory Practices (GLP) as defined by the OECD (1998) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. GLP encompasses a variety of practices including standard operating procedures, quality assurance and quality control practices, facilties to prevent cross-contamination, preserve identity, concentration, purity and stability of test substances, traceable calibration and inspection of laboratory equipment (e.g., pipettes, balances) to national or international standards of measurement etc.

- Periodic analyses of water and soil for potential contaminants were not performed according to GLP but were performed using certified laboratory and standard US EPA analytical methods.
- Stability of the test substance under storage conditions at the test site was not determined in accordance with GLP.

All of the above studies determined unbounded NOECs. Unbounded NOECs cannot be used to calculate the predicted no-effect concentrations (PNECs) as there is no quantifiable certainty to the threshold for effects and given that a dose-response relationship has not been demonstrated in any of the studies. Therefore, the unbounded NOEC values from the above studies were not used quantitatively to derive critical toxicity values (CTVs). Although the uncertainties associated with unbounded NOECs preclude the quantitative and specific use of these values, the general result indicating a low toxicity to organisms shown for mononononyl and dinonyl DPA can be qualitatively read-across to other SDPAs assuming analogous bioavailability and if their log K_{ow} is within the log K_{ow} range for mononononyl and dinonyl DPA (see Table 8-4). The lower and upper limit of the mononononyl and dinonyl DPA log K_{ow} range is 7.25 and >9, respectively. As SDPAs are considered neutral narcotics, other structures with a similar structural substitution can be read-across using the quantitative-structure relationship provided these other chemicals are within the log K_{ow} range.

Table 8-4 Summary of read-across potential for SDPAs based on the empirical sediment and soil toxicity studies for mononononyl and dinonyl SDPA

SDPA Component	Log K_{ow} (modelled)	Read-across potential using empirical sediment and soil toxicity studies
Mononononyl DPA	7.25[a]	Not applicable
Dinonyl DPA	>9 [b]	Not applicable
Dioctyl DPA	>9	Yes
Monooctyl DPA	6.76	No
Dimethyl distyrenated DPA	8.22	Yes
Monobutyl monooctyl DPA	8.67	Yes
Monostyrenated DPA	5.15	No
Distyrenated DPA	7.31	Yes
Diethyl mononononyl DPA	>9	Yes
Monobutyl DPA	4.45	No
Dibutyl DPA	6.81	No
Monooctyl	8.69	Yes

SDPA Component	Log K_{ow} (modelled)	Read-across potential using empirical sediment and soil toxicity studies
monostyrenated DPA		

[a] lower limit of log Kow for read-across potential
[b] upper limit of log Kow for read-across potential

8.1.5 Effects to Wildlife

Acute LD_{50} data generally reflect a low level of observed effects in rodents with median LD_{50}s of >500 mg/kg bw (Sample et al. 1996). Sub-chronic repeated oral dose effects data are considered to better reflect subtle chronic and potentially significant non-adaptive adverse effects (e.g., development and reproductive toxicity). For the purposes of this calculation, repeated oral dose data from rodents are available for CAS RN 184378-08-3 which has been previously identified to contain monooctyl DPA, monobutyl monooctyl DPA, dioctyl DPA, dibutyl DPA and monobutyl DPA (see section 2). CAS RN 184378-08-3 was read-across to the most bioavailable SDPAs, including monooctyl DPA, dimethyl distyrenated DPA, monononyl DPA, monostyrenated DPA, distyrenated DPA, monobutyl monooctyl DPA, dibutyl DPA, monobutyl DPA, and monooctyl monostyrenated DPA.

One study indicated a No-Observed Adverse Effect Level (NOAEL) of 5 mg/kg/bw/day from a 43-54 day oral gavage study in rats dosed with CAS RN 184378-08-3. At the next highest dose, 25 mg/kg bw/day (i.e., the Lowest-Observed Adverse Effect Level (LOAEL)), there was hepatocyte enlargement in female rats, decreased white blood cell counts in male rats and associated clinical chemistry effects in both sexes (decreased total plasma protein, albumin etc.). Males treated with 125 mg/kg bw/day displayed elevated liver weights and decreased adrenal weights. Histopathological examinations revealed centrilobular hepatocyte enlargement of the liver for rats of either sex treated with 125 mg/kg bw/day. Females treated at the 25 mg/kg bw/day were similarly affected with centrilobular hepatocyte enlargement of the liver (SafePharm Laboratories 2006b).

The geometric mean of the NOAEL and LOAEL is used to describe the threshold for effects in mammals for wildlife risk assessment. The mammalian critical toxicity value (CTV) of 11.2 mg/kg bw is derived from the geometric mean of the NOAEL and LOAEL (SafePharm Laboratories 2006b) and scaled according to body weight to approximate effects in a wildlife species (Sample et al. 1996). The body weight of the test rodents is unknown; therefore, a reference body weight of 0.48 kg and the generally accepted body weight scaling power of ¾ in accordance with Sample et al. (1996).

An upper body weight limit of 1.3 kg for a mink and 10.4 kg for river otter (used

as focal species in this assessment) yields a body weight normalized value of 8.7 and 5.2 mg/kg bw/day for mink and otter, respectively. This scaling essentially provides for interspecies toxicity differences. An assessment factor of 10 was applied to extrapolate to longer term exposures (e.g., multi-generational) and results in toxicity reference values (TRV) of 0.87 mg/kg bw/day and 0.52 mg/kg bw/day for the mink and river otter, respectively. These values are within the range of mammalian toxicity threshold values regarded as adverse (< 10 mg/kg bw/day).

8.2 Ecological Exposure Assessment and Critical Body Residue (CBR) Analysis

8.2.1 Environmental Releases

Anthropogenic releases of a substance to the environment depend upon various losses that occur during the manufacture, industrial use, consumer/commercial[9] use and disposal of a substance. In order to estimate releases to the environment (e.g., via wastewater and to air), occurring at different stages of the life cycle of the SDPAs, information was compiled on the relevant sectors, products, emission factors, and measured concentrations.[10] Recycling activities and transfer to waste disposal sites (landfill, incineration) are also considered.

Releases of SDPAs are expected to occur to water and soil. SDPA manufacturing is expected to be the most relevant sector relating to potential SDPAs effects seen in the environment. SDPAs are imported into Canada as part of additive packages for lubricants, compounded resins for the manufacturing of plastics and rubber products, and the polyol used in the manufacture of polyurethane foam. These intermediate products are used at industrial lubricant blending sites and at plastic, foam and rubber processing sites where there is further potential for SDPA releases to the environment.

Releases of SDPAs can also occur from products during their product life. Based on the analysis of the information collected through the section 71 notice (ECCC 2012a), at least 96% of SDPAs in Canada are used in the lubricants sector and less than 4% in the plastics (including foam) and rubber sectors combined. Releases to the environment from plastic, foam and rubber products are expected to be minimal, geographically disperse, and spread out over the

[9] Commercial use is the use of a chemical substance, or the use of a mixture, product or manufactured item containing a chemical substance, in a commercial enterprise providing saleable goods or services.
[10] An emission factor is generally expressed as the fraction of a substance released to a given medium such as wastewater, land or air during a lifecycle stage such as manufacture, processing, industrial application or commercial/consumer use. Sources of emission factors include emission scenario documents developed under the auspices of the Organization for Economic Cooperation and Development (OECD), and can also be derived from data reported to Environment Canada's National Pollutant Release Inventory (NPRI 2008), industry-generated data, monitoring data, etc.

duration of the service life and end of life of these products. As for lubricants, releases can occur through leaks, spills and improper disposal of the products containing the substances.

8.2.2 Exposure Scenarios

Many exposure scenarios were considered to represent the main industrial activities and overall uses of SDPAs in Canada. These scenarios are based on an analysis of known and anticipated use patterns in Canada (see section 5).

Two scenarios were identified as having the highest likelihood of environmental exposure (i.e., the manufacturing of SDPAs and the blending of lubricants in Canada). Other scenarios considered had lower potentials for environmental exposure. Given that SDPAs are potential replacements for each other, and measured concentrations did not include all relevant structures (i.e., monostyrenated DPA and distyrenated DPA were generally absent), the exposure scenarios focused on total SDPA representative structures. While only the potentially bioavailable forms (i.e. monooctyl DPA, dimethyl distyrenated DPA, monononyl DPA, monostyrenated DPA, distyrenated DPA, dibutyl DPA, monobutyl DPA, and monobutyl monooctyl DPA) are considered ecologically relevant, total SDPAs are considered in the exposure assessment to represent a potential future situation where product formulations change while leaving total usage relatively constant.

The conservative replacement lubricant blending scenarios assume that the total SDPA exposure may be represented by any one of the potentially bioavailable SDPAs given the similarity in structure and function within this group. The SDPA manufacturing exposure scenario uses the available measured concentrations for total SDPAs (presented in section 8.2.2.1) considered representative of this activity in Canada.

The environmental exposures for water, sediment, benthic organisms, fish and piscivorous mammals are identified as the most relevant for this assessment. When adequate measured concentrations data are available, they are preferentially considered over modeled or estimated values for the derivation of predicted environmental concentrations (PECs). The PECs attempt to be both spatially and temporally relevant for this purpose.

8.2.2.1 Manufacture of SDPAs

8.2.2.1.1 Sediments

A scenario was developed to assess the potential exposure resulting from the manufacture of SDPAs based on site-specific environmental sampling data.

The largest SDPA manufacturing site in Canada currently produces between 10 000 000 and 100 000 000 kg of total SDPAs per year in three major product

lines consisting of eight major SDPA representative structures (ECCC 2012a). All industrial wastewater from the manufacturing of SDPAs in Canada is treated on-site before being discharged to the local WWTS for further treatment and eventual discharge to the environment, downstream of the manufacturing facility. The facility building and areas involved in manufacturing and loading operations have secondary containment systems intended to redirect any spills from this area to the on-site treatment system. Rainwater collected on-site is typically discharged directly to the local receiving waterbody, after testing for water quality.

Site-specific sampling data indicates that the on-site treatment system at a manufacturing facility removes between 95% and 99.9% of all measured SDPAs (ECCC 2015). The off-site municipally owned WWTS further removes at least 90% of the measured SDPAs (ECCC 2015, and ECCC 2015). Sampling data confirms low levels of SDPAs in the effluent of the municipally owned WWTS. With only 22% of samples showing values above the method detection limit, the average total SDPA discharged via this waste stream is less than 30 ng/L for the time of sampling (ECCC 2015). The limited release levels also concur with the low SDPA levels found in the surface water, and sediment from the nearby receiving waterbody (ECCC 2015).

Sediment samples collected in a manufacturing facility's storm drain that discharges directly to the environment showed total SDPAs concentrations of >100 000 ng/g dw (Study Submission 2015a). Sediment sampling from the local receiving waterbody indicates elevated levels in the sediment within the boundaries of the manufacturing site and upstream of the municipally owned WWTS (Table 8-5) (Study Submission 2015a and ECCC 2017a). Available sediment core data were averaged to include SDPA concentrations from both the upper aerobic and lower anoxic zones (Section 6.1).

Thus, the largest source of SDPAs from this manufacturing site is likely surface water run-off which passes through storm drains and a holding tank and potential atmospheric deposition via stack air emissions. Although the exact mechanism responsible for depositing SDPAs onto the paved surface is unknown, it is suspected to be fugitive releases. It is noted that all SDPA concentrations measured in the environment were below the NOECs listed in Table 8-3.

Table 8-5 Average total SDPA sediment concentrations near a SDPA manufacturing facility (ECCC 2017a, Study Submission 2015a)

Location	Number of Samples	Total Potentially Bioavailable SDPAs (ng/g dw)	Total SDPAs (ng/g dw)
Upstream of the manufacturing facility	5	6	9
Receiving waterbody running through	7	3753	5489

Location	Number of Samples	Total Potentially Bioavailable SDPAs (ng/g dw)	Total SDPAs (ng/g dw)
property			
Downstream of WWTS outfall (20-100 m)	3	1025	1271
Further downstream (1.5-7 km)	7	470	649

8.2.2.1.2 SDPAs in Benthic Organisms

An internal total SDPA concentration of 0.04 mmol/kg bw in the benthic organism was conservatively obtained using the total concentration of SDPA sediment concentrations (5489 ng/g dw representing both bioavailable and non-bioavalaible SDPAs) from measured environmental concentrations (see Table 8-5). The assumptions included using the average organic carbon content in sediment for the samples of interest i.e. 2.4% (Study Submission 2015a), a lipid content of 2.1% for benthic organism(*Gammarus pulex*) (Arnot and Gobas 2004) and a conservative BSAF of 3 [kg OC / kg lipid]. The calculated total SDPA concentration of 0.04 mmol/kg bw for the tissues of benthic organisms is lower than the critical body residue thresholds of 2-8 mmol/kg for acute exposures and 0.2-0.8 mmol/kg for chronic exposures, and therefore there is minimal potential for risk to benthic invertebrates. *Chironomus riparius* also showed no effect at the highest treatment concentration of 100 mg/kg dw for a commercial product containing primarily monononyl DPA and dinonyl DPA

8.2.2.1.3 Fish

Biota, including fish, were sampled (Study Submission 2015a; ECCC 2017a, b) for SDPAs in the surface water adjacent to and receiving effluent from a manufacturing facility in Canada (see Section 6).

As previously described, there were a number of deficiencies regarding the acceptability of the data in the Study Submission (2015a) results; however, it is acknowledged that SDPA structures were not measured above their respective method detection limits (< 0.02 – < 0.2 µg/g bw) in any fish tissue samples.

White Sucker fish tissue samples were also collected by Environment and Climate Change Canada researchers within the same area (ECCC 2017a, b). This analysis, which used a lower detection limit, provides additional information on the presence of SDPAs in the environment. The fish (N=12) had an average total SDPA concentration of between 0.0036 and 0.0043 µg/g ww, of which greater than 90% consists of bioavailable components. A further study in an urban creek reported a maximum total SDPA concentration of 5.4 µg/g lw for crayfish (using a conversion factor of 1% result in 0.05 µg/g ww). Finallly, an industry provided study (Study Submission 2015a), with a much higher detection

limit, shows all values were below detection limit. The highest detection limit (0.2 µg/g bw) is used as a conservative upper bound for total SDPA in fish for further modelling in this assessment.

These low values may indicate either a lack of exposure or a lack of bioaccumulation due to a higher rate of metabolism than predicted from available studies. The highest method detection limit from Study Submission (2015a) (0.2 µg/g bw) was used as a conservative maximum total SDPA fish tissue concentration in an analysis of critical body residues to determine if this level could be associated with potential effects. An upper bound whole body burden of 0.0013 mmol/kg bw was calculated assuming a concentration equal to the reported method detection limit for each SDPA for which analyses were conducted (i.e. monooctyl DPA, dioctyl DPA, monobutyl DPA, dibutyl DPA, monobutyl monooctyl DPA, monononyl DPA, dinonyl DPA). This calculation becomes 0.0008 mmol/kg bw when considering only potentially bioavailable SDPAs. Both values are well below the internal concentrations of neutral narcotic chemicals causing death at 2-8 mmol/kg for acute exposures and 0.2-0.8 mmol/kg for chronic exposures (McCarty et al. 1992; Escher et al. 2011). They offer a greater than 100-fold margin of exposure for fish.

8.2.2.2 Lubricant Oil Blending Plants

There are more than 20 identified lubricating oil blending plants (LOBPs), with known or expected discharges into more than 10 different waterbodies in Canada (ECCC 2012a), representing the second largest industrial use of SDPAs. The available measured environmental concentrations are not considered sufficient either spatially or temporally to firmly conclude on risk potentially caused by the LOBPs (e.g., sample size is small, non-representative sample, and potential inputs from other sectors). Thus estimated environmental concentration data is used to support the analysis.

8.2.2.2.1 Surface water

A conservative replacement scenario was developed to determine the spatial (waterbody level) and temporal (yearly average) SDPA PECs for surface water that may be expected due to the operation of these LOBPs, assuming that all of the SDPAs can be used interchangeably. There are several assumptions in this scenario:

- Only the long-term average concentration is ecologically relevant.
- Only well mixed average concentration within any given waterbody is relevant.
- Other sources of SDPA release in Canada are assumed to be negligible. For instance, these sources may include:
    - LOBPs not located in Canada but discharging in the same waterbody (e.g., the Great Lakes);
    - consumer/commercial sources of SDPAs; and

    - other industrial sources of SDPAs (i.e., SDPA manufacturing, rubber/plastics manufacturing, etc.).
- All small capacity LOBPs discharge to a sewer system for further treatment prior to eventual discharge.

Further considerations made in the analysis include:

- The total SDPAs used at all LOBPs in Canada was between 1 000 000 and 10 000 000 kg based on 2011 data (ECCC 2012a). It was assumed that the total amount used could vary by 15% (coefficient of variation) which was extrapolated from the lubricant oil production data in Canada (HRD 2011).
- It is assumed that the total mass of SDPAs used by the LOBP industry could be used interchangeably, thus, results for identical scenarios were calculated one at a time, each time assuming the total mass of SDPAs (between 1000 000 to 10 000 000 kg) is comprised by one representative bioavailable SDPAs (i.e. Log K_{ow} < 9.0).
- Each plant was assigned a portion of the total use quantity of SDPAs (ECCC 2011a) based on known usage. It was then assumed that the use of SDPAs at each plant could vary within the total amount used in Canada insofar that any one plant is able to acquire market share at the expense of another plants' market share. The largest plant could thus vary its capacity by 20% while the smallest plant could vary its capacity by 200%.
- Site-specific details pertaining to mitigation technologies, effluent flow rates, oil and grease monitoring, site capacities, calculated emission factors, and effluent discharge location were used to estimate SDPA releases where such data were available.
- Where available, information about wastewater treatment levels was considered in the estimation of SDPA releases
- In relation to the above two parameters, where site specific information was not available, default parameters were used.
- A 0.25 % pre-mitigation emission factor was used for the small LOBPs (OECD 2004c).
- A post-mitigation emission factor for oil and grease ranging from 0.05% to 0.00005% was calculated for four separate plants based on production capacities, where data was available.
- For large LOBPs both the pre-mitigation and post-mitigation emission factor sources were considered and given equal weight.

A Monte Carlo analysis was performed, varying the following parameters:

- total Canadian SDPA market usage;
- percentage of total market obtained by each of the sites;
- estimated losses to wastewater;
- SDPA removal rate for oil-water separators;
- SDPA removal rate for biological treatment;
- SDPA removal rate for traditional physical treatment;

- SDPA removal rate for lagoons; and
- selected waterbody.

The PEC in surface water represents the maximum potentially bioavailable total SDPAs and is estimated to range from 0.0008 to 5 ng/L as the 5^{th} to 95^{th} percentiles (ECCC 2017c). The SDPAs with log Kows greater than 9 are considered to be hydrophobic chemicals and thus provide limited bioavailability to aquatic organisms for uptake and accumulation via water. Sensitivity analysis indicates that the largest variable is variation between dilutive capacities of the waterbodies analyzed. The next three most sensitive variables include removal efficiency of the oil/water separator, the selection of emission factors, and the secondary treatment removal rates. These variables all have a high degree of uncertainty that could be further refined if more precise data were available. Additional unquantified uncertainties exist pertaining to the validity of each above-listed assumption. However, the upper range of the calculated SDPA concentration (i.e., 5 ng/L) is comparable to the only data points available representing the highest total SDPA concentration measured in surface water at the outfall of a large-capacity LOBP operating in Canada (i.e., 6.3 ng/L if values reported as less than a value are set to that value; ECCC 2017c).

8.2.2.2.2 Sediments

Although there are some sediment concentrations of SDPAs near LOBPs, these are not enough to characterize SDPA exposure, and therefore, SDPA concentrations were predicted based on equilbrium partitioning from the predicted water concentrations above.

A surface sediment concentration of 335 ng/g dw was calculated (which is lower than the NOECs presented in Table 8-3) using the equilibrium partitioning approach and the surface water PEC of 5 ng/L. The analysis assumed a log K_{ow} of 8.67 (i.e., as a worst case scenario, it is the highest log K_{ow} value of any SDPA structures considered potentially bioavailable), a suspended solids concentration of 4 mg/L, an organic carbon fraction in suspended solids of 10% and an organic carbon fraction in surface sediments of 3%. The calculated SDPA concentration in surface sediments is higher than the highest measured sediment concentration potentially relevant to LOBPs in Canada of 60 ng/g dw; however, due to the low number of sites and samples taken which are potentially relevant for LOBP discharge (N=2), this concentration may not be representative of sediment concentrations downstream of other Canadian LOBPs. Therefore, the modelled SDPA concentration in sediments has been selected as the PEC for the LOBP scenario.

When comparing the sediment PEC of 335 ng/g dw to the empirical SDPA concentrations in sediments related to the manufacturing scenario (section 8.2.2.1), it is seen that it is significantly lower. Since risk to benthic organisms was not identified from sediments in the manufacturing scenario, it is judged that

there will be no risk for benthic organisms using the lower predicted sediment concentration from the LOBP scenario.

8.2.2.2.3 Fish

Exposure to fish living directly downstream from an LOBP was estimated using the range of expected total water concentrations estimated in section 8.2.2.2.1, as well as the estimated Log(BAF) of the mid-trophic level fish for the SDPA structure with the highest estimated BAF. Log (BAF) is 4.79 with a 95^{th} percent prediction interval between 4.17 and 5.42 (Arnot and Gobas 2003b). These values were subjected to a Monte Carlo simulation. The results estimated a median concentration of $2.6x10^{-5}$ mmol/kg and a 95^{th} percentile of $2.8x10^{-3}$ mmol/kg, well below the narcotic threshold of 0.2 mmol/kg.

8.2.2.3 Other Potential Contributors

Based on the results presented in Table 6-3, the highest reported total SDPA concentration in surface sediments in Canada not related to the SDPA manufacturing or LOBP industries is 229 ng/g dw (of which 80 ng/g dw is potentially bioavailable). This dataset is expected to include inputs from a number of industrial, commercial and consumer activities (e.g., plastics manufacturing, automotive assembly, disperse urban input and urban input concentrated in wastewater treatment plants). While not conclusive in its own right, it does lend weight to the argument that the other potential contributors (described in this section) are not expected to be significant contributors of SDPAs in the environment.

8.2.2.3.1 Use in the plastics and rubber sectors

The plastics (including foam) and rubber sectors are identified as having a low potential for releases of SDPA to the environment. The plastics and rubber sectors represent a minor use of SDPAs in Canada (less than 4% of the total quantity) (ECCC 2012a). As the process releases are small, it is considered that the exposure of SDPAs in the environment from the manufacturing of plastics and rubber is not significant.

These sectors do not handle the substances in a pure form but import and use SDPAs contained within intermediate products. For example, the molded plastic and rubber manufacturers import SDPAs already compounded in a resin (ECCC 2012a). The polyurethane foam producers import SDPAs as a component in polymeric polyols (ECCC 2012a). The emission factors for low volatile antioxidant additives are 0.1% to air and 0.05% to wastewater before treatment for industrial use (i.e., conversion) of plastics and rubber (European Commission 2003). Foam manufacturing accounts for 49% of the SDPAs used in the plastics and rubber sectors in Canada (ECCC 2012a) and does not discharge any process water to the environment (ECCC 2013c).

8.2.2.3.2 Use in automotive and powertrain assembly plants

Information was gathered from the automobile manufacturers in Canada through a voluntary survey (ECCC 2012b). This sector also does not handle SDPAs in a pure form. Both automotive and industrial lubricants containing some SDPAs are handled at automotive and powertrain assembly plants. Automotive lubricants (added to or already included within specific vehicle systems) typically contain SDPAs at concentrations less than 2% (ECCC 2013b). Industrial lubricants (used in mechanical systems at the plants) may contain SPDAs at concentrations up to 4% (ECCC 2013b).The plants are equipped with secondary containment, such as drip trays, to collect any drips or leaks during their operations. All plants send their oily waste to approved recyclers for reclamation or to waste-to-energy facilities (ECCC 2012b). The facilities also have spill prevention plans and materials handling procedures as part of their normal business operations. Considering these practices, environmental releases of SDPAs from automotive and powertrain assembly operations are expected to be insignificant.

8.2.2.3.3 Use of lubricants and their disposal

Engine crankcase oil is estimated to represent over 40% of the lubricants used in Canada (ECCC 2009b) and typically contains less than 2% of SDPAs (ECCC 2013b). Crankcase oils are altered during use due to breakdown of the additives, contamination with the combustion products, and the addition of metals from the wear and tear of the engine (CH2M Hill Engineering Ltd. 1992). Therefore, the composition of used crankcase oils (UCOs) is variable and difficult to characterize. UCOs were assessed by Environment and Climate Change Canada (ECCC, HC 1994, 2005) and found to meet the criteria under paragraph 64(*a*) of CEPA (ECCC 2005). However, the Government of Canada elected to take no further action with respect to UCOs since adequate risk management measures are in place (Canada 2007). This decision was maintained in 2011 after an evaluation of the effectiveness of the existing provincial and territorial controls (ECCC 2011a).

SDPAs may be released during consumer and industrial use from spills, leaks (e.g., drips from vehicles), and improper disposal of lubricants. An upper bound estimate of potential releases of SPDAs through improper use and disposal for Canada has been calculated. This calculation was based on:

- the estimated 2012 Canadian domestic sales of lubricating oil and greases is 1.1×10^6 m^3 (Statistics Canada 2013a);
- the estimated unaccounted used oil quantity for British Columbia, 500 m^3 (CRA 2011) that was extrapolated to Canada based on known oil sales data;
- a proportion of lubricants used for automotive applications and industrial applications (ECCC 2009b);
- a typical concentration of SDPAs in lubricating oil and greases used in each of these applications.

As antioxidants are consumed as a result of their function in lubricants, it is considered that a certain amount of the SDPAs present in the lubricant or grease are also consumed. The total quantity of SDPAs that is estimated to be lost through spills, leaks, and improper disposal of lubricants is between 10 to 20 tonne/yr for Canada (ECCC 2013d). SDPAs are sparingly soluble in water and can be released primarily to land within blended oil. In this scenario, SDPAs are considered as a non-aqueous phase liquid. Zytner et al. (1993) provides a method for determining the retention capacity of dry soil. While this method may not be fully applicable to SDPAs, it can offer a first approximation of the potential impact of SDPAs releases to land in this scenario. From this method, it is estimated that 14-50 m^3 of soil will be saturated by SDPAs each year in Canada. However, due to the dispersive nature of these losses (both spatially and temporally), they are not considered to represent a significant threat to the environment.

8.2.2.3.4 Spills and unintended releases

Environment and Climate Change Canada maintains an internal database of reported or discovered spills (ECCC 2013d). The data in this database may have some limitations for use in this assessment related to data completeness, representativeness, and quality. Thus, it is used only as an indicator for potential spills.

While spills of SDPAs were not actually reported to Environment and Climate Change Canada, estimated quantities of SDPAs that may have been spilled with the reported spills of petroleum products are presented (Table 8-6). It can be seen that reported spills of petroleum products that may have contained SDPAs (up to 4% in industrial lubricants used mechanical systems at plants) is relatively small in comparison to predicted releases of SDPAs during the use and disposal of lubricants (section 8.2.2.3.3), thus this data source will not be considered further).

Table 8-6 Estimated quantities of SDPAs from reported spills of petroleum products, derived from Environment and Climate Change Canada's Spills Database (EC 2013e)

Media	Spills/year	Total volume of spills which may contain SDPAs (litres of petroleum products/year)	Largest one time spill which may contain SDPAs 2008-2012 (litres of petroleum products)
Land	94	539	250
Air	2	3	10
Fresh water	71	505	750
Salt water	46	81	50

8.2.2.4 Biosolids application scenario

The CMP monitoring and surveillance program has collected data on the concentration of SDPAs in primary sludge, waste-activated sludge and biosolids, (ECCC 2017a, ECCC 2015). This dataset covers the majority of SDPA structures selected for this assessment (seven are considered potentially bioavailable) across nine WWTS and a few dozen samples Inputs from urban areas and all of the major implicated sectors, including both the SDPA manufacturing and LOBP sectors, are represented among the nine WWTS. These data are also considered to reflect a reasonable range of SDPA concentrations in biosolids for Canada. Table 8-7 shows a summary of this data organized by site, averaged where applicable.

Table 8-7 Average SDPA concentrations found in sludge and biosolids surveyed broken down by site (ECCC 2017a)

Site	Sample Type	Number of Samples	Total Potentially Bioavailable SDPAs (ng/g dw)[1]	Total SDPAs (ng/g dw)
1	Primary sludge	1	61	250
1	Waste activated sludge	1	66	607
2	Biosolids	10	725	1806
3	Biosolids	10	582	1923
4	Biosolids	2	989	2529
5	Biosolids	6	1571	3578
6	Biosolids	4	2415	4445
7	Biosolids	4	5865	13802
8	Biosolids	3	9883	22207

[1] Potentially bioavailable SDPAs: monooctyl DPA, dimethyl distyrenated DPA, monononyl DPA, monostyrenated DPA, distyrenated DPA, monobutyl monooctyl DPA, dibutyl DPA, monobutyl DPA, and monooctyl monostyrenated.

Using the largest average total SDPA concentration measured at a single site (22207 ng /g dw), it was estimated that the total SDPA concentration in soil would be 83 ng/g dw after 10 years (ECCC 2017c) of which 38 ng/g dw are considered as potentially bioavailable SDPAs. Conservative assumptions included no degradation and a biosolids application rate of 8.3 tonnes/ha every year, over a period of 10 years.

Following the same approach as identified in Section 8.2.2.1.2, a total internal SDPA concentration of 0.00043 mmol/kg bw is predicted for a target soil invertebrate (i.e., earthworm) using a conservative BSAF of 3 [kg OC / kg lipid] for all SDPAs, a soil organic carbon content of 2% and a target soil invertebrate

lipid content of 1.2% (BASL4 2011). Considering this scenario further, an estimated SDPA concentration of 0.004 mmol/kg bw in the shrew (ECCC 2017c) was obtained using the simple shrew model (Armitage & Gobas 2007). Conservative assumptions included no metabolism and correcting for the shrew body temperature using an estimate of -20 kJ/mol for the reaction enthalpy (personal communication, e-mail from J. Armitage to Environment and Climate Change Canada, Ecological Assessment Division, dated May 29, 2015, unreferenced).

Both internal body concentrations (i.e., 0.00043 mmol/kg and 0.004 mmol/kg) are below the critical body residue thresholds of 2-8 mmol/kg for acute exposures and 0.2-0.8 mmol/kg for chronic exposures. Toxicity studies for the earthworm indicate no effect below 1000 mg/kg (i.e., 1000 µg/g or 1 000 000 ng/g) for a commercial product containing primarily monononyl DPA and dinonyl DPA. This is higher than the PEC in soil of 83 ng/g dw.

8.2.2.5 Fish consumption by wildlife piscivores

Fish tissue concentrations relevant to the SDPA manufacturing scenario (ECCC 2017a) were compared to the estimated fish tissue values from the LOBP scenario. The LOBP scenarios fish tissue residue values were higher and are therefore used as a conservative scenario to assess risk to piscivorous mammals due to SDPA exposure from fish consumption.

Exposure to piscivorous wildlife from consumption of fish exposed to bioavailable SDPAs in waterbodies was estimated using a bioenergetics calculation for total daily intake (TDI) (modified from US EPA 1993). Mink and river otters are the chosen focal wildlife species in a riverine environment. The intent of the scenario is to assess the exposure of mink and river otter living near the discharge area only and is not extrapolated to the population of mammalian predators as a whole. PECs in the receiving waterbody, calculated for the LOBP scenario in section 8.2.2.2.1, were used and combined with modelled BAF values to estimate concentrations of the potentially bioavailable SDPAs in fish. Modeled BAF values were used instead of BAFs calculated from field measurements to be conservative. TDI values for mink and river otter (as predators) were estimated based on:

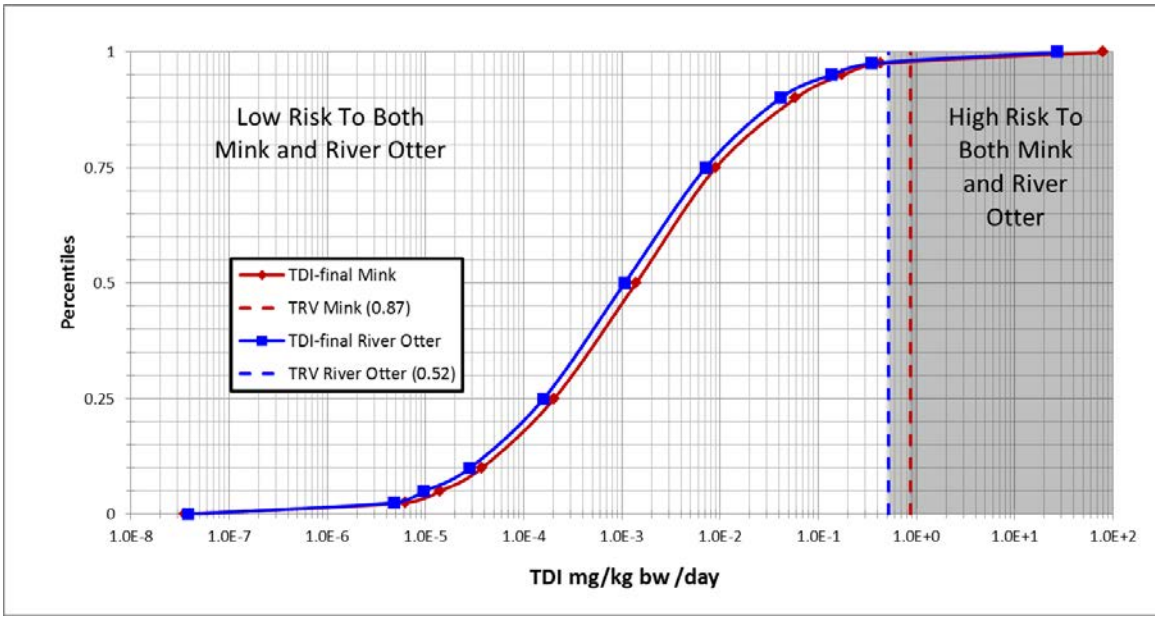
- Range of bioavailable SDPA concentrations in fish (as prey) and water;
- predators' eating habits;
- prey's gross energy;
- assimilation efficiency of the predators; and
- expected time spent by the predators near the discharge area.

Some additional details respecting the calculations are available in ECCC (2017c). The TDI model was subjected to Monte Carlo uncertainty analysis using the Crystal Ball Software (ORACLE c1998-2012).

This scenario considers the SDPA with the largest potential bioaccumulation factor and assumes conservative values for site-specific ecological parameters as follows:

- As a conservative scenario, only the waterbody with the highest probability of having the highest PEC was evaluated.
- Percentage of time each focal species spent in the affected area is assumed to be 100%; this value will likely be smaller for some places where adequate habitat does not exist to support these species.
- As a worst-case, the mink diet is assumed to contain the upper bound for fish (85%). This value is expected to be lower when dealing with smaller waterbodies.
- In the absence of data, the assimilation efficiency of the SDPA by the focal species was assumed to be 100%.
- All other values were derived from the US EPA exposure factors handbook (US EPA 1993).

Figure 8-1 Results for the total daily intake model compared to threshold values for the lubricant oil blending plant scenario



Long description:
Figure 8-1 summarizes the range of total daily intake concentrations, accounting for uncertainty in the model inputs. The vertical line indicates the threshold toxicity reference values (TRVs) of 0.87 mg/kg bw/day for the mink and 0.52 mg/kg bw/day for the river otter. Overall, the figure shows that there is a low probability that the estimated TDIs for mink and river otter will exceed the respective TRVs. Sensitivity analyses indicate that the largest cause of variances is the water concentration, followed by the BAF, and then species and model

specific parameters. The species and model specific parameters variability are minor compared to the water concentration and BAF.

9. Characterization of Ecological Risk

This screening assessment focused on fourteen SDPA substances, including five discrete substances, two isomeric mixtures (considered as discrete substances for the purpose of this assessment) and seven substances classified as UVCBs (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials). The SDPAs were assessed based on the representative chemical structures which are summarized in Table 2-2.

SDPAs are used in high quantities as antioxidants to prevent the degradation of the materials into which they are added. Their primary use is in the blending of lubricants, and to a lesser extent in the manufacturing of plastic, polyurethane foam, rubber, and adhesives. Releases of SDPAs are expected to occur to water (mainly from manufacturing activities and the blending of lubricants) and soil (mainly though application of biosolids). When released into the environment, SDPAs are expected to reside primarily in soil and sediment.

SDPAs are sparingly soluble in water, and are characterized by low vapour pressures and high to very high octanol-water partition coefficients. Among the SDPAs, those with the log K_{ow} of less than 9 (i.e., monooctyl DPA, dimethyl distyrenated DPA, monononyl DPA, monostyrenated DPA, distyrenated DPA, dibuty DPA, monobutyl DPA, monobutyl monooctyl DPA and monooctyl monostyrenated DPA) are considered to be bioavailable. Others (i.e., dioctyl DPA, dinonyl DPA, diethyl monononyl DPA and diethyl dinonyl DPA) are not easily absorbed from the exposure medium or diet and are considered to have very low bioavailability and unlikely to result in adverse effects. All SDPAs are considered to be persistent in the environment.

SDPAs contain no reactive functional groups and are anticipated to react only via a simple non-specific hydrophobic mechanism or narcosis. (Q)SAR modelling is difficult for some of the SDPAs due to their extreme physical-chemical characteristics that are not represented by the models' domain, and this can result in unreliable model results particularly for aquatic models. Their low water solubility restricts direct determination of toxicity in the water compartment. Empirical aquatic toxicity values determined for the SDPAs tested are above water solubility limits with no effects noted at saturation. As a result, the predicted no effect concentration (PNEC) values were not determined for the aquatic compartment based on these unbounded toxicity results. Critical body burden (CBR) analysis for fish using bioaccumulation data was conducted to evaluate ecological effects in the aquatic compartment. The CBR calculations at 0.0013 mmol/kg, and 0.0008 mmol/kg, when considering only the potentially bioavailable SDPAs, were well below the internal concentration of neutral narcotic chemical causing death of 2-8 mmol/kg for acute exposures and 0.2-0.8 mmol/kg for chronic exposures, offering a greater than 100-fold margin of exposure for fish. Similarly, the calculated total SDPA internal body concentrations of 0.04 mmol/kg

for the benthic organisms, and of 0.00043 mmol/kg and 0.004 mmol/kg for the shrew, were also lower than the critical body residue thresholds. Toxicity to the representative piscivorous species was evaluated using a body weight scaling approach from rodent data. Low toxicity to soil- and sediment-dwelling organisms was observed in SDPA exposure studies using the earthworm and freshwater midge as test species, respectively. These data and associated analyses suggest that concentrations of SDPAs reached in organisms in the environment are significantly lower than effects thresholds.

SDPA structures with log K_{ow} values greater than 9 (i.e. dioctyl DPA, dinonyl DPA, diethyl monononyl DPA and diethyl dinonyl DPA) are considered to have a limited bioaccumulation potential due to their physical-chemical properties and empirical evidence for substances with similar characteristics. For SDPA structures with log K_{ow} values of less than 9, i.e., those considered bioavailable, there is a discrepancy between modelled and empirical results. (Q)SAR modelling using an estimated slow metabolic rate yielded variable results, ranging from low to high bioconcentration factors; whereas recent field monitoring data in various aquatic receptors indicated low potential for bioaccumulation which were also suggestive of no effects. The tissue residue used in this assessment for the CBR analysis was the maximum total SDPA method detection limit of 0.2 µg/g bw (specified in a field study). This was again compared to critical body burden thresholds associated with acute and chronic lethality via narcosis. In addition, measured field BAFs are also not considered reliable due to limitations in the sampling methodology and calculations using total water concentrations generally below detection limits.

Measured concentrations of SDPAs in Canada are available for environmental media (i.e., water, sediments and biota), including at relevant locations such as near manufacturing sites, as well as for wastewater and wastewater treatment system (WWTS) biosolids. Data from WWTSs before and after treatment show that SDPAs are efficiently removed in the wastewater treatment process. Significant levels of SDPAs were found in WWTS biosolids. Surface water and effluent concentrations at WWTSs across Canada were observed at low ng/L levels. SDPA concentrations is sediments of Lake Ontario were below 6 ng/g dw, while measurements near a manufacturing site showed higher levels ranging from less than 2 µg/kg to up to about 2000 µg/kg dw for dimethyl distyrenated DPA downstream of manufacturing operations. SDPAs were found in very low ng/g dw in white sucker fish sampled near an industrial site.

Environmental exposure to SDPAs was examined in multiple scenarios representing industrial activities and overall uses of SDPAs in Canada. The key activities examined were manufacturing of SDPAs and the blending of lubricants. Other activities, thought to have a lower potential for environmental exposure, including the use of SDPAs in the plastics and rubber sectors, automotive and powertrain assembly lines, disposal of lubricants and biosolids amendment to agricultural land, were also examined. Where relevant, some scenarios also

considered the potential impact on piscivores from the consumption of fish in areas of exposure to SDPAs. The scenarios focused on the total representative structures, to be inclusive of all SDPAs, given that SDPAs are potential replacements for each other and that changes in product formulations could occur with the total SDPA usage remaining relatively constant. These analyses revealed that the potential for adverse effects from SDPAs in the environment, including benthic species, aquatic species (fish), piscivorous mammals, and soil-dwelling organisms, is low.

9.1 Consideration of the Lines of Evidence and Uncertainties

To characterize ecological risk of the fourteen SDPAs, technical information for various lines of evidence was examined in this screening assessment. A weight of evidence approach, where several lines of evidence are considered in an integrated manner and used in the decision-making, as well as precaution (as appropriate), were applied to develop a conclusion as required under CEPA. Uncertainties underlying the lines of evidence, stemming from data gaps or data variability, were identified and their impacts on the assessment were evaluated using a qualitative analysis. Uncertainties can lead to over- or under-estimation of risk, or the impacts can remain unknown.

The qualitative analysis presented in Table 9-1 serves to determine the overall confidence in the decision-making process that led to the assessment conclusion under CEPA. The level of uncertainty for each line of evidence was judged based on the abundance and quality of data, and its suitability. The analysis also included consideration of the relevance of each line of evidence and the qualitative assessment of the weight for each line of evidence to determine their impact on the overall conclusion. Qualifiers used in the analysis ranged from low to high.

Table 9-1. Uncertainty characterization and analysis of the weight of evidence in the risk assessment for SDPAs

Line of Evidence	Level of Uncertainty[1]	Relevance in Assessment[2]	Weight Assigned[3]
Modelled Physical-Chemical Properties (e.g., log $K_{ow,}$ log K_{oc}, water solubility)	Moderate	High	Moderate to High
Environmental Persistence/Residence Time	Low	High	High
Modelled bioconcentration	Moderate to	Moderate	Moderate to high

Line of Evidence	Level of Uncertainty[1]	Relevance in Assessment[2]	Weight Assigned[3]
and bioaccumulation data in fish	high		
Empirical bioconcentration data in fish	High	High	Low
Empirical bioaccumulation in fish	High	High	Low
Environment and Climate Change Canada and industry measured Site-specific fish tissue residue data and CBR analysis	Low	Moderate to High	Moderate to High
Mode of toxic action/receptor binding/chemical activity	Low	High	High
Modelled aquatic toxicity	Moderate to High	Low	Low
Empirical aquatic toxicity	High	Low	Low
Empirical mammalian toxicity	High	High	Moderate
Empirical product data for earthworm and benthic organism toxicity	Moderate to High	Moderate	Low to Moderate
Environment and Climate Change Canada and industry measured surface water concentrations	Low to Moderate	Low	Low
Environment and Climate Change Canada modelled sediment concentrations for LOBPs	High	High	Low
Wildlife model for LOBPs	Moderate to High	High	Low to Moderate
Environment and Climate Change Canada concentrations used in manufacturing scenario	Low	High	High
Models for CBR in benthic organisms	Moderate	High	Moderate to High
Environment and Climate Change Canada measured biosolids concentrations	Low	High	High

Line of Evidence	Level of Uncertainty[1]	Relevance in Assessment[2]	Weight Assigned[3]
Models for CBR in earthworm and shrew based on measured biosolids concentrations	High	High	Moderate

Abbreviations: LOBPs, lubricant oil blending plants; CBR, critical body residue
[1] Level of uncertainty is determined according to data quality, data variability, data gaps and if the data are fit for purpose
[2]Relevance refers to the impact of the evidence in the assessment scientifically and/or from a regulatory perspective
[3]Weight is assigned to each line of evidence and it is directly related to its relevance in the assessment as well as factors such as data suitability and quality.

The fate of SDPAs in the environment, their bioaccumulation potential and ecological effects, environmental levels and critical body residue analyses for key environmental compartments were described in the screening assessment report to characterize the potential of SDPAs to cause adverse effects in the Canadian environment.

SDPAs are hydrophobic chemicals, with certain SDPAs having very high octanol-water portion coefficient and very low water solubilites. Uncertainty remains with the capacity to characterize properties of these SDPAs using (Q)SAR models because these models are not well suited for substances with very high log k_{ow} values and ionizing potential (i.e., only the neutral forms can be assessed). Because of their hydrophobic nature, SDPAs will become associated with sediments, suspended particulate matter and soil when released to the environment. Those SDPAs with octanol-water partition coefficents greater than 9 are considered to have limited bioavailability.

SDPAs are considered to be persistent; the measured and modelled half-lives and slow rate of biodegradation of SDPAs indicate long residence time in the environment. They are not expected to undergo long-range transport in water or air, and long-term exposures are expected to be near discharge areas and closer to emission sources.

SDPAs are expected to be released into water and soil, and will reside mainly sediments and soil. If the water solubility and the log K_{oa} are considered in conjunction with the log K_{ow}, then dietary uptake is likely the more significant route of exposure for some SDPAs in both aquatic and terrestrial organisms. Available effects studies on aquatic organisms are at exposure concentrations well above water solubility limits, whereas model results are considered highly uncertain and they do not address the primary routes of exposure for SDPAs through the food chain. Therefore, critical body residue calculations were done for fish, as well as for soil/sediment organisms and piscivores to evaluate exposure levels associated with ecological effects.

Based on their intrinsic properties, some SDPAs are predicted to have a high level of bioaccumulation (i.e., predicted BAF), but under natural conditions given

their hydrophobicity and low bioavailability in the dissolved phase, tissue residues have been measured at very low or at non detectable levels in several taxa. This speaks to the uncertainty of using water-based metrics to explain bioaccumulation potential for very hydrophobic substances. In fact, the available empirical laboratory data suggests a low potential for bioconcentration from water even when solubilizing agents are used to increase bioavailability.

Site-specific studies on concentrations in biota are considered relevant in the assessment of SDPAs since long-term exposures are expected to be near sources of release. A study sampling fish tissue residues near a manufacturing site showed SDPAs below the method detection limits of < 0.02 – < 0.2 µg/g. Additional fish sampling conducted upstream and downstream near the same site showed values higher in the downstream fish (median and mean: 0.054 and 0.060 ng/g ww) compared to upstream fish (median and mean: 0.004 and 0.029 ng/g ww). It remains unclear if the lack of SDPAs measured denotes lack of exposure or lack of bioaccumulation.

The absence of bioaccumulation may be due to missing trophic level species at the site (benthic organisms) or due to a higher than expected rate of metabolism given the available laboratory data. Variable bioconcentration (BCF) and bioaccumulation (BAF) results were obtained from (Q)SAR models. These mass-balance models are highly sensitive to log K_{ow} error, metabolism rate error and dietary assimilation efficiency. Considerable effort was made to quantify the log K_{ow} and metabolic rate constant for fish using empirical BCF data and (Q)SAR estimates for bioavailable substances.

Numerous exposure scenarios were performed to assess risk to the aquatic, soil and sediment dwelling organisms from SDPAs. The highest potential for exposure to SDPAs in the Canadian environment was identified from manufacturing activities and blending of lubricants, but several other scenarios were also examined including biosolids amendment, uses in the plastics, rubber, and automotive sectors.

The potential for risk to soil and sediment-dwelling organisms from exposure to SDPAs is considered to be low. Internal SDPA body concentrations for the shrew and earthworm were estimated as below the critical body residue thresholds. Similarily, the calculated critical body residues for benthic organisms were below the acute and chronic internal toxicity thresholds. Low toxicity to a commercial product containing primarily monononyl DPA and dinonyl DPA was observed in studies using the earthworm and the freshwater midge.

Considering the lines of evidence presented in this screening assessment with a higher weighting on the knowledge of the mode of action for SDPAs (neutral narcosis), concentrations found in the environment and biota including the use of CBR analyses, there is low risk of harm to organisms and the broader integrity of the environment from the fourteen SDPAs in this assessment.

10. Potential to Cause Harm to Human Health

10.1 Exposure Assessment

10.1.1 Environmental Media and Food

As shown in section 6, concentrations of SDPAs were recently measured in water, sediments, biosolids, and biota in Canada. Although most of the concentration data were specific to one manufacturing site, Environment and Climate Change Canada also measured concentrations in environmental media in various sites in Ontario or associated with wastewater treatment plants across Canada. Concentrations in water resulting from wastewater treatment plant effluents were used as surrogates for concentrations in drinking water. The highest concentration recorded was 0.125 µg/L (see table 6.6. SDPA concentrations in biosolids resulting from wastewater treatment were used to model concentrations in soil. Assuming biosolids from wastewater treatment systems is applied to soil in an agricultural field, the approach outline Gobas (2010) model was used to predict a soil concentration of 83 ng/g (= 83 µg/kg; see Section 8.2.2). Although data on concentrations in food in Canada or elsewhere were not identified, attempts were made to measure SDPA concentrations in fish near one Canadian manufacturing site. SDPAs were not detected in fish tissue at this location; the upper bound method detection limit (< 0.2 µg/g; see Section 7.2.4) for the analyses conducted in fish was used in the estimate of daily intake from food. With low vapour pressure for these substances, SDPAs are not expected to be present in significant amounts in the air and thus, exposure via the inhalation route is expected to be negligible.

Despite favoured partitioning to soil and sediment, based on physical chemical properties of SDPAs, releases from industry are primarily to the aquatic environment. Based on the concentrations measured in the Canadian sites identified above (treatment plant effluent and biosolids, fish tissue) and a predicted soil concentration based on application of biosolids to agricultural land, a conservative upper bounding daily intake of SDPAs of 0.01 µg per kg-bw per day was estimated. Thus, exposure to SDPAs from environmental media is considered to be very low.

No Canadian data were identified for SDPAs in food packaging. Some SDPAs are approved for use as antioxidants in adhesives used in the manufacture of paper-based food packaging materials. While there is the potential for incidental food contact, the exposure potential is considered negligible (February 2013 email from Food Directorate, Health Canada to Risk Management Bureau, Health Canada; unreferenced). In the United States, some SPDAs are on the list of FDA indirect additives used in food packaging and food contact materials (CAS RNs 10081-67-1, 26603-23-6, 68411-46-1, 68442-68-2) (US FDA 2011).

The low volume of use in food packaging suggests negligible exposure from this route to the general population.

10.1.2 Products Available to Consumers

Products available to consumers that contain SDPAs are primarily lubricants (such as motor oil and transmission fluid) (ECCC 2012a; US EPA 2009). Flexible foam products represent a small fraction of products containing SDPAs. Due to their uses and physical-chemical properties, low volatility and negligible to low water solubility, the primary source of exposure to SDPAs from products available to consumers is expected to be dermal from automotive lubricants and oral from manufactured foam products.

SDPAs are a subclass of amine antioxidants that are used to prevent the degradation of the materials (e.g., lubricants, foams) into which they are added. Antioxidants are added in polyols imported for the production of polyurethane foam, resulting in concentrations of <0.1% SDPAs in the finished product (US EPA 2009). There are no studies to indicate the migration of SDPAs from foam products, but given the low volatility of these substances, release or potential off-gassing are expected to be minimal. In addition, any foams used in vehicles and household furniture would be covered by upholstery, further limiting exposure to SDPAs. A mouthing scenario of an infant and toddler of a couch cushion was considered as an upper bounding estimate[11]. Based on an algorithm suitable for a substance of low water solubility, a mouthing time of 60 min/day, saliva flow rate of 2.2×10^{-4} L/min and fractional extraction of 0.5 was applied to the SDPA with the highest water solubility (CAS RN 68411-46-1) to derive an estimate of 1.76 µg/kg-bw per day for infants and 0.85 µg/kg-bw per day for toddlers (Appendix C).

Motor oils are agents that serve anti-wear and cooling functions for running equipment parts and must be periodically replaced, either at the dealer, repair garage or by the consumer. Between 10 and 15% of all oil changes are done at home on the driveway (Stewardship Ontario 2013). Other automotive fluids, such as transmission fluids, also serve in extending the lifetime of a vehicle's mechanics and require replenishments during the life of the vehicle. Accordingly, an estimate of dermal exposure to SDPAs resulting from a do-it-yourself (DIY) motor oil change was derived. For automotive fluids and oil, the exposure is intermittent as the typical time between refilling fluids and oil is every few months.

[11] Although SDPAs may also be found in plastics, exposure of children to SDPAs in foam is considered to cover any potential exposure via plastics because SDPAs imported in plastics are already compounded in a resin, whereas SDPAs imported in polyurethane foam are a component in polymeric polyols (see Section 8.2.2.3.1).

A DIY motor oil change involves draining used oil, replacing the filter and pouring new oil into the engine crankcase using a funnel (eHow 2009). Motor oil composition changes over time with continued use of an engine, during which SDPAs are effectively consumed in their capacity as antioxidant additives. Given the altered chemistry of used motor oil (i.e., the expected loss of SDPAs), dermal exposure would result from new oil via potential spillage or using a finger to lubricate the filter. The use percentage of SDPAs used as antioxidants in oil is at a concentration up to 4% (ECCC 2012a). A range of dermal exposure to motor oil during an oil change was estimated between 0.75 to 11.4 µg/kg-bw per event. Detailed calculations for this dermal scenario are presented in Appendix C.

Other potential exposure scenarios involve the refilling of other automotive functional fluids (e.g., transmission fluid). These products require few changes during the service life of a vehicle and are typically done at a service station. General consumers, however, would likely need to top up these automotive fluids between every few months and up to 2 years. Given the scenario estimate similarities with motor oil, and the lower use pattern of transmission fluids and other automotive fluids, a DIY top-up scenario was not calculated and instead considered under the motor oil scenario.

The assumptions made in the above exposure estimate are conservative. Motor oils and similar automotive products are viscous, resulting in a relatively slow diffusion rate from the oil to the skin. Furthermore, the motor oil and other fluids usually stay on the skin for a short time before being washed or wiped off by the user, or not at all if wearing protective clothing and gloves. These factors will decrease the uptake fraction relative to value of 0.25 used in the exposure calculation.

SDPAs are also used in fuel additives (US EPA 2009); however, due to the low quantities used and the low volatility of these chemicals, exposure to SDPAs from refuelling a vehicle is not expected to be a significant source of exposure.

Adhesives and sealants are listed as uses for SDPAs; however, data received voluntarily from industry and from the public literature indicated that any use in adhesives and sealants would be in industrial settings only (ECCC 2012a). Other than the potential foam scenario, there were no reported consumer uses for plastic and rubber products containing SDPAs as an additive. Other plastic and rubber products were determined to be used in industrial settings only.

10.2 Health Effects Assessment

Detailed study information for each group member for selected endpoints are presented below. A data matrix summary table is available in Appendix D showing key effect levels for the substances with data.

10.2.1 Analogues in the Human Health Effects Assessment

To facilitate a more robust group analysis for the human health effects assessment, the OECD QSAR Toolbox was used to search for additional SDPAs with associated toxicity data. A custom profiler was created specifically for SDPAs. The profiler was used to search for substances that 1) have the diphenylamine backbone, and 2) have a molecular weight (MW) above 170 Daltons (the MW of diphenylamine; CAS RN 122-39-4) within the pre-loaded Toolbox databases**.** Similarly, the search conducted for physical chemical data, a number of potential additional analogues were found but they all had MWs below 200 Daltons. These substances and diphenylamine have lower melting points, higher vapour pressures and water solubility values, and lower log K_{ow} values than the SDPAs in the current grouping and thus were excluded from the group analysis. Therefore, no additional analogues were identified, compared to the 14 substances mentioned in Section 2 (Substance Identity) of this assessment.

Note that the SDPA, CAS RN 68921-45-9 (BNST), is included amongst the 14 substances mentioned in Section 2. A screening assessment for this substance was published in 2009 (ECCC, HC 2009), but that assessment focused principally on information relevant to the evaluation of ecological risks. There was little concern for human health exposure to BNST. In this assessment, hazard data relevant to human health for SPDAs, including BNST, are considered in the summary and analysis of each human health endpoint discussed below.

10.2.2 Toxicokinetics

There was no information on toxicokinetics in the US EPA's (2009) Screening-level Hazard Characterization document on SDPAs. However, a summary of a mammalian toxicokinetic study was identified. In this study, male rats were orally dosed with 10 or 80 mg/kg bw of CAS RN 10081-67-1, and tissue, plasma, urine, feces, and bile analyses were conducted over a period of 96 h. The test substance was absorbed into the blood and tissues of rats, with maximum concentrations observed within 16 h of dosing. Highest levels of radioactive dose in the spleen occurred at 8 h post-dosing and in the liver at 8-16 h post-dosing, depending on the dose. Excretion was mainly via feces over 4 days, with ≤ 0.4% of the radioactive dose recovered in urine and bile. Less than 3% of the radioactive dose remained in rat bodies after 96 h. Parent compound was the main substance identified in plasma and feces (70-95% of radioactive dose), but one unidentified metabolite was observed in both plasma and feces (5% of

radioactive dose in both media), and another unidentified metabolite was observed in feces (25% of the radioactive dose). These metabolites were thought to be hydroxy derivatives of CAS RN 10081-67-1 (ECHA 2008a) [12].

In addition to the rat toxicokinetic study mentioned above, industry submitted to ECHA an opinion on the toxicokinetics of CAS RNs 36878-20-3 and 68411-46-1. Industry stated that absorption via the oral route would occur in the gastrointestinal tract and inhalation exposure is of no relevance due to the low vapour pressure. Distribution of these substances would likely occur via the plasma to all organs, including the target organs of toxicity (kidneys, liver and haematopoietic system). It was assumed that these two substances undergo hydroxylation at the phenol ring and/or side chains. In addition, N-glucuronidation may be relevant (BASF SE 2010a,b). The toxicokinetic study via the oral route conducted with CAS RN 10081-67-1 confirms distribution to all organs via the plasma, and supports the hypothesis of hydroxylation at the phenol ring and/or side chains.

Based on the analysis of physical-chemical properties for the group members, dermal absorption may be limited. Due to the low vapour pressure for the group members, and consistent with the industry opinion stated above, exposure via the inhalation route is expected to be negligible. Therefore, absorption via inhalation was not considered.

As mentioned above, the target organs are most likely the liver and the haematopoietic system (most likely secondary to liver toxicity) after oral exposures in experimental animals, with the kidney also being a target organ at higher doses. Based on the limited empirical data for the 14 substances within the grouping, there appears to be consistent health effects observed for many of these substances. The toxicokinetic study via the oral route conducted with CAS RN 10081-67-1 demonstrates that the the liver and haematopeitic system are target organs (highest radioactivity in spleen at 8 h and in liver at 8-16 h post-dosing).

Using “Toxicokinetic considerations for the assessment of chemicals” (OECD 2011), as a guide to help determine potential toxicokinetic similarities/differences between the 14 substances, trends in molecular weight, pKa, log K_{ow} and other considerations (water solubility, vapour pressure, etc.) were compared within the group. As a result, key physical-chemical properties considered to primarily affect toxicokinetics showed generally the same ranges amongst the 14 substances.

[12] Summary information for this endpoint was obtained from the ECHA website because neither study reports nor published articles on toxicokinetics were available. The ECHA website also reports other endpoint studies (e.g. acute and repeated dose studies) for this substance. These are reported if no other study reports or published articles were available for the endpoint in question.

Molecular mass generally ranged from 225-422 g/mole, suggesting that these are relatively small molecules and will be distributed and excreted readily in mammalian organisms. Ionization constants (pK_a) were generally in the range of 0.8 to 1.3, indicating that the substances are uncharged in physiological environments and "…uncharged molecules more readily cross the lipid environment of biological membranes by passive diffusion...". The log K_{ow} (Log P) values were generally in the range of >4.5 to 13.5, indicating a tendency towards greater solubility in lipids rather than in water, and thus suggesting that the substances will distribute to target organs and be metabolized to more water soluble substances. The variation in the range of log K_{ow} values for these substances may translate to differences in oral bioavailability. However, substances with high log K_{ow} exhibited treatment related effects and oral absorption can be inferred. The category member with the lowest effect level for short-term toxicity was CAS RN 184378-08-3. This UVCB substance has five representative structures, as shown in Table 2-2, all of which show greater water solubility values (0.004 to 2 mg/L) and lower or similar log K_{ow} values (ranging from 5.1 to 8.8) values than those of dimethyl distyrenated diphenylamine, the representative structure for CAS RN 10081-67-1 (MW = 422 g/mole; water solubility = 1.3×10^{-5}; log K_{ow} = 8.2; see Appendix A for more information)[13]. Additionally, CAS RN 184378-08-3 shows lower molecular masses (225 to 393 g/mole; weighted average = 308 g/mole) than CAS RN 10081-67-1 (406 g/mole) (Health Canada 2003; US EPA 2009). This suggests that CAS RN 184378-08-3 may be absorbed more readily upon oral exposure, its representative structures and/or their metabolites may be more readily excreted and that the kidneys and urine may play an important role in excretion, when compared to the toxicokinetic results for CAS RN 10081-67-1 (feces was the major route of excretion for this substance). These attributes may explain the lower effect level of CAS RN 184378-08-3, with respect to the larger discrete SDPAs, such as CAS RN 10081-67-1. The UVCB substance, CAS RN 68411-46-1, contains three representative structures, as shown in Table 2-2, and they are the same as three of the five representative structures for CAS RN 184378-08-3. Likewise, it is reasonable to assume that the toxicokinetic profile for this substance would be similar to that CAS RN 184378-08-3.

Since the representative side chain substituents on the diphenylamine backbone were saturated or unsaturated carbon chains on one or both of the phenyl rings in most cases, it is reasonable to assume that most of the 14 substances would show similar metabolic profiles in mammalian organisms. The toxicokinetic study conducted with CAS RN 10081-67-1 confirms that the parent compound and minor metabolites can be detected in rats after oral dosing, but the extent of metabolism for other UVCB SDPAs may be greater, as suggested for CAS RNs 184378-08-3 and 68411-46-1 above.

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[13] Empirical data are presented for CAS RN 184378-08-3. However, empirical data were not available for CAS RN RN 10081-67-1 and thus modelled data are presented.

In summary, SDPA substances are considered similar with respect to their toxicokinetics. However, the extent of metabolism and importance of excretion route (urine or feces) may potentially differ between discrete SDPAs and UVCB SDPAs.

10.2.3 Genotoxicity

10.2.3.1 Available Data for Group Members

Genotoxicity data for the substances in this group are summarized below. Further details on the studies are available in Health Canada (2017).

Mutagenicity studies with CAS RN 101-67-7 using *S. typhimurium* and *S. cerevisiae* were negative when tested with and without metabolic activation (Brusick and Matheson 1978; Zeiger et al. 1992) and no chromosomal aberrations were found in Chinese Hamster Lung (CHL) cells or Chinese Hamster Ovary (CHO) cells with and without metabolic activation (Loveday et al. 1990; Sofuni et al. 1990). In mammalian *in vitro* systems, CAS RN 101-67-7 did not induce mutations in mouse lymphoma L5178Y cells (Brusick and Matheson 1978), but was weakly positive for unscheduled DNA synthesis in human lung WI-38 cells with metabolic activation. *In vivo* dominant lethal tests in both mice and rats were negative for post-implantation loss at doses as high as 2000 mg/kg bw/day. However, pre-implantation loss was statistically significantly higher than controls at all doses administered after the first and sixth mating weeks in rats (pre-implantation loss was not evaluated in mice; Brusick and Matheson 1978).

Mutagenicity studies with CAS RN 10081-67-1 using *S. typhimurium* and Chinese Hamster Lung (CHL) cells were negative when tested with and without metabolic activation (ECHA 2008b, 2009a)[14] and no chromosomal aberrations were observed in CHL cells with and without metabolic activation (ECHA 2009b)[13].

Mutagenicity studies with CAS RN 68921-45-9, *S. typhimurium* and *E. coli* were negative when tested with and without metabolic activation (US EPA 2009). Those studies with CAS RN 68442-68-2 in *S. typhimurium* and *E. coli* were negative when tested with and without metabolic activation as well as in a DNA damage and repair assay in *E. coli* with and without metabolic activation (BG RCI 1995; ACC 2006). *In vivo* tests for micronuclei formation in mice were negative at doses up to and including 2000 mg/kg bw via single oral gavage and up to and

[14] This is based on a summary submitted by Industry to ECHA, not the actual study report.

including 4000 mg/kg bw by intraperitoneal (*ip)* injection (BG RCI 1995; ACC 2006).

Mutagenicity studies with CAS RN 27177-41-9 using *S. typhimurium* and *E. coli* were negative when tested with and without metabolic activation (Safepharm Laboratories 1999a). A chromosomal aberration test in CHL cells also indicated that this substance did not elicit any effects when tested with and without metabolic activation (Safepharm Laboratories 1999b).

Mutagenicity studies with CAS RN 184378-08-3 using *S. typhimurium* were negative when tested with and without metabolic activation (Health Canada 2003; ACC 2006). Mutagenicity studies with CAS RN 68608-77-5 using *S. typhimurium* and *E. coli* were negative when tested with and without metabolic activation (ACC 2006).

Mutagenicity studies with CAS RN 68411-46-1 using *S. typhimurium* and *E. coli* were negative when tested with and without metabolic activation as well as in mouse lymphoma L5178Y cells with and without metabolic activation (Harlan Laboratories Ltd. 2013c,d; ACC 2003; ECHA 1989). An *in vitro* test for micronuclei formation using human lymphocytes was negative at doses up to and including 120 µg/ml with and without metabolic activation (Harlan Laboratories Ltd. 2013e).

10.2.3.2 Endpoint Summary and Analysis

No genotoxicity studies using CAS RNs 4175-37-5, 15721-78-5, 26603-23-6, 24925-59-5, 36878-20-3, and 68608-79-7 were identified.

The available empirical data for 8 of the 14 substances, do not provide evidence of genotoxicity. Based on the absence of genotoxicity for eight of the substances within the group, all 14 group members are considered to be non-genotoxic.

10.2.4 Acute and Short-Term Repeat Dose Toxicity

10.2.4.1 Available Data for Group Members

Acute and repeat dose toxicity data for the substances in this group are summarized below. Further details are available in Health Canada (2017).

The acute toxicity of CAS RN 101-67-7 was low via the oral route in rats (LD_{50}> 7940 mg/kg-bw) and the dermal route in rabbits (LD_{50}> 7940 mg/kg-bw) (ACC 2003). In the acute dermal study, a 40% solution of test material applied to rabbits resulted in minimal clinical signs for one or two days and all animals were

normal after the 14-day observation period (ACC 2003). No acute inhalation studies were identified. In a combined repeated dose reproductive/developmental toxicity study in rats, a lowest observed adverse effect level (LOAEL) of 75 mg/kg bw/day was determined based on a dose-related increase in the haematological measure, activated partial thromboplastin time in male rats, with prothrombin time increased in males at 250 mg/kg bw/day. Also, absolute and relative adrenal weights were increased in high-dose males after a 14-day recovery period (Japan CERI 2007).

The acute toxicity of CAS RN 10081-67-1 was low via the oral (LD_{50}> 10 000 mg/kg-bw in rats)) and dermal routes (LD_{50} > 2000 mg/kg-bw)[15] (Hill Top Research Institute, Inc. 1964; ECHA 2007a). No acute inhalation studies were identified. No short-term studies were identified. A summary of an oral short-term repeat dose toxicity study was identified. In an oral 28-day repeat dose toxicity in rats, a LOAEL of 80 mg/kg bw/day was determined based on increased relative liver weight in male rats coupled with an increase in alkaline phosphate (ALP)_ activity, increased bilirubin, increased triacylglycerols and decreased total cholesterol levels at this dose in males (ECHA 2008c)[14].

The acute toxicity of CAS RN 68608-77-5 was very low via the oral route (LD_{50}> 34 600 mg/kg bw in rats; ACC 2006). In a dermal toxicity study, 3000 mg/kg-bw of test material applied to rabbits for 4 hrs and observed for 14 days indicated that skin reactions were limited to mild erythema, desquamation, and edema. Barely perceptible to slight erythema and desquamation were present at day 14. No value for acute inhalation toxicity in rats could be determined based on the low volatility of this substance (ACC 2006). No short-term studies were identified via any route.

The acute toxicity of CAS RN 68442-68-2 was very low via the oral route in rats (LD_{50}> 20 000) and the dermal route in rabbits (> 10 000 mg/kg-bw; US EPA 2009). No acute inhalation studies were identified. Five repeat dose studies were identified using CAS RN 68442-68-2 (BG RCI 1995; Safepharm Laboratories 2006a). These studies were all via the oral route in rats and ranged from a short 7-day exposure to 54 consecutive days. Toxicity appeared to be targeted to the liver and kidney with effects including, but not limited to, liver weight increases, centrilobular hepatocyte enlargement, alterations in enzymes, protein, cholesterol and bilirubin, disturbances of blood clotting, macroscopic and microscopic effects. Kidney effects were limited to changes in plasma electrolytes and in urinary volume, specific gravity and pH, as well as macro- and microscopic structural changes (BG RCI 1995). The Lowest Observed Adverse Effect Level (LOAEL) identified for this substance was 250 mg/kg bw/day based on toxicity in the liver and thyroid glands (follicular cell hypertrophy) and increased liver and adrenal weights at this dose. The No Observed Adverse Effect Level (NOAEL) in

[15] This is based on a summary submitted by Industry to ECHA, not the actual study report.

this study was 50 mg/kg bw/day (Safepharm Laboratories 2006a; US EPA 2009). No short-term dermal or inhalation studies were identified.

No acute studies using CAS RN 27177-41-9 were identified via any route. One oral short-term study was submitted where the test substance was administered by gavage to rats at dose levels of 0, 15, 150 or 500 mg/kg bw/day for 28 days. Two recovery groups (5/sex/group) were treated with the high dose (500 mg/kg bw/day) or the vehicle alone for 28 consecutive days and then maintained without treatment for a further 14 days. The NOAEL was determined to be 15 mg/kg bw/day based on clinical signs of toxicity (increased salivation), increased relative liver weights, histopathological effects in the liver and spleen, as well as changes in haematological and clinical chemistry parameters in both sexes at the next highest dose of 150 mg/kg bw/day. At 500 mg/kg bw/day, recovery animals showed some recovery in the hepatic conditions. However, females from this treatment group showed no evidence of recovery in the splenic pigment accumulation, and there was also an indication of a delayed splenic effect in males (Safepharm Laboratories 1999c).

The acute toxicity of CAS RN 184378-08-3 is low via the oral route (LD_{50}> 2000 mg/kg-bw in rats; Health Canada 2003). No acute dermal or inhalation studies were identified. Two repeat dose studies were identified. One study used rats administered CAS RN 184378-08-3 via gavage for 43 days (males) or 54 days (females, PND4), consecutively, at dose levels of 0, 5, 25 or 125 mg/kg bw/day. A NOAEL of 5 mg/kg bw/day was determined based on liver hepatocyte enlargement in females at the next highest dose of 25 mg/kg bw/day (observed in males at 125 mg/kg bw/day), with associated clinical chemistry effects in both sexes and decreased white blood cell counts in males. No other histopathological effects were observed in the liver, but skeletal muscle effects were also observed in females at 125 mg/kg bw/day (SafePharm Laboratories 2006b). According to the US EPA (2009), the biochemical effects (decreased total plasma protein, albumin and the albumin/globulin ratio levels, with elevated aspartate aminotransferase and alkaline phosphatase levels) were indicative of liver toxicity, which were consistent with observed centrilobular hepatocytes enlargement in females at ≥ 25 mg/kg bw/day and in males at 125 mg/kg bw/day.

In another study using CAS RN 184378-08-3, rats were administered 0, 50, 250/150, or 600[16] mg/kg bw/day of the test material via oral gavage (males up to 43 consecutive days and females up to postpartum day 5). Effects in the liver and spleen were observed in females at the lowest dose tested (LOAEL of 50 mg/kg bw/day), as indicated by histopathological findings (hepatocyte vacuolation, extramedullary haemopoiesis of spleen) and decreased motor

[16] Due to the severity of clinical signs observed at the top dose level, this group was terminated on Day 17. Due to the deterioration in health of animals in the mid-dose group, dosing ceased on Days 19-20 and the intermediate dose was reduced to **150 mg/kg bw/day** from Day 21. Due to two deaths at the reduced dose level, this dose level was also terminated on Day 31.

activity in females and clinical chemistry effects in both sexes (increased alkaline phosphatase levels). Also, slightly decreased kidney and adrenal weights, both absolute and relative to terminal body weight, were detected for animals of both sexes treated with 50 mg/kg bw/day. Males from this treatment group also showed slightly increased absolute and relative liver weights and females showed slightly decreased absolute and relative spleen weights (SafePharm Laboratories 2006b).

The acute toxicity of CAS RN 68411-46-1 was low via all routes in rats (LD_{50}> 5000 mg/kg-bw via oral, LD_{50}> 2000 mg/kg-bw via dermal, and LC_{50}> 5.8 mg/L via inhalation, respectively; ACC 2003; BASF SE 2010b; Biosearch, Inc. 1979a,b; ECHA 1982). In the acute dermal study where 2000 mg/kg bw of this substance was applied to rats, clinical signs were observed (piloerection, abnormal body positions, and dyspnea), but all animals recovered within 9 days. At autopsy, no deviations from normal morphology were found (ACC 2003). Two repeat dose studies were identified, in which rats were administered CAS RN 68411-46-1 in corn oil vehicle via gavage. One study used rats administered CAS RN 68411-46-1 for 28 days (males) or up to 39-45 days (females) at dose levels of 0, 25, 75 or 225 mg/kg bw/day. A LOAEL of 75 mg/kg bw/day was determined based on clinical signs of toxicity (increased salivation), and hepatocyte hypertrophy and vacuolation in both sexes with associated clinical chemistry effects (decreased albumin, increased total bilirubin and increased ALP levels in both sexes; decreased plasma protein levels in females) at 75 and 225 mg/kg bw/day (BASF 2014).

The second study, designed for metabolome analysis[17], used male rats administered CAS RN 68411-46-1 for 29 days at dose levels of 0, 125 or 300 mg/kg bw/day. At both doses, there were significant decreases or increases in 20 different plasma metabolites with some indication of liver toxicity (and indication of kidney toxicity at 300 mg/kg bw/day); levels of many complex lipids, fatty acids and related compounds were significantly increased, suggesting an altered lipid metabolism; and increases or decreases in other clinical chemistry parameters at one or both doses indicated decreased protein metabolism (based on urea and amino acid levels), suggestive of a change in liver cell metabolism, and a slight effect on the kidneys or alteration of the urea cycle (based on changes in levels of citrulline, uric acid, ornithine, phosphate, creatine, creatinine, phosphocreatine, and urea). The metabolome profile for CAS RN 68411-46-1 was compared to the metabolome profile from the 90-day study in rats using CAS RN 36878-20-3. Although the metabolome analysis for CAS RN 36878-20-3 was not available, the 90-day repeated dose study is described in the :Subchronic and Chronic Toxicity" section. Of 74 plasma metabolites common to both substances in the

[17] The metabolome is defined as the full complement of metabolites present in a cell, tissue, or organism in a particular physiological or developmental state (from Dictionary.com). In other words, it is the metabolite profile.

respective 29-day and 90-day studies, 5 metabolites showed statistically significant decreases in both studies at the tested doses (125 and 300 mg/kg bw/day for CAS RN 68411-46-1; 300 and 1000 mg/kg bw/day for CAS RN 36878-20-3), and several other metabolites showed decreasing (5 metabolites) or increasing (7 metabolites) trends in both studies at all doses tested. However, when comparing the two studies with the MetaMap®Tox database (consisting of more than 500 substances), no clear toxicological mode of action could be identified (BASF 2014b).

The acute oral toxicity of CAS RN 36878-20-3 is very low in rats (LD_{50} > 16 000 mg/kg-bw; European Commission 2000).). A 28-day range-finding study in male rats found no effects up to the top dose of 1000 mg/kg bw/day, but only clinical signs and body weights were recorded in this study (ECHA 2012). No other acute or short-term studies were identified via the dermal or inhalation routes.

10.2.4.2 Endpoint Summary and Analysis

Acute and repeat dose toxicity data for the substances in this group are summarized below. Further details are available in Health Canada (2017). Acute studies were limited to 7 substances and for all 7 substances, the oral LD_{50} values in rats ranged from > 2000 to > 20 000 mg/kg bw; for the five substances with available acute dermal studies, LD_{50} values ranged from > 2000 to > 10 000 mg/kg bw (rat or rabbit); and for the two substances with available acute inhalation data (CAS RNs 68411-46-1 and 68608-77-5), LC_{50} values ranged from not determined due to low volatility to > 5.8 mg/L in rats. No mortalities were observed in any of these studies. Overall, the consideration of the empirical data available for the substances in this group indicates that this group has low toxicity via the oral and dermal routes and acute inhalation toxicity is unlikely based on the low volatility of the substances (inhalation exposure is expected to be negligible).

Short-term oral studies were limited to seven substances. For the oral short-term studies, toxicity appeared to be targeted to the liver and in some studies, haematological and/or clinical chemistry parameters were affected, with the kidney also being a target organ at higher doses. The lowest oral short-term NOAEL of 5 mg/kg bw/day (CAS RN 184378-08-3) was determined based on liver toxicity in females at the next highest dose of 25 mg/kg bw/day and above, as well as decreased white blood cell counts in males (SafePharm Laboratories 2006b). The US EPA (2009) also determined a NOAEL of 5 mg/kg bw/day for the same study, stating that the biochemical effects were indicative of liver toxicity, which was consistent with the observed centrilobular hepatocytes enlargement in females at ≥ 25 mg/kg bw/day.

CAS RN 184378-08-3 is considered the ‘worst-case’ substance in the group as this UVCB contains representative structures that are considered to be the most

bioavailable SDPAs within the grouping. Although this approach is conservative and may overestimate toxicity, particularly where the untested SDPAs may be less bioavailable, it is considered appropriate given the relative number of SDPAs without short-term oral toxicity data (7 of 14). It is expected that in short-term oral toxicity studies conducted with the untested substances, liver toxicity and haematological/biochemical changes in the blood may be observed.

10.2.5 Subchronic and Chronic Toxicity

10.2.5.1 Available Data for Group Members

Subchronic and chronic toxicity data for the substances in this group are summarized below. Further details are available in Health Canada (2017). Only one subchronic study for one group member and one chronic toxicity study for another group member were identified.

Subchronic toxicity data were available for CAS RN 36878-20-3. The test substance was administered by gavage to rats for 92-93 days at dose levels of 0, 100, 300 or 1000 mg/kg bw/day. A LOAEL of 100 mg/kg bw/day, the lowest dose tested, was determined based on salivation (in both sexes), a dose-related decrease in male body-weight gain, dose-related increases in male relative liver weights and female relative spleen weights, histopathological effects in the liver and thyroid gland (hypertrophy in both organs and other effects including liver cell necrosis, thyroid follicular cell hyperplasia, etc.) as well as changes in clinical chemistry parameters (in both sexes) at this dose. Kidney effects and haematological parameters were also affected at the mid- and high-dose in this study (BASF 2013).

Chronic toxicity data were available for BNST, CAS RN 68921-45-9. In this study, rats were administered the test substance in the diet for 64 weeks at dose levels of 0, 125, 250 or 500 mg/kg bw/day. A LOAEL of 125 mg/kg bw/day, the lowest dose tested, was determined based on decreased body weight gain in all females, hepatomegaly in both sexes, and diffuse hepatic degeneration in all animals. It is reported that “Diffuse hepatic degeneration was observed in all test animals. The degenerative changes in the liver were described as diffuse cloudy swellings and fatty metamorphosis of the cytoplasm of the hepatocytes” (US EPA 2009)[18].

[18] Note that the screening assessment report (SAR) for BNST (Environment Canada, Health Canada 2009) cited a draft US EPA report dated 2008, whereas this assessment cites the final US EPA report dated 2009. As a result, effects described for this study and the quotation cited above differ slightly between this assessment and the BNST SAR.

10.2.5.2 Endpoint Summary and Analysis

Similar to the results observed in the oral short-term studies, the subchronic toxicity study conducted with CAS RN 36878-20-3, showed effects in the liver and in haematological and clinical chemistry parameters, with the kidney also being a target organ at higher doses. In regards to effects in the thyroid gland, note that follicular cell hypertrophy was also observed at similar doses (250 and 600 mg/kg bw/day) in both sexes of rats in a 43-54 day reproductive/developmental toxicity study conducted with CAS RN 68442-68-2 (See “Reproductive and Developmental Toxicity” section below). In regards to salivation, note that an increased incidence of salivation was also observed at similar doses (150 and 500 mg/kg bw/day) in both sexes of rats in a 28-day oral toxicity study conducted with CAS RN 27177-41-9 (See “Acute and Short-term Repeat Dose Toxicity” section above).

The liver was a target organ in the chronic toxicity study using BNST (CAS RN 68921-45-9), as well as in short-term oral studies for group members with data. Since the LOAELs identified in the two studies conducted with CAS RN 36878-20-3 and CAS RN 68921-45-9, were at the lowest dose tested, and that effects were observed at lower doses in shorter term studies, there is uncertainty regarding the level at which effects would begin to be observed in subchronic or chronic studies across the group. The structural features and physical-chemical properties of group members with available subchronic or chronic data do not adequately cover the more bioavailable representative structures of certain UVCB SDPAs (e.g. CAS RN 184378-08-3). To address data gaps for chronic toxicity for untested members, the conservative effect level related to liver toxicity from a short-term repeat dose study of the ‘worst case’ substance within the group (described under "Acute and Short-Term Repeat Dose Toxicity") is used for the risk characterization.

10.2.6 Reproductive and Developmental Toxicity

10.2.6.1 Available Data for Group Members

Reproductive and developmental toxicity data for the substances in this group are summarized below. Further details are available in Health Canada (2017).

A combined reproductive/developmental study (mentioned in the previous Acute and Short-Term Repeat Dose Toxicity") in rats using CAS RN 68442-68-2 showed pre-implantation loss and a deficit in surface righting of offspring. Male and female rats were administered CAS RN 68442-68-2 via gavage for 43 days (males) or 54 days (females, up to PND5), consecutively, at dose levels of 0, 50,

250 or 600 mg/kg bw/day. Liver effects were observed in the maternal animals at doses as low as 50 mg/kg bw/day, although effects at this dose were not considered to be adverse. However, the systemic LOAEL of 250 mg/kg bw/day is based on toxicity in the liver and thyroid glands and increased liver and adrenal weights (ACC 2006; US EPA 2009). The NOAEL for reproductive toxicity and developmental toxicity was 250 mg/kg bw/day based on a higher percentage of pre-implantation losses, lower total litter weights in females as well as observations of offspring showing less successful completion of surface righting assessments at the next highest dose of 600 mg/kg bw/day (but in the presence of maternal toxicity at 250 mg/kg bw/day) (SafePharm Laboratories 2006a; ACC 2006; US EPA 2009).

In a combined reproductive/developmental study (mentioned in the previous "Acute and Short-Term Repeat Dose Toxicity" section), male and female rats were administered CAS RN 68411-46-1 via gavage for 28 days (males) or 39-45 days (females, up to PND6), consecutively, at dose levels of 0, 25, 75 or 225 mg/kg bw/day. The LOAEL for reproductive toxicity was 225 mg/kg bw/day based on a decreased viability index, increased postnatal loss/litter, and decreased total and mean number of living pups/litter. The LOAEL for developmental toxicity was also 225 mg/kg bw/day based on slightly decreased pup weights (BASF 2014).

In a combined repeated dose reproductive/developmental toxicity study in rats using CAS RN 101-67-7 (mentioned in the previous "Acute and Short-Term Repeat Dose Toxicity" section), no reproductive or developmental effects were observed up to the highest dose of 250 mg/kg bw/day (Japan CERI 2007).

Two reproductive/developmental studies were identified for CAS RN 184378-08-3. One study (mentioned in the previous "Acute and Short-Term Repeat Dose Toxicity" section) administered this substance to rats via gavage for 43 days (males) or 54 days (females, up to PND5), at dose levels of 0, 5, 25 or 125 mg/kg bw/day (Safepharm Laboratories 2006b). As stated above, the NOAEL for maternal toxicity was determined to be 5 mg/kg bw/day based on liver toxicity at the next highest dose of 25 mg/kg bw/day. Reproductive and developmental toxicity were observed at the highest dose level of 125 mg/kg bw/day based on shorter gestation lengths, lower viability indices, and slightly lower mean offspring weights. Therefore, the NOAEL for developmental toxicity is 25 mg/kg bw/day, but in the presence of maternal toxicity (Safepharm Laboratories 2006b).

In the second study, rats were administered 0, 50, 250/150, or 600 mg/kg bw/day of CAS RN 184378-08-3 via oral gavage (males up to 43 consecutive days and females up to postpartum day 5). Due to the severity of clinical signs observed at the top dose level, this group was terminated on Day 17. Due to the deterioration in health of animals in the mid-dose group, this dose was reduced to 150 mg/kg bw/day from Day 21. However, due to two deaths, this dose level was also terminated on Day 31. At 50 mg/kg bw/day, no reproductive nor developmental toxicity was observed. For systemic toxicity, effects were observed at the lowest dose tested (LOAEL of 50 mg/kg bw/day) as indicated by histopathological

findings in the liver and spleen and decreased motor activity in females and clinical chemistry effects in both sexes (SafePharm Laboratories 2006b).

A summary of a reproductive toxicity study was identified for CAS RN 10081-67-1. Rats were administered 0, 5, 25 or 50 mg/kg bw/day of CAS RN 10081-67-1 via oral gavage for 28-days (males) or 44-54 day (females up to postpartum day 4). No reproductive nor developmental toxicity was observed up to the top dose. For systemic toxicity, effects in the kidneys in both sexes (16.7% incidence of glomerular atrophy) and in the liver of females (mononuclear nodules in 2/2 females examined for histopathology although 12 animals/sex/dose were utilized in the study) were observed at the top dose, resulting in a systemic LOAEL of 50 mg/kg bw/day (ECHA 2009c)[19]. An *in vitro* study examining the endocrine effects of CAS RN 1008-67-1 showed no response as an androgen receptor (AR) agonist and antagonist using the AR-EcoScreen^{TM} (Araki et al. 2005). Endocrine studies were not identified for the other SDPAs.

A developmental toxicity study was identified for CAS RN 36878-20-3. Pregnant female rats were administered CAS RN 36878-20-3 via gavage at doses of 0, 50, 150 or 500 mg/kg bw/day during gestation days 6 to 19, according to OECD Guideline 414. A maternal LOAEL of 50 mg/kg bw/day was determined based on a dose-related decrease in corrected body weight and corrected body-weight gain in dams. A developmental NOAEL of 150 mg/kg bw/day was determined, based on increased incidences of small fetuses and fetuses with kidney effects (ectopic kidney, pelvic dilatation) at 500 mg/kg bw/day (BASF 2014c)..

10.2.6.2 Endpoint Summary and Analysis

The available empirical data available for the reproductive and developmental toxicity were limited to 5 of the 14 substances in this group (CAS RNs 101-67-7, 10081-67-1, 36878-20-3, 68411-46-1, 68442-68-2 and 184378-08-3). As observed in short-term oral studies, toxicity appeared to be targeted to the liver and haematopoietic system in parental animals. Any effects on reproduction and/or development of offspring were observed in the presence of maternal toxicity. The lowest oral LOAEL for reproductive/developmental toxicity is 125 mg/kg bw/day (using CAS RN 184378-08-3) based on shorter gestation lengths, lower viability indices, and slightly lower mean offspring weights and a higher incidence of haemorrhaging/bruising in pups at this dose. The reproductive/developmental NOAEL in this study is 25 mg/kg bw/day in the presence of maternal toxicity at the LOAEL (Safepharm Laboratories 2006b).

As stated in the section on "Acute and Short-term Repeat Dose Toxicity", CAS RN 184378-08-3 is considered the ‘worst-case’ substance in the group as this

[19] This is based on a summary submitted by Industry to ECHA, not the actual study report.

UVCB contains component substances that are considered to be the most bioavailable SDPAs within the grouping. Although this approach is conservative and may overestimate toxicity, particularly where the untested SDPAs may be less bioavailable, it is considered appropriate given the relative number of SDPAs without reproductive and/or developmental toxicity data (8 of 14).

10.2.7 Irritation and Sensitization

10.2.7.1 Available Data for Group Members

Irritation and sensitization data for the substances in this group are summarized below. Further details on these studies are available in Health Canada (2017).

CAS RN 101-67-7 showed slight, non-persistent, eye irritation and no skin irritation in rabbits (US EPA 2009). Technical products containing CAS RN 101-67-7, "Naugalube 438" (refined, very pure, no exact details) and “Octamine” (relatively pure, no exact details) did not induce skin sensitization in the guinea pig. In a patch test in humans using “Octamine”, there was no indication of sensitization (BG RCI 1990).

CAS RN 68411-46-1 showed slight or no skin irritation, and no eye irritation in rabbits in studies by different researchers (Biosearch Inc. 1979c,d; BASF SE 2010b). Skin sensitization results were also equivocal from different studies. High sensitization was reported in Pirbright White guinea pigs using the maximisation test (90% of animals; Ciba-Geigy Corp 1984), but no skin effects were observed in Hartley Albino guinea pigs using two other maximisation tests and a Buehler test (BASF SE 2010b). One of the producers of CAS RN 68411-46-1, claims that the positive sensitization in the Pirbright White strain of guinea pigs was due to an old production process and that a change in the process resulted in the substance being no longer sensitizing (ACC 2017).

CAS RN 36878-20-3 showed slight to no eye irritation and no skin irritation in rabbits and no skin sensitization was evident after being tested on guinea pigs (European Commission 2000).

CAS RN 68442-68-2 showed slight eye irritation and no skin irritation in rabbits (BG RCI 1995; ACC 2006). No skin sensitization information was identified for this substance. CAS RNs 10081-67-1 showed no skin or eye irritation in rabbits (ACC 2003;) but a mouse local lymph node assay indicated potential sensitization at concentrations of 49% and higher (ECHA 2007b)[20].

[20] This is based on a summary submitted by Industry to ECHA, not the actual study report.

CAS RN 68608-77-5 showed slight eye irritation in rabbits (ACC 2006). No skin irritation, or skin sensitization information was identified for this substance. No eye or skin irritation studies using CAS RN 184378-08-3 were identified; however, this substance did not cause skin sensitization in guinea pigs (Health Canada 2003; ACC 2006). Likewise, no eye or skin irritation studies using CAS RN 15721-78-5 were identified; however, a 50% concentration of this substance (highest concentration tested) did not cause skin sensitization in a mouse local lymph node assay (Harlan Laboratories Ltd. 2013f).

For CAS RN 68921-45-9, no skin irritation or sensitization was observed in a patch test using 50 human volunteers (US EPA 2009).

10.2.7.2 Endpoint Summary and Analysis

No eye or skin irritation or sensitization studies using CAS RN 4175-37-5, 26603-23-6, 24925-59-5, 27177-41-9, or 68608-79-7 were identified. Additionally, no eye or skin irritation studies were identified for CAS RNs 157821-78-5 184378-08-3 and no sensitization studies were identified for CAS RN 68442-68-2 and 68608-77-5.

Overall, based on the consideration of the empirical irritation data available for 7 of the 14 substances, there is an indication of the potential for slight eye and skin irritation. Since skin and eye irritation data were not identified for 7 of the 14 substances in this qroup, the skin and eye irritation potential for these substances is considered to be equivocal and may not be uniform amongst all 14 substances.

Of the seven substances tested for skin sensitization, one was positive (CAS RN 10081-67-1) and one was negative (CAS RN 15721-78-5) in a mouse local lymph node assay, four were negative in guinea pigs or humans, and one (CAS RN 68411-46-1) gave equivocal results in the same assay (maximisation test) in different guinea pig strains (Pirbright White vs. Hartley Albino), with the Hartley Albino strain also showing negative results in a Buehler test. Consideration of the empirical irritation data available for 7 of the 14 substances, suggests the possibility of skin sensitization. Since sensitization data were not identified for 7 of the 14 substances in this qroup, the skin sensitization potential for these substances is considered to be equivocal and may not be uniform amongst all14 substances.

10.3 Characterization of Risk to Human Health

As shown under the "Uses" section, SDPAs are primarily used as antioxidants in the blending of lubricants in Canada, with lesser quantities of SDPAs used in the

manufacturing of plastic, polyurethane foam, rubber, and miscellaneous products. Based on these uses as well as exposure via environmental media, comparison of exposure estimates to conservative effect levels for the 14 SDPAs in this group will result in margins of exposure (MOEs). When an MOE is considered adequate using conservative assumptions, further refinement to a read-across approach, although scientifically desirable, may not alter the conclusion within the context of Screening Level Risk Assessments conducted under Canada's Chemical Management Plan. As stated in the "Introduction", screening assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA, by examining scientific information to develop conclusions by incorporating a weight of evidence approach and precaution. Thus, a screening level approach is followed for both hazard and exposure in the assessment. Refinement in both hazard and exposure methods would follow only if the MOE is deemed inadequate, which may or may not include consideration of a more refined read-across approach. Although section 8.1.5 of this assessment uses one of the SDPAs (CAS RN 184378-08-3) for read-across to the most bioavailable SDPAs, note that the read-across strategy in the environmental portion of the assessment (sections 7 and 8) was used for components of the individual substances, and not across the 14 substances themselves.

Characterization of this group of SDPAs in this assessment is based on limited empirical data available for this substance group, and the use of a weight of evidence approach. Although carcinogenicity data were not available for any of the 14 substances, the overall consideration of the empirical data available for 8 of the 14 substances in this group suggests that these substances are not genotoxic. Based on the empirical data available for this substance group, health effects appear to be targeted to the liver and sometimes haematological and/or clinical chemistry parameters, after short-term oral exposure, with the kidney also being a target organ at higher doses.

Consideration of the available information for the substances in this group, indicates that this group is not acutely toxic via the oral and dermal routes and acute inhalation toxicity is unlikely based on the low volatility of the substances.

For characterizing the risk from environmental media, tthe critical effect level selected is the lowest oral NOAEL of 5 mg/kg bw/day in a rat study, based on liver hepatocyte enlargement in females at the next highest dose of 25 mg/kg bw/day, with associated clinical chemistry effects in both sexes and decreased white blood cell counts in males in a combined repeated-dose reproductive/developmental toxicity study (SafePharm Laboratories 2006b). There were no repeated dose studies available via the dermal or inhalation routes.

Based on their use patterns and physical chemical properties, the potential for exposure of the general population to SDPAs through environmental media is

expected to be low. Comparison of the upper bounding estimate of environmental SDPA concentration of 0.01 µg/kg-bw per day to the critical effect level of 5 mg/kg-bw per day results in a margin of exposure (MOE) of 500 000. This MOE is considered adequate to account for uncertainties in the health effects and exposure databases for chronic exposure of SDPAs via environmental media.

Exposure of the general population to SDPAs in Canada may occur through dermal exposure to motor oil and other automotive functional fluids (i.e., transmission fluid) or through oral exposure of infants and toddlers to foam products (e.g., sofa cushion) containing SDPAs.

For dermal exposures to products available to consumers (automotive lubricants), the upper bounding estimate of exposure determined to encompass all substances in the group ranged from 0.75 to 11.4 µg/kg-bw per event. Exposure is expected to occur only intermittently. Acute toxicity data suggested low toxicity by the dermal route. Given the lack of short-term studies by the dermal route, an oral short-term study was used to characterize risk from dermal exposure to SDPAs.

The shortest repeated dose oral studies with sufficient information to determine NOAELs were two 28-day oral rat studies, one using CAS RN 27177-41-9, and the other using CAS RN 68422-68-2 (NOAELs of 15 and 100 mg/kg bw/day, respectively, based on liver toxicity at higher doses for both substances, as well as spleen and blood effects for CAS RN 27177-49-9). Although shorter duration range-finding studies were available, no observed effect levels/lowest observed effect levels (NOELs/LOELs) determined for these studies, not NOAELs/LOAELs.

A comparison between the NOAEL of 15 mg/kg bw/day derived from the 28-day oral study using CAS RN 27177-41-9 and the upper bounding estimate of dermal exposure from use of automotive functional fluids, results in margins of exposure (MOE) of approximately 1300 to 20 000. These margins are considered to be very conservative based on the following additional considerations:

1. No adverse effects were observed in shorter-term (7 to 21-days) oral range-finding studies in rats at doses up to 1000 mg/kg bw/day.

2. Two acute dermal studies with sufficient information on effects observed included one using CAS RN 101-67-7 on both sexes of rabbits, and the other using CAS RN 68411-46-1 on both sexes of rats. Both studies indicated clinical signs of toxicity with recovery to normal after a few days and normal appearance of viscera on necropsy. The acute dermal LD_{50} in rabbits for CAS RN 101-67-7 was > 7940 mg/kg bw and the acute dermal LD_{50} in rats for CAS RN 68411-46-1 was > 2000 mg/kg bw.

3. One acute dermal study that measured skin reactions in rabbits using CAS RN 68608-77-5, showed mild effects which almost completely recovered at the end of the 14 day observation period. Although clinical signs and gross pathology were not reported, the acute dermal LD_{50} was > 3000 mg/kg bw.

For oral exposures to foam products containing SDPAs, the mouthing scenario of an infant and toddler of a sofa cushion, described in section 10.3, is considered to be an acute to short-term oral scenario. The upper bounding estimate of exposure determined to encompass all substances in the group ranged from 0.85 to 1.76 µg/kg-bw per day for infants and toddlers. As shown above, lowest oral short-term NOAELs of 5 and 15 mg/kg bw/day were determined based on a 43-54 day rat study conducted with CAS RN 184378-08-3 and on a 28-day rat study conducted with CAS RN 27177-41-9, respectively. A comparison between oral short-term NOAELs and the upper bounding estimates of oral exposure results in margins of exposure of 2800 to 17 600. These margins are considered adequate to account for uncertainties in the health effects and exposure databases.

10.4 Uncertainties in Evaluation of Risk to Human Health

Based on the physical chemical properties of these substances, and their use pattern, exposure to the general population via the environment is expected to be low. There was limited empirical data on the concentration of SDPAs in environmental media in Canada. Also, conservative assumptions were used to derive exposure estimates to products containing SDPAs which are available to consumers. The uncertainties associated with the assumptions made in the exposure estimate algorithm, both for consumer DIY products and in estimating the exposure from mouthing foam furniture give an overall moderate confidence of exposure to products available to consumers.

This screening assessment does not include an analysis of the mode of action of effects of SDPAs in mammalian organisms due to the lack of mechanistic studies and very limited information on toxicokinetics. A grouping and weight of evidence approach was used in this assessment to infer effects for substances without data for certain endpoints. Uncertainty associated with the weight of evidence approach for genotoxicity, acute toxicity and sensitization is considered moderate.

For short-term repeat dose toxicity, uncertainty in the weight of evidence is considered low. The worst-case substance contained SDPAs deemed to be the most bioavailable via the oral or dermal route. Also, most members in this SDPAs grouping exhibited similar effects at higher doses. The conservative effect level selected for development of margins of exposure was considered protective for other effects that occur for group members at higher doses.

Uncertainty associated with the weight of evidence for developmental and reproductive toxicity (DART) is considered high due to low concordance of effects across group members with data. However, in general, DART effects were observed at higher doses in these studies when compared to systemic effects observed in short-term repeat dose studies.

11. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from the fourteen SDPAs considered in this assessment. It is concluded that the fourteen SDPAs do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

Based on the available information on their potential to cause harm to human health, it is concluded that the fourteen SDPAs considered in this assessment do not meet the criteria under paragraph 64*(c)* of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is concluded that the fourteen SDPAs considered in this assessment do not meet any of the criteria set out in section 64 of CEPA. This conclusion also applies to BNST, also included among the fourteen substances; this substance had previously been found to meet the criteria set out in section 64 of CEPA in a 2009 screening assessment conducted during the Challenge initiative of the Chemicals Management Plan.

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Appendix A. Physical- Chemical Properties for the Various SDPA Structures.

Table A-1 Key physical and chemical properties for the dioctyl DPA structures[a]

CAS RN	Modelled Value	Reference	Empirical Value[c]	Reference
Water Solubility (mg/L)	$3.46x10^{-6}$ – $2.09x10^{-5}$	EPiSuite 2010	0.06 – 2	BASF SE 2010a; SafePharm Laboratories 2002a
Henry Law's Constant ($(Pa.m^3/mol)$	17.50; 17.51	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)[e]	10.52[b]; 10.82	EPiSuite 2010	8.8 ; > 6.20	Intertek Pharmaceutical Services 2013; SafePharm Laboratories 2002a
Vapour pressure (Pa)	$3.38x10^{-9}$ – $5.60x10^{-7}$	calculated[b] from water solubility and Henry Law's Constant	<1; < $1.1x10^{-5}$; $9.40x10^{-5}$	BASF SE 2010a; Intertek Pharmaceutical Services 2012; SafePharm Laboratories 2002a
Log K_{oa} (dimensionless)	13.08	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	6.37	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; NA: not available

[a] Physical-chemical properties may differ as SMILEs/chemical structures may differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

[b] Calculated using the Experimental Value Adjustment method

[c] Empirical values are for CAS RN: 68411-46-1 or 184378-08-3 only

Table A-2 Key physical and chemical properties for the monooctyl DPA structures[a]

CAS RN	Modelled Value	Reference	Empirical Value[c]	Reference
Water Solubility (mg/L)	0.037 – 0.047	EPiSuite 2010	0.097; 2	SafePharm Laboratories

				2002a; BASF SE 2010a
Henry Law's Constant ($Pa.m^3/mol$)	2.19 ; 2.9	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	6.76[b]	EPiSuite 2010	>6.20;	SafePharm Laboratories 2002a;
Vapour pressure (Pa)	$4.84x10^{-4}$ – $2.9x10^{-4}$	calculated[b] from water solubility and Henry Law's Constant	<1; $9.40x10^{-5}$	BASF SE 2010a; US EPA 2009
Log K_{oa}	10.23	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	4.64	EPIWIN 2011	5.63	SafePharm 2002a

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available

[a] Physical-chemical properties may differ as SMILEs/chemical structures may differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

[b] Calculated using the Experimental Value Adjustment method

[c] Empirical values are for CAS RN: 68411-46-1 and 184378-08-3 only

Table A-3 Key physical and chemical properties for the dimethyl distyrenated DPA structure

CAS RN	Modelled Value	Reference	Empirical Value[a]	Reference
Water Solubility (mg/L)	$1.29x10^{-5}$	EPiSuite 2010	NA	NA
Henry Law's Constant ($Pa.m^3/mol$)	$6.72x10^{-3}$	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	8.22[b]	EPiSuite 2010	NA	NA
Vapour pressure (Pa)	$2.14x10^{-5}$	calculated[b] from water solubility and Henry Law's Constant	NA	NA
Log K_{oa}	14.48	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	7.30	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;l-NA: not available

[a] Empirical values are for CAS RN: 68411-46-1 and 184378-08-3 only

[b] Calculated using the Experimental Value Adjustment method

Table A-4 Key physical and chemical properties for the dinonyl DPA structures[a]

CAS RN	Modelled Value	Reference	Empirical Value[c]	Reference
Water Solubility (mg/L)	$1.14x10^{-6}$ – $3.21x10^{-6}$	EPiSuite 2010	<0.005	BASF SE 2010b
Henry Law's Constant ($Pa.m^3/mol$)	30.9	EPiSuite 2010	1.21	BASF SE 2010b
Log K_{ow} (dimensionless)	11.36– 11.51[b]	EPiSuite 2010	NA	NA
Vapour pressure (Pa)	$2.35x10^{-7}$ – $8.35x10^{-8}$	calculated[b] from water solubility and Henry Law's Constant	<1	BASF SE 2010b
Log K_{oa}	13.82	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	7.18	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;NA: not available

[a] Physical-chemical properties may differ as SMILEs/chemical structures may differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

[b] Calculated using the Experimental Value Adjustment method

[c] Empirical values are for CAS RN: 36878-08-3 only

Table A-5 Key physical and chemical properties for the monononyl DPA structures[a]

CAS RN	Modelled Value	Reference	Empirical Value[c]	Reference
Water Solubility (mg/L)	0.0084 – 0.0113	EPiSuite 2010	0.0113	SafePharm 2002b
Henry Law's Constant ($Pa.m^3/mol$)	1.13 – 2.9	EPiSuite 2010	0.113	BASF SE 2010b
Log K_{ow} (dimensionless)	7.25[b] – 7.55	EPiSuite 2010	7.25	SafePharm 2002c
Vapour pressure (Pa)	$1.00x10^{-4}$ – $1.11x10^{-4}$	calculated[b] from water solubility and Henry Law's Constant	<1	BASF SE 2010b
Log K_{oa}	10.59	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	5.05	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;NA: not available

[a] Physical-chemical properties may differ as SMILEs/chemical structures may differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

[b] Calculated using the Experimental Value Adjustment method

[c] Empirical values are for CAS RN: 27177-41-9 or 36878-08-3 only

Table A-6 Key physical and chemical properties for the monobutyl DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	4.79	EPiSuite 2010	2	SafePharm 2002a
Henry Law's Constant ($Pa.m^3/mol$)	$7.04x10^{-1}$	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	4.45[a]	EPiSuite 2010	5.11	SafePharm 2002a
Vapour pressure (Pa)	0.012	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	8.4	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	3.75	EPIWIN 2011	5.34	SafePharm 2002a

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-7 Key physical and chemical properties for the monobutyl monooctyl DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	$1.02x10^{-3}$	EPiSuite 2010	0.08	SafePharm 2002a
Henry Law's Constant ($Pa.m^3/mol$)	5.64	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	8.67[a]	EPiSuite 2010	> 6.20	SafePharm 2002a
Vapour pressure (Pa)	$1.70x10^{-5}$	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	11.72	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	5.48	EPIWIN 2011	> 5.63	SafePharm 2002a

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-8 Key physical and chemical properties for the dibutyl DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	0.049	EPiSuite 2010	0.08-0.01	SafePharm 2002a
Henry Law's Constant ($Pa.m^3/mol$)	1.82	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	6.81[a]	EPiSuite 2010	> 6.20	SafePharm 2002a
Vapour pressure (Pa)	$3.17x10^{-4}$	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	10.35	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	4.59	EPIWIN 2011	5.63	SafePharm 2002a

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-9 Key physical and chemical properties for the monostyrenated DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	0.078	EPiSuite 2010	0.41	US EPA 2009
Henry Law's Constant ($Pa.m^3/mol$)	$3.22x10^{-2}$	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	5.15[a]	EPiSuite 2010	4.64	US EPA 2009
Vapour pressure (Pa)	$9.19x10^{-6}$	calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	10.45	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	4.94	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient;NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-10 Key physical and chemical properties for the distyrenated DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	$5.78x10^{-5}$	EPiSuite 2010	0.41	US EPA 2009
Henry Law's Constant ($Pa.m^3/mol$)	$3.81x10^{-3}$	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	7.31[a]	EPiSuite 2010	4.64	US EPA 2009
Vapour pressure (Pa)	$5.83x10^{-10}$	calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	13.53	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	6.96	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient ; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-11 Key physical and chemical properties for the diethyl dinonyl DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	$4.78x10^{-7}$	EPiSuite 2010	NA	NA
Henry Law's Constant ($Pa.m^3/mol$)	66.3	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	13.58[a]	EPiSuite 2010	NA	NA
Vapour pressure (Pa)	$7.00x10^{-8}$	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	15.66	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	8.17	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available

[a] Calculated using the Experimental Value Adjustment method

Table A-12 Key physical and chemical properties for the diethyl monononyl DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	$6.05x10^{-5}$	EPiSuite 2010	NA	NA
Henry Law's Constant ($Pa.m^3/mol$)	6.23	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	9.32[a]	EPiSuite 2010	NA	NA
Vapour pressure (Pa)	$1.07x10^{-6}$	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	12.39	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	6.04	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient; log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available
[a] Calculated using the Experimental Value Adjustment method

Table A-13 Key physical and chemical properties for the monooctyl monostyrenated DPA structure

CAS RN	Modelled Value	Reference	Empirical Value	Reference
Water Solubility (mg/L)	$5.11x10^{-5}$	EPiSuite 2010	NA	NA
Henry Law's Constant ($Pa.m^3/mol$)	$1.01s10^{-1}$	EPiSuite 2010	NA	NA
Log K_{ow} (dimensionless)	8.69[a]	EPiSuite 2010	NA	NA
Vapour pressure (Pa)	$1.32x10^{-9}$	Calculated[a] from water solubility and Henry's Law Constant	NA	NA
Log K_{oa} (dimensionless)	13.6	EPIWIN 2011	NA	NA
Log K_{oc} (dimensionless)	6.66	EPIWIN 2011	NA	NA

Abbreviations: log K_{ow}: octanol-water partition coefficient; log K_{oa}: octanol-air partition coefficient;log K_{oc}: Soil Organic Carbon-Water Partitioning Coefficient; NA: not available

[a] Calculated using the Experimental Value Adjustment method

Appendix B. Modelled Data for Persistence for the Various SDPA Structures.

Table B-1 Modelled data for primary and ultimate biodegradation for dioctyl DPA structures[f]

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.03[c] "biodegrades fast (CAS RN: 101-67-7; 26603-23-6;)	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.56[c] "biodegrades slowly|" (CAS RN:15721-78-5; 68411-46-1; 184378-08-3)	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	1.34[c] "biodegrades slowly" (CAS RN;15721-78-5; 68411-46-1;184378-08-3)	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.04[c] "biodegrades fast" (CAS RN:101-67-7; 26603-23-6)	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.671 - -0.176[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0003 – 0.0016[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly"	≤182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.91 9.1 [e] “biodegrades slowly”	≤182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score
[e] primary degradation of the parent compound with a stable degradation product
[f] Physical-chemical properties may differ as SMILEs/chemical structures may be differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

Table B-2 Modelled data for primary and ultimate biodegradation for monooctyl DPA structures[f]

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.03;3.27[c] “biodegrades fast”	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.39[c] “biodegrades fast (CAS RN 4175-37-5)”	≤ 182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.04[c] “biodegrades slowly” (CAS RN: 68411-46-1; 184378-08-3)	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.022 - -0.269[d] “biodegrades slowly”	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0056 – 0.0119 [d] “biodegrades slowly”	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0 [d] "biodegrades slowly"	≤182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.79 – 7.9[e] "biodegrades slowly"	≤182

[a] EPIsuite (2000-201).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.
[e] primary degradation of the parent compound with a stable degradation product
[f] Physical-chemical properties may differ as SMILEs/chemical structures may be differ to account for differences in the placement of the alkyl groups and differences in branching characteristics

Table B-3 Modelled data for primary and ultimate biodegradation for the dimethyl distyrenated DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.86[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	1.79[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	- 0.367[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0006 [d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly"	≥182
Biodegradation	CATALOGIC	% BOD = 18.24	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
(aerobic)	c2004−2008 % BOD (biological oxygen demand)	“biodegrades slowly”	

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.

Table B-4 Modelled data for primary and ultimate biodegradation for the dinonyl DPA structures

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.99[c] “biodegrades slowly”	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	1.98[c] “biodegrades slowly”	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.261 - -0.656[d] “biodegrades slowly”	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0004 – 0.0058[d] “biodegrades slowly”	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] “biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 1[e] “biodegrades slowly”	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.
[e] primary degradation of the parent compound with a stable degradation product

Table B-5 Modelled data for primary and ultimate biodegradation for the for the monononyl DPA structures[a]

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.25[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.36[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.261[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0058[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.93[e] "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.
[e] primary degradation of the parent compound with a stable degradation product

Table B-6 Modelled data for primary and ultimate biodegradation for monobutyl DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4:	3.27[c] "biodegrades fast"	≤182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	Expert Survey (qualitative results)		
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.38[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.0269[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0249[d] "biodegrades slowly (mono butyl)	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.38 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Table B-7 Modelled data for primary and ultimate biodegradation for monobutyl monooctyl DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.79[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3:	1.68[c] "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	Expert Survey (qualitative results)		
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.1285[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0033[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.62 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Table B-8 Modelled data for primary and ultimate biodegradation for dibutyl DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.03[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.02[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear	-0.0794[d] "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	probability		
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0269[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 0.25 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Table B-9 Modelled data for primary and ultimate biodegradation for monostyrenated DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.29[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.43[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.153[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.0097[d] "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 2.7 "biodegrades slowly" (mono)	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Table B-10. Modelled data for primary and ultimate biodegradation for distyrenated DPA structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.07[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.12[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.439[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 6: MITI non-linear probability	0.001[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD	% BOD = 3.3 "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	(biological oxygen demand)		

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.

Table B-11. Modelled data for primary and ultimate biodegradation for diethyl dinonyl structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.78[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	1.71[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.9496[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-20108[a] Sub-model 6: MITI non-linear probability	0[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 9.5 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.

Table B-12. Modelled data for primary and ultimate biodegradation for diethyl monononyl structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	3.03[c] "biodegrades fast"	≤182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	2.06[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.5552[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-20108[a] Sub-model 6: MITI non-linear probability	0.0007[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0[d] "biodegrades slowly	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 7.4 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.

Table B-13. Modelled data for primary and ultimate biodegradation for monooctyl monostyrenated structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4:	2.81[c] "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	Expert Survey (qualitative results)		
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey (qualitative results)	1.73[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.3085[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-20108[a] Sub-model 6: MITI non-linear probability	0.0013[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 1.76 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Table B-14. Modelled data for primary and ultimate biodegradation for dioctyl monostyrenated structure

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 4: Expert Survey (qualitative results)	2.34[c] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 3: Expert Survey	1.06[c] "biodegrades slowly"	≥182

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
	(qualitative results)		
Biodegradation (aerobic)	BIOWIN 2000-2010[a] Sub-model 5: MITI linear probability	-0.4639[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	BIOWIN 2000-20108[a] Sub-model 6: MITI non-linear probability	0.0002[d] "biodegrades slowly"	≥182
Biodegradation (aerobic)	CATALOGIC c2004−2008 % BOD (biological oxygen demand)	% BOD = 1.65 "biodegrades slowly"	≥182

[a] EPIsuite (2000-2010).
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d]Output is a probability score.

Appendix C. Potential Exposure to Substituted Diphenylamines from Products Available to Consumers.

Table C-1. Estimate of Potential Exposure to Substituted Diphenylamines from Products Available to Consumers.

Product type	Assumptions	Estimated intakes
Mouthing cushion scenario	**Oral exposure from mouthing couch cushion for infant** Reference: Environ 2003a,b Water solubility: 2 mg/L (CAS RN 68411-46-1) V_S = saliva flow rate: 2.2×10^{-4} L/min FR = fractional extraction by saliva: 0.5 (factoring in SDPAs are considered to be immobile in foam matrix) EF = exposure frequency: 60 min/day BW = body weight: 7.5 kg (infant); 15.5 kg (toddler) (Health Canada 1998) Dose of SDPA from mouthing for infant: D = WS x V_S x FR x EF / BW = 2 mg/L x 2.2×10^{-4} L/min x 0.5 x 1 x 60 min/day / 7.5 kg = 1.76 µg/kg-bw per day	Estimated oral intake: Infant: 1.76 µg/kg-bw per day Toddler: 0.85 µg/kg-bw per day
Do it yourself Motor oil change	**Dermal exposure while changing your own motor oil in a personal vehicle** Weight fraction range: 0.25 – 3.8% (1 to 4%; RAPA 2003) Surface area of fingertips: 6 cm^2 (RIVM 2006) Density of motor oil: 0.89 g/mL (Unocal 2002) Film thickness retained on skin: 15.88×10^{-3}cm (US EPA 2011) Adult body weight: 70.9 kg (Health Canada 1998) Retention factor: 0.25 (factoring for the properties of SDPAs; professional judgement) Volume of product retained on one hand: (6 cm^2)(15.88 10^{-3} cm) = 0.0953 cm^3 = 0.0953 mL Amount of product in contact with skin = (volume of product retained)(density) = (0.0953 mL)(0.89 g/mL) = 0.0848 g **Low end of range:** Amount substituted diphenylamine absorbed	Estimated short-term dermal intake: 0.75 to 11.4 µg/kg-bw per event

Product type	Assumptions	Estimated intakes
	= (uptake fraction)(amount of product)(minimum weight fraction) / (adult body weight) = (0.25)(0.0848 g)(0.0025) / (70.9 kg) = 0.75 µg/kg-bw **High end of range:** Amount substituted diphenylamine absorbed = (uptake fraction)(amount of product)(maximum weight fraction) / (adult body weight) = (0.25)(0.0848 g)(0.038) / (70.9 kg) = 11.4 µg/kg-bw	

Appendix D. Effect Levels from Key Studies for Human Health Endpoints.

Table D-1. Summary of Effect Levels from Key Studies for Human Health Endpoints.

DSL Name (CAS RN)	***In Vitro* Geno-toxicity**	***In Vivo* Geno-toxicity**	**Sub-chronic and Chronic Toxicity**	**Short Term Toxicity**	**Acute Toxicity**	**Irrita-tion and Sensiti-zation**	**Repro-ductive Toxicity**	**Deve-lop-mental Toxicity**
Benzen-amine, 4-octyl-N-(4-octyl-phenyl)-(101-67-7)	Mutation *S. typhi/S. cere.* +/- S9 Nega-tive Mouse Lymph. L5178Y Nega-tive Chrom. Ab. CHO/ CHL +/- S9 Nega-tive	Dom. Lethal Mouse Nega-tive Dom. Lethal Rat Positive	No Data	LOAEL = 75 mg/kg bw/day Haema-tological effects 43-54 day gavage study (Rat)	Oral LD_{50} >7940 mg/kg bw (Rat) Dermal LD_{50} >7940 mg/kg bw (Rabbit)	Slight Eye Irritation (Rabbit) Nega-tive Skin Irritation (Rabbit) Nega-tive Skin Sensiti-zation (Guinea Pig; Human)	NOAEL = 250 mg/kg bw/day highest dose no effects; 43-54 days one gen. (Rat)	NOAEL = 250 mg/kg bw/day highest dose no effects; 43-54 days one gen. (Rat)
Benzen-amine, 4-octyl-N-phenyl-(4175-37-5)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data

Benzen-amine, 4-(1-methyl-1-phenyl-ethyl)-N-[4-(1-methyl-1-phenyl-ethyl)-phenyl]-(10081-67-1)	Mutation *S. typhi.* +/- S9 Nega-tive CHL cells +/- S9 Nega-tive Chrom. Aberr. CHL cells +/- S9 Nega-tive	No Data	No Data	NOAEL = 40mg/kg bw/day Liver / clinical chem. effects 28 day oral study (Rat)	Oral LD_{50} >10000 mg/kg bw (Rat) Dermal; LD_{50} >2000 mg/kg bw (Rat)	Nega-tive Eye Irritation (Rabbit) Nega-tive Skin Irritation (Rabbit) Positive Skin Senitiza-tion (Mouse LLNA)	NOAEL = 50 mg/kg bw/day highest dose no effects; 44-54 days one gen. (Rat)	No Data
Benzen-amine, 4-(1,1,3,3-tetra-methyl-butyl)-N-[4-(1,1,3,3-tetra-methyl-butyl)-phenyl]-(15721-78-5)	No Data	No Data	No Data	No Data	No Data	Nega-tive Skin Sensiti-zation (Mouse LLNA)	No Data	No Data
Benzen-amine, 4-nonyl-N-(4-nonyl-phenyl)-(24925-59-5)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data

Benzen-amine, ar-octyl-N-(octyl-phenyl)-(26603-23-6)	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Benzena mine, ar-nonyl-N-phenyl-(27177-41-9)	Mutation *S. typhi/ E. coli .* +/- S9 Nega-tive Chrom. Aberr. CHL cells +/- S9 Nega-tive	No Data	No Data	NOAEL = 15 mg/kg bw/day Liver / Spleen/ Haema-tological and clinical chem. effects 28 day oral study (Rat)	No Data	No Data	No Data	No Data
DSL Name (CAS RN)	***In Vitro* Geno-toxicity**	***In Vivo* Geno-toxicity**	**Sub-chronic and Chronic Toxicity**	**Short Term Toxicity**	**Acute Toxicity**	**Irrita-tion and Sensiti-zation**	**Repro-ductive Toxicity**	**Deve-lop-mental Toxicity**
Benzena mine, ar-nonyl-N-(nonyl-phenyl)-(36878-20-3)	No Data	No Data	LOAEL = 100 mg/kg bw/day ↓ BW gain; liver and thyroid, and clinical chem. effects 13 wk oral gavage study (Rat)	NOEL = 1000 mg/kg bw/day 28-days oral gavage (Rat; highest dose tested)	Oral LD_{50} >16000 mg/kg-bw (Rat)	Slight Eye Irritation (Rabbit) Nega-tive Skin Irritation (Rabbit) Nega-tive Skin Sensiti-zation (Guinea Pig)	No Data	NOAEL = 150* mg/kg bw/day ↑ inci-dence of small fetuses Develop-mental study (Rat) * with maternal toxicity

Benzen-amine, N-phenyl-, reaction products with 2,4,4-trimethyl pentene (68411-46-1)	Mutation *S. typhi/ E. coli.* +/- S9 Nega-tive Mouse Lymph. L5178Y Nega-tive Micro-nucleus human lymph. +/- S9 Nega-tive	No Data	No Data	NOAEL = 25 mg/kg bw/day. Clinical signs of toxicity, liver / clinical chemis-try effects. 28-45 day oral gavage (Rat)	Oral LD_{50} >5000 mg/kg-bw (Rat) Dermal LD_{50} >2000 mg/kg-bw (Rat) Inhala-tion LC_{50} >5.8 mg/L (Rat)	Nega-tive Eye Irritation (Rabbit) Slight or Negativ eSkin Irritation (Rabbit) Equivo-cal Skin Sensiti-zation (Guinea Pig)	No Data	No Data
DSL Name (CAS RN)	***In Vitro* Geno-toxicity**	***In Vivo* Geno-toxicity**	**Sub-chronic and Chronic Toxicity**	**Short Term Toxicity**	**Acute Toxicity**	**Irrita-tion and Sensiti-zation**	**Repro-ductive Toxicity**	**Deve-lop-mental Toxicity**
Benzen-amine, N-phenyl-, styrena-ted (68422-68-2)	Mutation *S. typhi/ E. coli.*+/- S9 Nega-tive DNA damage/ repair *E. coli.* +/- S9 Nega-tive	Micro-nucleus Nega-tive (Mouse)	No Data	NOAEL = 50 mg/kg bw/day Liver / Thyroid effects 43-54 days gavage study (Rat)	Oral LD_{50} >20000 mg/kg-bw (Rat) Dermal LD_{50} >10000 mg/kg-bw (Rabbit)	Slight Eye Irritation (Rabbit) Nega-tive Skin Irritation (Rabbit)	NOAEL = 600 mg/kg bw/day highest dose, no effects; 43-54 days one gen. (Rat)	NOAEL = 250 mg/kg bw/day pre-impl. loss ↓ litter wt, ↓ surface righting one gen. (Rat)

Benzen-amine, 2-ethyl-N-(2-ethyl-phenyl)-, (tri-propenyl) derivs. (68608-77-5)	Mutation *S. typhi/ E. coli.* +/- S9 Nega-tive	No Data	No Data	No Data	Oral LD_{50} >34600 mg/kg-bw (Rat) Dermal LD_{50} >3000 mg/kg bw (Rabbit)	Nega-tive Eye Irritation (Rabbit)	No Data	No Data
Benzen-amine, N-phenyl-, (tri-propenyl) derivs. (68608-79-7)	No Data	No Data	No Data	No Data	No Data	No Data	No Data (	No Data
DSL Name (CAS RN)	***In Vitro* Geno-toxicity**	***In Vivo* Geno-toxicity**	**Sub-chronic and Chronic Toxicity**	**Short Term Toxicity**	**Acute Toxicity**	**Irrita-tion and Sensiti-zation**	**Repro-ductive Toxicity**	**Deve-lop-mental Toxicity**
Benzen-amine, *N*-phenyl-, Reaction Products with Styrene and 2,4,4-Tri-methyl-pentene (BNST) (68921-45-9)	Mutation *S. typhi/ E. coli.* +/- S9 Nega-tive	No Data	LOAEL = 125 mg/kg bw/day ↓ BW; liver effects 64 wk diet study (Rat)	No Data	No Data	Nega-tive Skin Irritation (Human) Nega-tive Skin Sensiti-zation (Human)	No Data	No Data

Benzen-amine, 2-ethyl-N-(2-ethyl-phenyl)-, (tri-propenyl) derivs. (184378-08-3)	Mutation *S. typhi.* +/- S9 Nega-tive	No Data	No Data	NOAEL = 5 mg/kg bw/day Liver effects and clinical chem./ haema-tological effects 43-54 days gavage study (Rat)	Oral LD_{50} >2000 mg/kg-bw (Rat)	Nega-tive Skin Sensiti-zation (Guinea Pig)	NOAEL = 25* mg/kg bw/day short gesta-tion, ↓viability index; 43-54 days one gen. (Rat) * with maternal toxicity	NOAEL = 25* mg/kg bw/day ↓ pup bw; 43-54 days one gen. (Rat) * with maternal toxicity

Acronyms: CHO/L, Chinese Hamster Ovary/Lung Cells; WOE, Weight of Evidence; NOAEL, No Observed Adverse Effect Level; LOAEL, Lowest Observed Adverse Effect Level.