Draft Screening Assessment

Aromatic Amines Group

Chemical Abstracts Service Registry Numbers
86-30-6
90-30-2
95-55-6
101-14-4
101-96-2
121-69-7
122-39-4
63449-68-3

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of eight of 15 substances referred to collectively under the Chemicals Management Plan as the Aromatic Amines Group. Benzenamine, 4,4'-methylenebis[2-chloro-] or MBOCA (CAS RN 101-14-4[1]) was included in the Aromatic Amines subgroup of the Aromatic Azo and Benzidine-based Substance Grouping. However, it was removed to better align with other international assessment activities focused on this substance and has been added to the Aromatic Amines Group. These eight substances were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns. Seven of the 15 substances were determined to be of low concern through other approaches, and decisions for these substances are provided in separate reports.[2,3] Accordingly, this screening assessment addresses the eight substances listed in the table below. The eight substances addressed in this screening assessment will hereinafter be referred to as the Aromatic Amines Group. The Chemical Abstracts Service Registry Numbers (CAS RN), their *Domestic Substances List* (DSL) names and their common names and/or abbreviations are listed in the table below.

Substances in the Aromatic Amines Group

CAS RN	DSL name	Common name/abbreviation
86-30-6	Benzenamine, N-nitroso-N-phenyl-	NDPhA
90-30-2	1-Naphthalenamine, N-phenyl-	P1NA
95-55-6[a]	Phenol, 2-amino-	2-aminophenol
101-14-4	Benzenamine, 4,4'-methylenebis[2-chloro-	MBOCA
101-96-2	1,4-Benzenediamine, N,N’-bis(1-methylpropyl)-	44PD
121-69-7	Benzenamine, N,N-dimethyl-	Dimethylaniline
122-39-4	Benzenamine, N-phenyl-	Diphenylamine
63449-68-3	2-Naphthalenol, 2-aminobenzoyl ester	2-naphthyl anthranilate

[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.

[2] Conclusions for substances bearing CAS RNs 793-24-8, 3081-14-9, 5285-60-9 are provided in the Screening assessment substances identified as being of low concern using the ecological risk classification of organic substances and the threshold of toxicological concern (TTC)-based approach for certain substances.

[3] Conclusions for substances bearing CAS RNs 91-66-7, 95-54-5, 134-09-8, and 13680-35-8 are provided in the Rapid Screening of Substances with Limited General Population Exposure.

[a] This substance was not identified under subsection 73(1) of CEPA but was included in this assessment as it was considered a priority on the basis of other human health concerns.

The substances in the Aromatic Amines Group do not occur naturally, except for diphenylamine, which may occur naturally in certain food items.

According to information submitted pursuant to a CEPA section 71 survey, NDPhA (< 100 kg), dimethylaniline (< 100 kg) and diphenylamine (1 000 to 10 000 kg) were manufactured in Canada in 2008, while 44PD (1 000 to 10 000 kg) was manufactured in Canada in 2011. Reported Canadian imports of MBOCA in 2000 ranged from 100 000 to 1 000 000 kg. In 2008, total reported Canadian import quantities were 1 000 to 10 000 kg for NDPhA, less than 100 kg for 2-aminophenol, 10 000 to 100 000 kg for dimethylaniline, and 159 800 to 698 100 kg for diphenylamine. In 2011, reported Canadian import quantities ranged from 100 000 to 1 000 000 kg for diphenylamine and totalled 41 176 kg for 44PD. In the same year, no Canadian manufacturing or importing activities were reported for 2-naphthyl anthranilate above the reporting threshold of 100 kg. Reported uses of these substances in Canada include use in adhesives and sealants, lubricants and greases, munitions, in plastic and rubber materials, and in the automotive, aircraft and transportation sector. They may also be used in incidental additives, food packaging materials, hair dye and pest control products.

The ecological risks of the substances in the Aromatic Amines Group were characterized using the ecological risk classification of organic substances (ERC), which is a risk-based approach that employs multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. Hazard profiles are based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Metrics considered in the exposure profiles include potential emission rate, overall persistence, and long-range transport potential. A risk matrix is used to assign a low, moderate or high level of potential concern for substances on the basis of their hazard and exposure profiles. Based on the outcome of the ERC analysis, substances in the Aromatic Amines Group are considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, dimethylaniline, diphenylamine and 2-naphthyl anthranilate. It is proposed to conclude that the eight substances in the Aromatic Amines Group 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.

For the human health assessment, each substance was assessed individually. NDPhA was classified as a probable human carcinogen by the United States Environmental Protection Agency (US EPA). The target organ for both cancer and non-cancer effects is the bladder. Exposure to NDPhA is also associated with developmental effects.

Exposure of the general population in Canada to NDPhA may occur from the use of products available to consumers predominantly through its presence in inks from children's markers and as a contaminant in textiles such as clothing. Comparison of levels to which the general population may be exposed from daily or intermittent use of textiles or children's marker ink containing NDPhA with critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases for both cancer and non-cancer effects.

Critical health effects for P1NA include effects on the hematological system, kidney, spleen and liver. Exposure of the general population in Canada to P1NA may occur from the use of grease and lubricants (such as motor oils and transmission fluid). The margins of exposure between estimated levels of exposure and the critical effect levels for P1NA are considered adequate to address uncertainties in the health effects and exposure databases.

2-aminophenol was classified as a Category 2 mutagen by the European Union. Additional critical health effects identified for 2-aminophenol include effects in the kidney and liver, as well as decreased body weights and increased thyroid weights. Exposure of the general population in Canada to 2-aminophenol occurs predominantly through the use of hair dyes. The margins of exposure between estimated levels of exposure and the critical effect levels for 2-aminophenol are considered adequate to address uncertainties in the health effects and exposure databases.

MBOCA is classified by the International Agency for Research on Cancer (IARC) as a Group 1 carcinogen with strong evidence of genotoxic mechanisms of action. Other health effects of concern include effects on the liver. Exposure of the general population in Canada to MBOCA is not expected. However, individuals living in the vicinity of facilities that release MBOCA into the environment, primarily into air, may be exposed to low levels of MBOCA. The estimated lifetime cancer risk value attributed to MBOCA does not represent a concern for human health for residents living within the vicinity of facilities using MBOCA for processing and manufacturing.

The critical health effects of 44PD are effects on the liver and red blood cells. Exposure of the general population in Canada to 44PD may occur through the use of certain grease and lubricants (such as certain motor oils for lawn trimmers). However, the critical health effects observed in the health effects database are not likely to occur after infrequent (i.e., 1 to 2 times per year) dermal exposure to 44PD from use of lawn trimmer motor oil.

Dimethylaniline is classified by the European Union as a Category 2 carcinogen (suspected human carcinogen). Other critical health effects occur in the spleen and red blood cells. Exposure of the general population in Canada to dimethylaniline occurs from the use of certain automotive products available to consumers (including a 2-component adhesive, body filler and spray paint primer). The margins of exposure between estimated levels of exposure and the critical effect levels for dimethylaniline

are considered to be potentially inadequate to address uncertainties in the health effects and exposure databases.

The critical health effects for diphenylamine are effects in red blood cells, kidneys, spleen and liver. Exposure of the general population in Canada to diphenylamine may occur from environmental media and food, as well as from use of certain motor oils used in lawn trimmers and chainsaws. A comparison of estimated levels of exposure to diphenylamine and critical effect levels results in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

Limited information on the health effects of concern was identified for 2-naphthyl anthranilate, and a threshold of toxicological concern (TTC)-based approach was used. The estimate of exposure to 2-naphthyl anthranilate from its potential use as a food flavouring agent (no other exposures identified) was estimated to be lower than the TTC value assigned to 2-naphthyl anthranilate. Therefore, 2-naphthyl anthranilate is considered to be of low concern for human health at current levels of exposure.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that dimethylaniline meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

However, NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, diphenylamine, and 2-naphthyl anthranilate 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.

It is therefore proposed to conclude that dimethylaniline meets one or more of the criteria set out in section 64 of CEPA and that NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, diphenylamine and 2-naphthyl anthranilate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed to conclude that dimethylaniline meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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1. Introduction

Pursuant to section 68 or 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 of eight of 15 substances referred to collectively under the Chemicals Management Plan as the Aromatic Amines Group to determine whether these substances present or may present a risk to the environment or to human health. The substances in this group were identified as priorities for assessment as they met categorization criteria under subsection 73(1) of CEPA or were considered a priority on the basis of other human health concerns (ECCC, HC [modified 2017]).

The other seven substances (the CAS RN[4] are listed in Table 1-1, below) were considered in the Ecological Risk Classification of Organic Substances (ERC) Science Approach Document (ECCC 2016a) and in either the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Science Approach Document (Health Canada 2016), or via the approach applied in the Rapid Screening of Substances with Limited General Population Exposure (ECCC, HC 2018a). They are therefore not further addressed in this report. Proposed conclusions for these seven substances are provided in the Substances Identified as Being of Low Concern using the Ecological Risk Classification of Organic Substances and the Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances Screening Assessment (ECCC, HC 2018b) and the Rapid Screening of Substances with Limited General Population Exposure Draft Screening Assessment (ECCC, HC 2018a).

Table 1-1. Substances in the Aromatic Amines Group that were addressed under other approaches

CAS RN	*Domestic Substances List* (DSL) name	Approach under which the substance was addressed	Reference
91-66-7	Benzenamine, N,N-diethyl-	ERC/Rapid Screening	ECCC, HC 2018a
95-54-5	1,2-Benzenediamine	ERC/Rapid Screening	ECCC, HC 2018a
134-09-8	Cyclohexanol, 5-methyl-2-(1-methylethyl)-, 2-aminobenzoate	ERC/Rapid Screening	ECCC, HC 2018a

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CAS RN	*Domestic Substances List* (DSL) name	Approach under which the substance was addressed	Reference
793-24-8	1,4-Benzenediamine, N-(1,3-dimethylbutyl)-N'-phenyl-	ERC/TTC	ECCC, HC 2018b
3081-14-9	1,4-Benzenediamine, N,N'-bis(1,4-dimethylpentyl)-	ERC/TTC	ECCC, HC 2018b
5285-60-9	Benzenamine, 4,4'-methylenebis[N-(1-methylpropyl)-	ERC/TTC	ECCC, HC 2018b
13680-35-8	Benzenamine, 4,4'-methylenebis[2,6-diethyl-	ERC/Rapid Screening	ECCC, HC 2018a

The eight substances addressed in this screening assessment will hereinafter be referred to as the Aromatic Amines Group.

A State of the Science Report for a Screening Health Assessment of benzenamine, 4,4'-methylenebis[2-chloro-] or MBOCA (CAS RN 101-14-4) was published on the Health Canada website in 2005 (Health Canada 2005). MBOCA was subsequently identified as a priority for assessment and included in the Aromatic Amines subgroup of the Aromatic Azo and Benzidine-based Substance Grouping (ECCC, HC 2016). However, it was removed from that initiative to better align with other international assessment activities focused on this substance.

The ecological risks of substances in the Aromatic Amines Group were characterized using the Ecological Risk Classification of Organic Substances (ERC) approach (ECCC 2016a). The ERC describes the hazard of a substance using key metrics, including mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity, and considers the possible exposure of organisms in the aquatic and terrestrial environments on the basis of such factors as potential emission rates, overall persistence, and long-range transport potential in air. The various lines of evidence are combined to identify substances as warranting further evaluation of their potential to cause harm to the environment or as having a low likelihood of causing harm to the environment.

Some of the substances in the Aromatic Amines Group have been reviewed internationally through the Organisation for Economic Cooperation and Development (OECD) Cooperative Chemicals Assessment Programme, and screening information data sets (SIDS) and SIDS initial assessment reports (SIARs) are available. These assessments undergo rigorous review (including peer review) and endorsement by international governmental authorities. Health Canada and Environment and Climate Change Canada are active participants in these processes and consider these assessments to be reliable. The OECD (2013) SIARs were used to inform the health

effects characterization in this screening assessment (OECD 2013). In addition, health effects for some of the substances in this group have been evaluated by the IARC Monographs Programme, the US EPA Integrated Risk Information System (IRIS), the US EPA Provisional Peer-Reviewed Toxicity Values (PPRTVs) Program, the European Chemicals Agency's Committee for Risk Assessment, the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). These evaluations were also used to inform the health effects characterization in this screening assessment (JECFA 2006a, 2006b, 2006c).

This draft screening assessment includes consideration of information on chemical properties, environmental fate, hazards, uses and exposures, including additional information submitted by stakeholders. Relevant data were identified up to February 2019. Targeted literature searches were conducted up to May 2019. Empirical data from key studies as well as results from models were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered. While external comments were taken into consideration, the final content and outcome of this draft screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

This draft screening assessment was prepared by staff in the CEPA Risk Assessment Program at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The human health portions of this assessment have undergone external review and/or consultation. Comments on the technical portions relevant to human health were received from scientists selected by Risk Sciences International, including Dr. T. Schupp (Muenster University of Applied Science, Germany) and Dr. B.J. Brüschweiler (Federal Food Safety and Veterinary Office, Switzerland). The ecological portion of this assessment is based on the ERC document (published July 30, 2016), which was subject to an external peer review, as well as a 60-day public comment period.

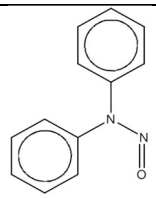
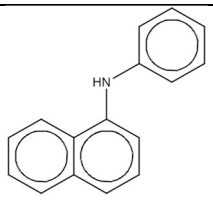
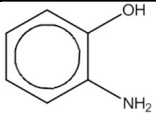
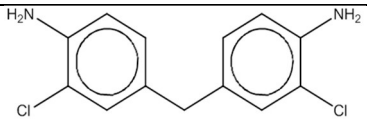
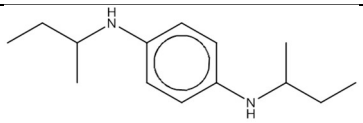
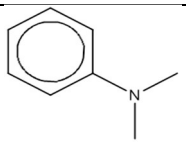
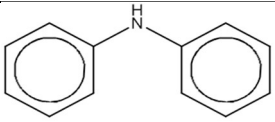
This draft screening assessment focuses on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA by examining scientific information and incorporating a weight of evidence approach and precaution.[5] This draft screening assessment presents the critical information and considerations on which the proposed conclusions are based.

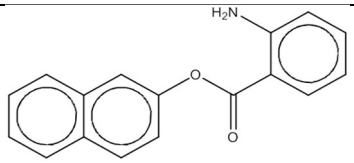
[5]A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient 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

The CAS RN, DSL names, common names and abbreviations for the individual substances in the Aromatic Amines Group are presented in Table 2-1.

Table 2-1. Substance identities

CAS RN	DSL name (common name or abbreviation)	Chemical structure and molecular formula	Molecular weight (g/mol)
86-30-6	Benzenamine, N-nitroso-N-phenyl- (NDPhA)	 $C_{12}H_{10}N_2O$	198.23
90-30-2	1-Naphthalenamine, N-phenyl- (P1NA)	 $C_{16}H_{13}N$	219.29
95-55-6	Phenol, 2-amino- (2-aminophenol)	 C_6H_7NO	109.13
101-14-4	4,4' - Methylenebis (2-chlorobenzenamine) (MBOCA)	 $C_{13}H_{12}Cl_2N_2$	267
101-96-2	1,4-Benzenediamine, N,N'-bis(1-methylpropyl)- (44PD)	 $C_{14}H_{24}N_2$	215.92
121-69-7	Benzenamine, N,N-dimethyl- (Dimethylaniline)	 $C_8H_{11}N$	121.18
122-39-4	Benzenamine, N-phenyl- (Diphenylamine)	 $C_{12}H_{11}N$	169.23

CAS RN	DSL name (common name or abbreviation)	Chemical structure and molecular formula	Molecular weight (g/mol)
63449-68-3	2-Naphthalenol, 2-aminobenzoyl ester (2-naphthyl anthranilate)	 $C_{17}H_{13}NO_2$	263.3

3. Physical and chemical properties

A summary of experimental and modeled physical and chemical property data of the substances in the Aromatic Amines Group are presented in Table 3-1 and 3-2. Additional physical and chemical properties are reported in ECCC (2016b).

Table 3-1. Experimental and modeled physical and chemical property values for substances in the Aromatic Amines Group

Property	NDPhA	P1NA	2-Aminophenol	MBOCA
Physical state	Solid[b]	Solid[b]	Solid[b]	Solid[b]
Melting point (°C)	66.5[a] (modeled)	62[a] (modeled)	174[a] (modeled)	110[a] (modeled)
Vapour pressure (Pa)	13.3[a] at 25 °C (modeled)	1.11E-3[a] at 25 °C (modeled)	1.27[a] at 25 °C (modeled)	3.81E-05[a] at 25 °C (modeled)
Henry's law constant ($Pa \cdot m^3/mol$)	0.123[a] at 25 °C (modeled)	0.010[a] at 25 °C (modeled)	2.006E-05[c] (modeled)	4.114E-06[a] at 25 °C (modeled)
Water solubility (mg/L)	35[a] at 25 °C (modeled)	60[a] at 25 °C (experimental)	2.00E+04[a] at 25 °C (experimental)	13.9[a] at 24 °C (experimental)
log K_{ow} (dimensionless)	3.13[a] (modeled)	4.2[a] (experimental)	0.62[a] (experimental)	3.91[a] (experimental)
log K_{oc} (dimensionless)	3.08[b] (not specified)	3.66[b] (modeled)	1.95[b] (modeled)	3.75[b] (modeled)

Abbreviations: K_{ow}, octanol-water partition coefficient; K_{oc}, organic carbon-water partition coefficient
[a] ChemIDplus 2018
[b] PubChem 2018.

Table 3-2. Experimental and modeled physical and chemical property values for substances in the Aromatic Amines Group

Property	44PD	Dimethylaniline	Diphenylamine	2-Naphthyl anthranilate
Physical state	Liquid[b]	Liquid[b]	Solid[b]	Solid[c]
Melting point (°C)	18[a] (modeled)	2.5[a] (modeled)	52.9[a] (experimental)	118[c] (modeled)
Vapour pressure (Pa)	0.21[a] at 25 °C (modeled)	93.3[c] at 25 °C (experimental)	8.93E-02[a] at 25 °C (unspecified)	3.24E-04[a] at 25 °C (modeled)
Henry's law constant (Pa·m^3/mol)	1.80E-03[a] at 25 °C (modeled)	5.76[c] at 25 °C (modeled)	2.73E-01[a] at 25 °C (modeled)	4.49E-05[b] at 25 °C (modeled)
Water solubility (mg/L)	95.8[a] at 25 °C (modeled)	1450[a] at 25 °C (experimental)	53[a] at 20 °C (experimental)	2.23[a] at 25 °C (modeled)
log K_{ow} (dimensionless)	3.50[a] (modeled)	2.31[a] (experimental)	3.5[a] (experimental)	4.66[a] (modeled)
log K_{oc} (dimensionless)	2.03[a] (modeled)	2.26[b] (modeled)	3.3[b] (modeled)	3.72[c] (modeled)

Abbreviations: K_{ow}, octanol-water partition coefficient; K_{oc}, organic carbon-water partition coefficient
[a] ChemIDplus 2018
[b] PubChem 2018
[c] ChemSpider 2018.

4. Sources and uses

All of the substances in the Aromatic Amines Group have been included in surveys issued pursuant to a CEPA section 71 notice (Environment Canada 2001a, 2009, 2013). Table 4-1 presents a summary of information reported on the total manufacture and total import quantities for the Aromatic Amines Group.

Table 4-1. Summary of information on Canadian manufacturing and imports of substances in the Aromatic Amines Group submitted pursuant to CEPA section 71 surveys

Common name or abbreviation	Total manufacture[a] (kg)	Total imports[a] (kg)	Reporting year	Survey reference
NDPhA	< 100	1 000 – 10 000 kg	2008	Environment Canada 2009
P1NA	NR	100 000 – 1 000 000	2011	Environment Canada 2013
2-aminophenol	NR	< 100 kg	2008	Environment Canada 2009
MBOCA	NR	100 000 – 1 000 000	2000	Environment Canada 2001b
44PD	1 000 – 10 000	41 176	2011	Environment Canada 2013
Dimethylaniline	< 100	10 000 – 100 000	2008	Environment Canada 2009
Diphenylamine	1 000 – 10 000	159 800 – 698 100	2008	Environment Canada 2009
2-naphthyl anthranilate	NR	NR	2011	Environment Canada 2013

Abbreviations: NR, not reported above the DSL IU reporting threshold of 100 kg
[a] Values reflect quantities reported in response to the surveys conducted under section 71 of CEPA. See surveys for specific inclusions and exclusions (schedules 2 and 3).

In Canada, substances in the Aromatic Amines Group are used in various applications for consumer and commercial products and materials. Table 4-2 presents a summary of the major uses for six of the substances in the Aromatic Amines Group according to information submitted pursuant to CEPA section 71 surveys (Environment Canada 2009, 2013). No Canadian uses were reported for 2-naphthyl anthranilate in 2011. In 2000, MBOCA was reportedly used as a curative for castable polyurethane prepolymers as well as in paints and as a catalyst (Environment Canada 2001b). According to the Ontario Ministry of the Environment, Conservation and Parks (OMECP 2019), approximately 84 000 kg and 70 000 kg of MBOCA were used in the province of Ontario in 2011 and 2012, respectively. Data from the National Pollutant Release Inventory (NPRI) in 2017 indicated that MBOCA was released by two companies in Canada, indicating that the substance was being used for processing and manufacturing (NPRI 2018). Additional Canadian uses were identified for some of the substances in the Aromatic Amines Group and are presented in Table 4-3.

Table 4-2. Summary of Canadian uses of substances in the Aromatic Amines Group (on the basis of information submitted pursuant to CEPA section 71 surveys)

Major uses[a]	NDPhA	P1NA	2-aminophenol	44PD	Dimethylaniline	Diphenylamine
Adhesives and sealants	N	N	N	N	Y	Y
Automotive, aircraft and transportation	N	Y	N	Y	Y	Y
Fuels and related products, mixtures or manufactured items	N	N	N	Y	N	N
Lubricants and greases	N	Y	N	Y	N	Y
Medical devices	N	N	Y	N	N	Y
Munitions	Y	N	N	N	N	Y
Paints and coatings	N	N	N	N	Y	N
Plastic and rubber materials not otherwise covered in this table	N	N	N	N	Y	Y
Toys, playground and sporting equipment	N	N	N	N	N	Y
Other[b]	N	Y	N	Y	N	N

Abbreviations: N, no this use was not reported for this substance; Y, yes this use was reported for this substance;
[a] Non-confidential uses reported in response to the surveys conducted under section 71 of CEPA (Environment Canada 2001b, 2009, 2013). See surveys for specific inclusions and exclusions (schedules 2 and 3).
[b] Other refers to minor uses and/or uses that cannot be disclosed as a result of confidentiality claims.

Table 4-3. Additional uses in Canada for certain substances in the Aromatic Amines Group

Use	P1NA	2-aminophenol	Dimethylaniline	Diphenylamine	2-naphthyl anthranilate
Incidental additives[a]	Y	N	N	Y	N
Food packaging materials[a]	N	N	Y	N	N
Notified to be present in cosmetics under the *Cosmetic Regulations*[b]	N	Y	N	N	N
Active ingredient or formulant in registered pest control products[c]	N	N	N	Y (Active)	Y (Formulant)

Abbreviations: Y, yes this use was reported for this substance; N, no this use was not reported for this substance
[a] Personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2017 and September 2018; unreferenced.
[b] Personal communication, email from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated August 2016 and September 2018; unreferenced.
[c] Personal communication, email from the Pest Management and Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated October 2018; unreferenced.

P1NA and diphenylamine may be used in lubricants employed in food processing establishments with no food contact. Dimethylaniline may also be used as a component in fibreglass reservoirs for holding water in food processing establishments with the potential for direct contact with food with negligible exposure (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2017 and September 2018; unreferenced). Diphenylamine is an active ingredient in pest control products and is used as a plant growth regulator in five products used on apples as a treatment to reduce scald during storage (personal communication, email from the Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated October 2018; unreferenced; Health Canada 2017a).

Globally, NDPhA is used as a vulcanization retardant in the production of rubber tires (ATSDR 2017a). It has also been detected by the Washington State Department of Ecology in various products intended for children 12 years and younger including kids'

crafts, toys and games, children's jewellery, baby and children's bedding, clothing as well as footwear (Ecology 2018). NDPhA has been identified as a nitrosamine disinfection by-product in drinking water in Canada and the United States (Zhao et al. 2006).

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC (ECCC 2016b), 2-aminophenol and 2-naphthyl anthranilate are not expected to persist in water, air, sediment or soil.

According to models used in ERC (ECCC 2016b), NDPhA, P1NA, MBOCA, 44PD, dimethylaniline and diphenylamine are expected to persist in water, sediment and soil, but are not expected to persist in air.

5.2 Potential for bioaccumulation

Given their low K_{ow} and low bioconcentration factors (ECCC 2016b), NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, dimethylaniline, diphenylamine and 2-naphthyl anthranilate are not expected to significantly bioaccumulate in organisms.

6. Potential to cause ecological harm

The ecological risks of the substances in the Aromatic Amines Group were characterized using the ecological risk classification of organic substances (ERC) approach (ECCC 2016a). The ERC is a risk-based approach that considers multiple metrics for both hazard and exposure, with weighted consideration of multiple lines of evidence for determining risk classification. The various lines of evidence are combined to discriminate between substances of lower or higher potency and lower or higher potential for exposure in various media. This approach reduces the overall uncertainty with risk characterization compared to an approach that relies on a single metric in a single medium (e.g., median lethal concentration [LC_{50}]) for characterization. The following summarizes the approach, which is described in detail in ECCC (2016a).

Data on physical-chemical properties, fate (chemical half-lives in various media and biota, partition coefficients, and fish bioconcentration), acute fish ecotoxicity, and chemical import or manufacture volume in Canada were collected from the scientific literature, available empirical databases (e.g., OECD QSAR Toolbox 2017), and responses to surveys issued pursuant to CEPA section 71 notices, or they were generated using selected quantitative structure-activity relationship (QSAR) or mass-

balance fate and bioaccumulation models. These data were used as inputs to other mass-balance models or to complete the substance hazard and exposure profiles.

Hazard profiles were based principally on metrics regarding mode of toxic action, chemical reactivity, food web-derived internal toxicity thresholds, bioavailability, and chemical and biological activity. Exposure profiles were also based on multiple metrics, including potential emission rate, overall persistence, and long-range transport potential. Hazard and exposure profiles were compared to decision criteria in order to classify the hazard and exposure potentials for each organic substance as low, moderate, or high. Additional rules were applied (e.g., classification consistency, margin of exposure) to refine the preliminary classifications of hazard or exposure.

A risk matrix was used to assign a low, moderate or high classification of potential risk for each substance on the basis of its hazard and exposure classifications. ERC classifications of potential risk were verified using a two-step approach. The first step adjusted the risk classification outcomes from moderate or high to low for substances that had a low estimated rate of emission to water after wastewater treatment, representing a low potential for exposure. The second step reviewed low risk potential classification outcomes using relatively conservative, local-scale (i.e., in the area immediately surrounding a point-source of discharge) risk scenarios, designed to be protective of the environment, to determine whether the classification of potential risk should be increased.

ERC uses a weighted approach to minimize the potential for both over and underclassification of hazard and exposure, and of subsequent risk. The balanced approaches for dealing with uncertainties are described in greater detail in ECCC (2016a). The following describes two of the more substantial areas of uncertainty. Error with empirical or modeled acute toxicity values could result in changes in classification of hazard, particularly metrics relying on tissue residue values (i.e., mode of toxic action), many of which are predicted values from (Q)SAR models (OECD QSAR Toolbox 2016). However, the impact of this error is mitigated by the fact that overestimation of median lethality will result in a conservative (protective) tissue residue value used for critical body residue (CBR) analysis. Error with underestimation of acute toxicity will be mitigated through the use of other hazard metrics such as structural profiling of mode of action, reactivity and/or estrogen binding affinity. Changes or errors in chemical quantity could result in differences in classification of exposure as the exposure and risk classifications are highly sensitive to emission rate and use quantity. The ERC classifications thus reflect exposure and risk in Canada on the basis of what is estimated to be the current use quantity, and may not reflect future trends.

Critical data and considerations used to develop the substance-specific profiles for the substances in the Aromatic Amines Group, and the hazard, exposure and risk classification results are presented in ECCC (2016b).

The hazard and exposure classifications for the eight substances in the Aromatic Amines Group are summarized in Table 6-1.

Table 6-1. Ecological risk classification results for the eight substances in the Aromatic Amines Group

Common name or abbreviation	ERC hazard classification	ERC exposure classification	ERC risk classification
NDPhA	low	low	low
P1NA	moderate	high	moderate
2-aminophenol	high	low	low
MBOCA	high	low	moderate
44PD	moderate	moderate	moderate
Dimethylaniline	low	low	low
Diphenylamine	moderate	low	low
2-naphthyl anthranilate	low	low	low

Given the low hazard and low exposure classifications according to information considered under ERC, NDPhA, dimethylaniline, and 2-naphthyl anthranilate were classified as having a low potential for ecological risk. It is unlikely that these substances are resulting in concerns for the environment in Canada.

According to information considered under ERC, P1NA was classified as having a high exposure potential on the basis of a long overall persistence and a large annual import quantity according to information submitted pursuant to a CEPA section 71 survey (Environment Canada 2013). P1NA was classified as having moderate hazard on the basis of its potential to cause adverse effects in aquatic food webs given its bioaccumulation potential. P1NA was classified as having moderate potential for ecological risk. Given its overall classification as having a moderate potential for ecological risk, it is unlikely that this substance is resulting in concerns for the environment in Canada. As P1NA is currently being used in high quantities in Canada, fluctuations in use patterns are unlikely to result in a significant increase in risk to the environment. The potential effects and how they may manifest in the environment were not further investigated.

According to information considered under ERC, 2-aminophenol was classified as having low exposure potential. It was classified as having a high hazard potential on the basis of the agreement between reactive mode of action and elevated toxicity ratio, both of which suggest that this chemical is likely of high potency. 2-aminophenol was classified as having a low potential for ecological risk. However, the risk classification was decreased to low potential for ecological risk following the adjustment of risk classification based on current use quantities (see section 7.1.1. of the ERC approach document [ECCC 2016a]). The potential effects and how they may manifest in the environment were not further investigated due to the low exposure of these substances. On the basis of current use patterns, these substances are unlikely to be resulting in concerns for the environment in Canada.

According to information considered under ERC, MBOCA was classified as having low exposure potential. MBOCA was classified as having a high hazard potential on the basis of structural alerts from the OECD Toolbox which identified this substance as

being a potential endocrine receptor binder. MBOCA was classified as having moderate potential for ecological risk. The potential effects and how they may manifest in the environment were not further investigated due tothe low exposure of this substance. On the basis of current use patterns, MBOCA is unlikely to be resulting in concerns for the environment in Canada.

According to information considered under ERC, 44PD was classified as having a moderate exposure potential on the basis of a long overall persistence and a moderate annual import quantity according to information submitted pursuant to a CEPA section 71 survey (Environment Canada 2013). 44PD was classified as having a moderate hazard on the basis of its potential to cause adverse effects in aquatic food webs given its moderate bioaccumulation potential. 44PD was classified as having moderate potential for ecological risk. Given its overall classification as having a moderate potential for ecological risk, it is unlikely that this substance is resulting in concerns for the environment in Canada. On the basis of current use patterns, this substance is unlikely to be resulting in concerns for the environment in Canada.

According to information considered under ERC, diphenylamine was classified as having low exposure potential. Diphenylamine was classified as having a moderate hazard potential due to a moderate potential to cause adverse effects in aquatic food webs given its moderate bioaccumulation potential. Diphenylamine was classified as having a low potential for ecological risk. On the basis of current use patterns, this substance is unlikely to be resulting in concerns for the environment in Canada.

7. Potential to cause harm to human health

7.1 NDPhA (CAS RN 86-30-6)

7.1.1 Exposure assessment

7.1.1.1 Environmental media and food

NDPhA has been identified as a by-product of drinking water disinfection when disinfectants (chlorine, chloramines, etc.) react with naturally occurring substances in water (Zhao et al. 2006). NDPhA was measured in 8 drinking water systems in Canada and the United States. It was detected (method detection limit (MDL) of 0.04 ng/L) in 4 out of 8 collection sites, with concentrations in the distribution system ranging from 0.1 to 1.0 ng/L. Concentrations of NDPhA in the plant influent and effluent were below the method quantification limit (MQL) of 0.12 ng/L (Qian et al. 2015). In another Canadian study that examined the presence of nitrosamines in four locations within one drinking water distribution system, NDPhA concentrations ranged from not detected (MDL of 0.1 ng/L) to 1.86 ng/L (Zhao et al. 2006). The maximum concentration of NDPhA identified in a drinking water distribution system (1.86 ng/L) was used to derive estimated daily intakes to the general population of Canada.

ChemCAN (2003), a level III fugacity model, was used to derive potential environmental concentrations of NDPhA in air and soil in Canada using the upper-end import and manufacturing volume data from Table 4-1 (i.e., 10 100 kg). The estimated concentrations from air and soil were 0.0288 ng/m^3 and 0.105 ng/g, respectively, which were used to derive estimated daily intakes of NDPhA for the general population of Canada.

NDPhA has been detected in processed meats sold in Canada at concentrations below the limit of quantification (LOQ) of 1.24 µg/kg (Scheeren et al. 2015). No other studies reporting concentrations of NDPhA in foods sold in Canada, or elsewhere, have been identified. The LOQ concentration reported in this paper was conservatively used in the derivation of estimated daily dietary intakes of NDPhA for the general population by assuming this concentration is in all luncheon meats, cold cuts and canned meats sold in Canada. Quantitative exposure estimates were derived using consumption data from the Canadian Community Health Survey (CCHS) 2.2 Food Consumption Table (Health Canada 2015b).

Estimated exposures to NDPhA for the general population of Canada from environmental media and food using the information described above resulted in total daily intakes that are considered negligible (i.e., < 2.5 ng/kg bw/day).

7.1.1.2 Products available to consumers

No consumer uses of NDPhA were identified in Canada. However, under the state of Washington Children's Product Safety Act, NDPhA was detected in 80 products intended for children 12 years and younger, including kids' crafts, baby bibs, children's toys and games, children's jewellery, baby and children's bedding, clothing as well as footwear (Ecology 2018). The presence NDPhA in these products was primarily as a contaminant, but it was also present as an antioxidant, colouration/pigment/dye/ink, and manufacturing additive (Ecology 2018). NDPhA was identified as a contaminant in children's clothing by the Washington State Department of Ecology (WSDE) (Ecology 2018), with concentrations less than 100 ppm. NDPhA is listed as a component in the inks/dyes/pigments, metals (including alloys), synthetic polymers or textiles of the clothing (Ecology 2018). It is considered that these products may be present on the Canadian market on the basis of the information obtained from the WSDE. The potential dermal and oral exposures from textiles containing NDPhA were estimated using overalls/bodysuits as the sentinel exposure scenario. It was assumed that clothing for older children and adults might also contain NDPhA as a contaminant, and dermal exposures were therefore considered for all age groups (see Table 7-1). Details on the approach used to estimate exposures can be found in Appendix B.

Table 7-1. Estimated exposures to NDPhA from textiles

Exposure scenario	Maximum concentration (mg/kg)[a]	Estimated acute[b] exposure (mg/kg bw/event)	Estimated daily exposure (mg/kg bw/day)

Full body textiles – 0- to 5-month-olds (dermal)	100	5.56×10^{-4}	5.56×10^{-5}
Full body textiles – 6- to 11-month-olds (dermal)	100	4.95×10^{-4}	4.95×10^{-5}
Full body textiles – 1-year-olds (dermal)	100	4.82×10^{-4}	4.82×10^{-5}
Full body textiles – 2- to 3-year-olds (dermal)	100	4.33×10^{-4}	4.33×10^{-5}
Full body textiles – 4- to 8-year-olds (dermal)	100	3.87×10^{-4}	3.87×10^{-5}
Full body textiles – 9- to 13-year-olds (dermal)	100	3.19×10^{-4}	3.19×10^{-5}
Full body textiles – 14- to 18-year-olds (dermal)	100	2.77×10^{-4}	2.77×10^{-5}
Full body textiles – 19 years and older (dermal)	100	2.53×10^{-4}	2.53×10^{-5}
Mouthing of textile objects – 0- to 5-month-olds (oral)	100	Not applicable	3.17×10^{-7}
Mouthing of textile objects – 6- to 11-month-olds (oral)	100	Not applicable	2.20×10^{-7}
Mouthing of textile objects – 1-year-olds (oral)	100	Not applicable	1.82×10^{-7}
Mouthing of textile objects – 2- to 3-year-olds (oral)	100	Not applicable	1.33×10^{-7}

[a] Ecology 2018
[b] Acute exposure scenario refers to exposure to newly bought unwashed garments

NDPhA was identified by the WSDE as a component in ink/pigment/dye with a chemical function of colouration/pigments/dyes/inks used in toy drawing boards/accessories (Ecology 2018), with concentrations ranging from greater than or equal to 1 000 ppm but less than 5 000 ppm. Based on this information, it was assumed that NDPhA is likely a component in children's marker ink. The potential dermal and oral exposure to NDPhA from use of markers was selected as a sentinel exposure scenario (see Table 7-2). Refer to Appendix B for more details on the derivation of these estimates.

Table 7-2. Estimated exposure for NDPhA from markers

Exposure scenario	Concentration range (% w/w) [a]	Acute exposure (mg/kg bw)	Daily exposure (mg/kg bw/day)
Markers – 1-year-olds (oral/dermal)	0.1 – 0.5	0.0045 – 0.023	2.3×10^{-4} – 1.1×10^{-3}

Markers – 2- to 3-year-olds (oral/dermal)	0.1 – 0.5	0.0033 – 0.017	$1.7x10^{-4}$ – $8.3x10^{-4}$
Markers – 4- to 8-year-olds (oral/dermal)	0.1 – 0.5	0.0022 – 0.01	$1.1x10^{-4}$ – $5.4x10^{-4}$
Markers – 9- to 13-year-olds (oral/dermal)	0.1 – 0.5	0.0012 – 0.0060	$6.0x10^{-5}$ – $3.0x10^{-4}$
Markers – 14- to 18-year-olds (oral/dermal)	0.1 – 0.5	0.0008 – 0.0040	$4.0x10^{-5}$ – $2.0x10^{-4}$
Markers –19 years and older (oral/dermal)	0.1 – 0.5	0.00068 – 0.0034	$3.4x10^{-5}$ – $1.7x10^{-4}$

[a] Ecology, 2018

NDPhA is also used in the production of rubber tires (ATSDR 2017a). Recycled tires may be used as infill or top dressing in sports fields as well as in sport centre and playground surfaces in Canada (AR 2017; Cantin 2009). A study was conducted in New York State to evaluate the potential release of chemicals found in crumb rubber samples to air or to leachate (New York State Department of Environmental Conservation 2009). NDPhA was included in the leachate testing (using the simulated precipitation leaching procedure) and was detected in all 31 leachate samples, with average concentrations ranging from 3.3 to 3.6 µg/L (New York State Department of Environmental Conservation 2009). In another study from the United States, a concentration of 7 ppb (7 µg/L) of NDPhA was measured in field leachate (groundwater collected from shredded tire trench; no further information available) (CIWMB 2007). On the basis of this information, potential exposure to NDPhA from crumb rubber in Canada, including exposures to artificial turf or use of products containing crumb rubber, is considered to be minimal.

7.1.1.3 Biomonitoring information

No Canadian biomonitoring data was identified. NDPhA was measured in the urine of healthy subjects (55 smokers and 57 non-smokers) and in 73 patients with urinary tract infections (UTI) in Taiwan. In healthy non-smokers, it was measured at levels up to 0.28 ng/mL (mean = 0.04 ng/mL). In healthy smokers, it was measured at levels ranging from 0.001 to 0.20 ng/mL (mean = 0.03 ng/mL). In UTI patients, it was measured at levels ranging from 0.005 to 0.11 ng/mL (mean = 0.04 ng/mL) (Hu et al. 2016).

7.1.2 Health effects assessment

NDPhA was reviewed by the IARC (1982), the US EPA Integrated Risk Information System (IRIS) (1987, updated in 2002), the US EPA Provisional Peer-Reviewed Toxicity

Values (PPRTV) assessment (US EPA 2007), the Agency for Toxic Substances and Disease Registry (ATSDR) (1993, addendum in 2010, updated in 2017a) and the Australian Government Department of Health (AGDH) (2017a). The IARC review determined that "NDPhA is not classifiable as to its carcinogenicity to humans" (Group 3) based on limited evidence in experimental animals and no evaluations in humans (IARC 1982). The US EPA IRIS program considered NDPhA as "a probable human carcinogen (Group B2)". These international reviews were used to inform the health effects assessment of NDPhA. A search of the literature from the year prior to the AGDH review (2017a) to February 2019 was conducted, and critical studies of NDPhA conducted after the aforementioned reviews were also considered in this assessment.

7.1.2.1 Repeated dose toxicity

Female F344 rats (10 per dose group and time point) were administered NDPhA via the diet at 0, 250, 1 000, 2 000, 3 000 or 4 000 ppm (equivalent to 0, 15, 60, 123, 183 or 251 mg/kg bw/day) for up to 13 weeks (scheduled necropsy was conducted at day 5, 2 weeks, 4 weeks and 13 weeks). A dose and exposure duration associated increase in the incidence and severity of histopathological changes, such as mixed cell infiltrate and diffuse hyperplasia in the bladder, was observed. The effects occurred during week 4 of exposure in the 123 mg/kg bw/day dose group and during week 2 in the 183 mg/kg bw/day dose group. Significantly increased absolute and relative bladder weights were reported in the top two dose groups (Dodd et al. 2013). A no observed adverse effect level (NOAEL) of 60 mg/kg bw/day was determined based on histopathologic effects observed at 123 mg/kg bw/day (ATSDR 2017a).

A dermal study of NDPhA in mice was identified (Iversen 1980 cited in ATSDR 2017a), but the significance of the results cannot be determined due to the study design and limited information reported.

A short-term, combined repeated-dose and reproductive/developmental screening study was conducted in rats via the oral (gavage) route. Sprague-Dawley (SD) rats (10/sex/dose) were administered the test material containing NDPhA at 0, 15, 50 or 150 mg/kg bw/day for 2 weeks before mating, during mating and, for females, throughout gestation and until day 13 post-partum. A NOAEL of 50 mg/kg bw/day was established based on microscopic findings in the urinary bladder (hyperplasia and single cell necrosis of the urothelium) for males and females, as well as microscopic findings (cardiac atrial thrombosis and hypertrophy) in one female in the highest dose tested (ECHA c2007-2019a).

7.1.2.2 Reproductive and developmental toxicity

In the aforementioned short-term, combined repeated-dose and reproductive/developmental screening study, a NOAEL of 150 mg/kg bw/day for reproductive toxicity was established based on the absence of adverse effects on reproductive performance. A NOAEL of 15 mg/kg bw/day was established for developmental toxicity in the absence of maternal toxicity based on increased

incidences of reduction in live births and viability and increased incidences of clinical signs (generalized pallor, bluish appearance, coldness to the touch, dyspnea, emaciated appearance, absence of milk in the stomach and/or hematoma on the abdomen) in an increased number of litters at the next dose levels compared to control (ECHA c2007-2019a).

7.1.2.3 Genetic toxicity

There are multiple studies that examined the genotoxic effects of NDPhA, but the results were mixed (ATSDR 2017a). NDPhA was not mutagenic in most of the bacterial gene mutation assays (Ames, preincubation) and showed negative results in mouse lymphoma, rat embryo and Chinese hamster V79 cells gene mutation assays (IARC 1982; ATSDR 1993). With regard to clastogenicity of NDPhA, inconclusive results were reported for chromosomal aberrations (Chinese hamster fibroblasts and Don cells), and negative results were reported for micronuclei induction (Chinese hamster ovary cells) (ATSDR 2017a). Assays for DNA damage in rodent and human cells were mainly positive. Mixed (positive and negative) results were reported for sister chromatid exchanges (SCE). In indicator assays for DNA damage (rec assay, differential killing test), NDPhA was mainly negative in bacterial strains (ATSDR 2017a).

With regard to in vivo assays, DNA damage, DNA synthesis inhibition, micronucleus formation and abnormal sperm morphology were negative after exposure of mice and rats to NDPhA (ATSDR 2017a). A negative result was also obtained in a wing-spot test and sex-linked recessive lethal mutation assay with *Drosophila melanogaster* (IARC 1982; ATSDR 2017a).

7.1.2.4 Carcinogenicity

In a chronic study, male and female F344/N rats (50/group) were administered NDPhA in their diet at 0, 1 000 or 4 000 ppm (equivalent to 0, 50, 200 mg/kg bw/day) for 100 weeks. Mortality occurred in 30% of females at the highest dose. A dose-related decrease in body weight compared to controls and a dose-related increase in the bladder epithelial hyperplasia were reported in all treated groups. The bladder transitional-cell carcinomas were observed in the high-dose groups in both sexes of rats (16/45, p=0.001 in males; 40/49, p<0.001 in females). A dose-related increase in fibromas of the integumentary system (i.e., subcutis and skin) occurred in male rats (controls 1/20, low-dose 1/50, high-dose 10/50, p =0.003). Higher incidences of corneal opacity were reported in high-dose males (15/50) and low-dose females (16/50) compared to the controls. However, the study author did not consider the observed opacities to be treatment-related (NCI 1979). A LOAEL of 50 mg/kg bw/day was derived for dose-related decreases in body weights and increases in bladder epithelial hyperplasia (ATSDR 2017a).

Given the uncertainty of the mode of action (MOA) leading to the preneoplastic hyperplasia observed in this study, a default view of a non-threshold linear response was adopted by US EPA PPRTV (2007). An oral cancer slope factor of 4.9 E-3 (mg/kg

bw/day)$^{-1}$ derived by IRIS (US EPA 2002) based on the bladder transitional cell carcinomas observed in this study was considered acceptable by US EPA PPRTV (2007) and was used to address the cancer and hyperplasia risk.

Bladder effects were also observed in mice at higher dose levels. In a chronic dietary study in B6C3F1 mice (50/group), males were administered NDPhA at 0, 1 300, or 2 600 mg/kg bw/day for 101 weeks and females were dosed at 0, 301, or 711 mg/kg bw/day for 98 weeks. Up to 38% of the high-dose females died, while male survival was not significantly affected. In the low-dose groups, an approximately 40% reduction in body weight was reported in females and a 15% reduction was reported in males (no information on body weight changes were reported in the high-dose groups in ATSDR 2017a). A dose-dependent increase in the incidence of bladder submucosal inflammation was significant in all treated groups, while the bladder mucosa epithelial hyperplasia was significant only in high-dose groups (Cardy et al. 1979 cited in ATSDR 2017a).

7.1.3 Characterization of risk to human health

Exposures of the general population of Canada to NDPhA through environmental media and food are expected to be negligible. Canadians may be exposed to NDPhA via the use of products available to consumers predominantly through its presence in children's markers and as a contaminant in textiles such as clothing. Table 7-3 and Table 7-4 provide relevant exposure and hazard levels, as well as the resultant cancer risk and margins of exposure (MOEs).

NDPhA is classified by the US EPA as a Group B2 carcinogen. Studies indicate that the most sensitive effect via oral exposure to NDPhA was urinary bladder lesions in rats, which developed into carcinomas as dose and exposure duration increased. Preneoplastic lesions in the bladder occurred after two weeks of exposure to NDPhA; the urinary bladder transitional-cell carcinomas were formed in rats after long-term exposure.

An oral cancer slope factor (SF) of 4.9 x 10^{-3} (mg/kg bw/day)$^{-1}$ for bladder transitional cell carcinomas derived by US EPA (IRIS 1993) was used to calculate quantitative cancer risk estimates for NDPhA for the Canadian population. The lifetime average daily doses for NDPhA from use of children's markers and textiles were calculated for a range of concentrations (see Appendix C).

Table 7-3. Relevant exposure estimates, cancer slope factor, and cancer risk for NDPhA

Exposure scenario	Lifetime average daily dose (mg/kg bw/day)	Critical effect level (mg/kg bw/day)$^{-1}$	Critical health effect endpoint	Cancer risk value[a,b]
Markers (oral/dermal)	2.3 x 10^{-4}	SF = 4.9 x 10^{-3}	Bladder transitional cell carcinomas	1.1 x 10^{-6}
Full body textiles (dermal)	2.8 x 10^{-5}	SF = 4.9 x 10^{-3}	Bladder transitional cell carcinomas	1.4 x 10^{-7}
Mouthing of textile objects (oral)	9.0 x 10^{-8}	SF = 4.9 x 10^{-3}	Bladder transitional cell carcinomas	4.4 x 10^{-10}

[a] Cancer risk was determined by multiplying the oral slope factor by the lifetime average daily dose.
[b] The LADD is based on the highest concentration identified in markers (5 000 ppm) (see Appendix C).

The cancer risk values from potential exposure to children's markers and textiles containing NDPhA (see table 7-3) were not identified as a concern for human health.

For non-cancer risk estimation, developmental and histopathology effects were identified for short-term and chronic exposure to NDPhA. A developmental NOAEL of 15 mg/kg bw/day from an oral (gavage) combined repeated dose and reproductive and developmental toxicity screening study in adult rats for increased litters with reduced live births and viability observed at higher doses (50, 100 mg/kg bw/day) compared to control was used in the characterization of risk for those of reproductive age (considered to be 9 years and older). For the scenarios in children with the highest exposure estimates, a critical effect that does not consider reproduction was considered more appropriate for risk characterization. A NOAEL of 50 mg/kg bw/day was selected based on histopathological lesions of the bladder and heart reported at 150 mg/kg bw/day in male and female rats from an oral combined repeated dose and reproductive and developmental toxicity screening study (for infants, toddlers and children 8 years and younger).

Table 7-4. Relevant acute/per event exposure estimates and non-cancer hazard values, as well as margins of exposure for the determination of risk

Exposure scenario	Highest exposure (age group)	Critical effect level	Critical health effect endpoint	MOE
Markers (oral/dermal, per event)	0.0045 – 0.023 mg/kg bw/event (1-year-olds)[a]	NOAEL = 50 mg/kg bw/day	Bladder hyperplasia and single cell necrosis (rat; oral (gavage); pre-mating, mating,	2.2 x 10^{3} – 1.1 x 10^{4}

Exposure scenario	Highest exposure (age group)	Critical effect level	Critical health effect endpoint	MOE
			gestation (female), 13 days post-partum (female))	
Markers (oral/dermal, per event)	0.0008 – 0.0040 mg/kg bw/event (14- to 18-year-olds)[b]	NOAEL = 15 mg/kg bw/day	Decreased live births, reduced viability in rat pups (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	3.8×10^3 – 1.9×10^4
Full body textiles (acute dermal)	5.56×10^{-4} mg/kg bw/event (0- to 5-month olds)[a]	NOAEL = 50 mg/kg bw/day	Bladder hyperplasia and single cell necrosis (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	9×10^4
Full body textiles (acute dermal)	2.77×10^{-4} mg/kg bw/event (14- to 18-year-olds)[b]	NOAEL = 15 mg/kg bw/day	Decreased live births, reduced viability in rat pups (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	5.4×10^4
Full body textiles (chronic dermal)	2.53×10^{-5} to5.56×10^{-5} mg/kg bw/day (0- to 5-month olds)[a]	NOAEL = 50 mg/kg bw/day	Bladder hyperplasia and single cell necrosis (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	9.0×10^5 – 2.0×10^6

Exposure scenario	Highest exposure (age group)	Critical effect level	Critical health effect endpoint	MOE
Full body textiles (chronic dermal)	2.77×10^{-5} mg/kg bw/day (14- to 18-year-olds)[b]	NOAEL = 15 mg/kg bw/day	Decreased live births, reduced viability in rat pups (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	5.4×10^{5}
Mouthing of textile objects (oral)	3.17×10^{-7} mg/kg bw/day (0- to 5-month-olds)	NOAEL = 50 mg/kg bw/day	Bladder hyperplasia and single cell necrosis (rat; oral (gavage); pre-mating, mating, gestation (female), 13 days post-partum (female))	$>1.6 \times 10^{8}$

[a] Represents the highest exposure estimates for children (non-reproductive age)
[b] Represents the highest exposure estimates for adults (reproductive age)

The calculated MOEs associated with daily or occasional dermal and oral contact with textiles and children's markers containing NDPhA for non-cancer health effects are considered adequate to address uncertainties in the health effects and exposure databases.

While exposure of the general population to NDPhA is not of concern at current levels, this substance is considered to have a health effect of concern on the basis of its carcinogenicity. Therefore, there may be a concern for human health if exposures were to increase.

7.1.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-5. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Limited environmental monitoring data for NDPhA, so needed to use modelled concentrations for air and soil.	+/-
Limited experimental data on the release of NDPhA from crumb rubber was identified.	+/-
The dermal absorption data for NDPhA is not identified and was considered equivalent to oral absorption.	+
There are no reliable sub-chronic or chronic animal studies for dermal exposure.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.2 P1NA (CAS RN 90-30-2)

7.2.1 Exposure assessment

7.2.1.1 Environmental media and food

No empirical concentration data were identified for P1NA in air, water and soil in Canada or elsewhere. Therefore, ChemCAN (2003), a level III fugacity model, was used to derive potential environmental concentrations of P1NA in Canada using the upper-end import volume data from Table 4-1 (i.e., 1 000 000 kg). The estimated concentrations from air, water and soil were 0.211 ng/m^3, 30.3 ng/L, and 12.7 ng/g, respectively, which resulted in negligible daily intakes (i.e., <2.5 ng/kg bw/day) of the general population of Canada to P1NA.

Exposures of the general population of Canada to P1NA through environmental media are expected to be negligible. No data were identified on the presence of P1NA in food in Canada or elsewhere. Exposure to this substance from food is unlikely and not considered further.

7.2.1.2 Products available to consumers

Products available to consumers that contain P1NA are primarily grease and lubricants (such as transmission fluid) (Environment Canada 2013; HSDB 1983-) with concentrations of P1NA ranging from 0.01% to 3% (Environment Canada 2013; SDS 2013a, 2013b, 2007). P1NA belongs to a subclass of amine antioxidants that are used to prevent the degradation of the materials into which they are added (ECCC, HC 2017). The primary route of exposure to P1NA from use of products available to consumers is expected to be dermal as a result of direct skin contact.

Use of a do-it-yourself (DIY) lubricant was identified as the sentinel scenario. A range of dermal exposures resulting from the use of a lubricant containing P1NA were estimated at 0.00026 to 0.077 mg/kg bw/event for concentrations of 0.01% to 3%, respectively (Environment Canada 2013; SDS 2013a, 2013b, 2007). Parameters used in the model are outlined in Appendix B.

7.2.2 Health effects assessment

P1NA was reviewed by the World Health Organization's International Programme on Chemical Safety (IPCS 1998). This review was used to inform the health effects assessment of P1NA. A search of the literature from the year prior to the IPCS (1998) review to February 2019 was conducted. The critical studies of P1NA conducted after

the aforementioned review were also considered in this assessment. AGDH (2018) had also conducted a Tier I IMAP assessment on a group of chemicals, including P1NA.

Toxicology studies on P1NA not otherwise identified in the public domain were cited from the Registration, Evaluation, Authorisation and Restriction of Chemicals' dossier on this substance (ECHA c2007- 2018).

7.2.2.1 Repeated dose toxicity

Sprague-Dawley rats (5 sex/dose) were administered P1NA via gavage at 0, 4, 20, 100 or 500 mg/kg bw/day for 28 days, followed by a 14-day recovery. Significantly decreased red blood cell counts, hemoglobin concentration, hematocrit and mean corpuscular hemoglobin concentration and significantly increased reticulocyte counts were observed in both sexes in the high-dose groups. Increased blood urea nitrogen and sodium levels in male rats, increased serum total protein, albumin and calcium levels, and increased albumin/globulin ratio in female rats were also reported in the high-dose groups. Increases in relative liver weight in females that received 100 mg/kg bw/day and increases in the absolute and relative liver weights in both males and females that received 500 mg/kg bw/day were observed. In top-dose females, increases in the absolute and relative spleen weights and increases in absolute kidney weight were reported. Hypertrophy of centrilobular hepatocyte and extramedullary hematopoiesis in the spleen were observed in both sexes in the 100 and 500 mg/kg bw/day dose groups. Renal tubular dilatation and papillary necrosis were observed in the highest dose groups in both sexes. A NOAEL of 20 mg/kg bw/day was derived on the basis of increased relative liver weight in females and hypertrophy of centrilobular hepatocyte and splenic extramedullary hematopoiesis in both sexes at 100 mg/kg bw/day (Tanabe et al. 2017).

In another oral study, male and female Wister rats (15/sex/ group) were administered P1NA via gavage at 0, 5, 25 and 125 mg/kg bw/day for 90 days. Neurobehaviour was evaluated in addition to systemic effects. Signs of systemic toxicity, such as degeneration/regeneration of kidney proximal tubules and chronic nephropathy in mid- and high-dose males, and increased absolute and relative liver weights and centrilobular hepatocyte hypertrophy in mid-dose males and high-dose males and females (increased severity with high-dose exposure), were reported. Extramedullary hematopoiesis in the spleens of high-dose females was observed. Regenerative anemia was reported by the authors in high-dose males and females - no incidence data for hematological parameters were presented. No neurobehavioural effects were reported. A NOAEL for systemic effects of 5 mg/kg bw/day in male rats was determined based on observed effects at higher doses (ECHA c2007-2018).

7.2.2.2 Reproductive and developmental toxicity

In a reproductive/developmental toxicity study conducted from July 6, 2010, to July 7, 2011, by the National Institute of Health Sciences of Japan (NIH 2011), male and female SD rats were administered P1NA in the diet at 0, 4, 20 and 100 mg/kg bw/day

from 14 days prior to mating, through the mating period, for 42 days in total for males and from gestation day (GD) 0 to 20 and up to day 4 of the weaning period for females. Hypertrophy of central hepatocytes was observed in both sexes in the high-dose groups. Increased hematopoiesis and brown pigmentation in spleens were reported in high-dose males. Significantly increased relative liver weights were observed in high-dose females while significantly increased absolute and relative liver and spleen weights were observed in high-dose males. A NOAEL of 20 mg/kg bw/day was determined for parental health effects (NIH 2011).

In a prenatal toxicity study submitted to ECHA (c2007-2018), pregnant Wistar rats were administered P1NA at 0, 15, 50 and 150 mg/kg bw/day via gavage from GD 6 to19. Decreased body weight gain and increased regenerative anemia were reported in high-dose dams. Single variations affected some elements of the vertebral column and ribs of high-dose pups at an incidence rate outside the historical control range. Single variations of the vertebral column and ribs of high-dose pups were considered in connection with significant maternal health effects by the authors, but not as an adverse effect. A NOAEL of 50 mg/kg bw/day was determined for maternal health effects (ECHA c2007-2018).

7.2.2.3 Genotoxicity

IPCS (1998) determined that P1NA does not appear to be genotoxic. In vitro, P1NA did not induce chromosomal aberrations in mammalian cells or cause mutagenic reaction in bacteria or mouse lymphoma (L5178Y) cells in tests conducted in the presence or absence of metabolic activation. In the presence of metabolic activation, P1NA was marginally positive in sister chromatid exchange assays with Chinese hamster ovary cells. In an unscheduled DNA synthesis assay with human lung cells, P1NA showed non-concentration dependent positive results. In vivo, P1NA was negative in a dominant lethal test conducted in male mice at dose levels up to 500 mg of P1NA for 5 days (IPCS 1998; NIH 2011).

7.2.2.4 Chronic study

In a dated chronic oral study, bladder tumours (the only organ examined) were not observed in dogs (n=3, control not specified) that were orally administered P1NA at 290 mg/kg bw/day, 5 days per week for up to 3.5 years (DuPont 1945 cited in IPCS 1998).

In a chronic dermal study, approximately 0.75 mg /kg bw of P1NA (dissolved in 50 µl toluene) was applied to the skin of male C3H mice (site not specified) twice per week for 80 weeks. Pigmentation, fibrosis, scar formation and hyperkeratosis were observed on the skin. No increases in the incidence of skin tumours were observed. Histopathological examinations were only performed on the skin (Mobil Oil Corp 1985 cited in IPCS 1998).

7.2.3 Characterization of risk to human health

Exposure of the general population of Canada to P1NA through environmental media is expected to be negligible, and exposure to this substance from food is unlikely. Canadians may be exposed to P1NA from the use of lubricants and greases including transmission fluids.

P1NA does not appear to be genotoxic. Chronic studies of P1NA are limited. The available carcinogenicity studies conducted with the isomer of P1NA did not show evidence of carcinogenicity (IPCS 1998).

There are no reliable dermal toxicity studies available for P1NA. Therefore, the critical health effect levels derived from short-term oral studies were used to calculate the margins of exposure associated with the infrequent uses of products containing P1NA with the assumption of 100% dermal absorption. A developmental study which determined a maternal NOAEL of 50 mg/kg bw/day based on decreased body weight and increased regenerative anemia at 150 mg/kg bw/day in dams (rats, oral, GD 6 to 19, developmental study) is acknowledged. However, the scope of systemic examination was limited. A NOAEL of 20 mg/kg bw/day based on hepatic effects in females from an oral short-term study in rats was used for the risk characterization of dermal exposure to P1NA from use of DIY lubricants and greases.. A comparison of the maximum per-event exposure level of 0.077 mg/kg bw with the NOAEL of 20 mg/kg bw/day resulted in a margin of exposure (MOE) of 260.

The calculated margins of exposure (MOEs) associated with use of DIY lubricants and greases, including transmission fluids, are considered adequate to address uncertainties in the health effects and exposure databases.

7.2.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-6. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
No environmental monitoring data for P1NA was available, so needed to use modeled concentrations for air, water and soil.	+/-
The dermal absorption data for P1NA is unavailable and was considered equivalent to oral absorption.	+
There are no reliable short-term or sub-chronic animal studies for dermal exposure.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.3 2-aminophenol (CAS RN 95-55-6)

7.3.1 Exposure assessment

7.3.1.1 Environmental media and food

No data were identified on the presence of 2-aminophenol in environmental media or food in Canada or elsewhere. Given that 2-aminophenol is not manufactured or imported in Canada in quantities greater than 100 kg (see section 4.0), and taking into account its physical and chemical properties, exposure to this substance from environmental media and food is unlikely and is not considered further.

7.3.1.2 Products available to consumers

Based on notifications submitted to Health Canada under the *Cosmetic Regulations*, 2-aminophenol is used in temporary and permanent hair dyes in Canada at concentrations ranging from 0.1% to 10.5% (personal communications, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, dated September 2018; unreferenced). Estimated dermal and inhalation exposures were derived using ConsExpo Web (2016). Estimated inhalation exposures were considered insignificant in comparison to the dermal exposure estimates. Therefore, only the dermal estimates are presented (see Table 7-7). Refer to Appendix B for details on the parameters used.

Limited dermal absorption studies were identified for 2-aminophenol. For that reason, a dermal absorption factor of 15% was incorporated in the calculation of the dermal exposure estimates based on several lines of evidence described below.

In an in vivo rat study, the percutaneous absorption of hair dye formulations containing radiolabelled 0.8% 2-aminophenol (0.32% concentration on the scalp after mixing with hydrogen peroxide) in hairless rats was investigated (Rougier and Dupuis 1985 cited in SCCS 2010). Human hair was added to some of the rats prior to treatment with the hair dye. The skin was shampooed and rinsed after 30 minutes of exposure on the backs of the animals. Ninety-six hours after treatment, the rats were sacrificed and radioactivity was observed in the epidermis (without stratum corneum), dermis, carcass, urine and feces. Dermal penetration ranged from 2.91 to 4.24 µg/cm^2 depending the conditions tested (Rougier and Dupuis 1985 cited in SCCS 2010). This study was not considered further given the limitations reported in SCCS 2010. In an in vitro study using human breast epidermis, a hair dye formulation containing 2% 2-aminophenol was mixed with 20% hydrogen peroxide, resulting in a final concentration of 1%. The formulation was applied to the dermatomed membranes in the presence or absence of human hair. After 30 minutes, the applications were rinsed off. The penetration of 2-aminophenol was then observed over a 4-hour period and the amount of 2-aminophenol in the receptor fluid was measured at the end of the exposure period. In the absence of hair, 0.24% and 0.04% of the 2-aminophenol applied was measured in the receiving chamber (in two separate experiments). In the presence of human hair, 0.105% and 0.04% of the 2-

aminophenol was measured (in two separate experiments) (Cottin et al. 1989 cited in SCCS 2010).

This study was not considered further due to limitations identified by SCCS.

The dermal absorption of 4-aminophenol, an isomer of 2-aminophenol, was also investigated. 4-Aminophenol is also used in hair dyes at similar concentrations to 2-aminophenol. One in vivo and two in vitro human studies were identified, which reported dermal absorptions of 13%, 7.84% and 6%, respectively (Berufsgenossenschaft der chemischen Industrie 1995; Bristol-Myers Squibb Worldwide Beauty Care Research and Development 1997; University of Newcastle upon Tyne 1999 cited in SCCS 2011). One in vivo rat study and one in vitro rat study were identified, in which dermal absorptions of 0.08% to 0.27% and 10% , respectively, were reported (Hofer et al. 1984; University of Newcastle upon Tyne 1999 cited in SCCS 2011). On the basis of the information from these various studies, and given that 2-aminophenol has a lower water solubility than 4-aminophenol, it is unlikely that the dermal absorption of 2-aminophenol would exceed 15%.

Table 7-7. Estimated dermal exposures to 2-aminophenol from hair dye

Exposure scenario	Concentration range[a]	Estimated dermal exposure[b,c] (mg/kg bw/event)
Temporary hair dye – 4- to 8-year-olds	0.1 – 1%	0.0044 – 0.044
Temporary hair dye – 19 years and older	0.1 – 1%	0.0014 – 0.014
Permanent hair dye – 14- to 18-year-olds	0.1 – 1%	0.016 – 0.16
Permanent hair dye – 19 years and older	0.1 – 1%	0.013 – 0.13
Powder permanent hair dye – 14-to 18-year-olds	10.5%[d]	0.17
Powder permanent hair dye – 19 years and older	10.5%[d]	0.14

[a] Personal communication, emails from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada, September 2018; unreferenced.
[b] The estimated inhalation exposures were insignificant in comparison to the dermal exposures. Therefore, only the dermal exposures are presented.
[c] A 15% dermal absorption factor was applied.
[d] The powder hair dye is diluted with water prior to application. The 10.5% concentration is diluted to approximately 1.1%. Refer to Appendix B.
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7.3.2 Health effects assessment

2-Aminophenol was reviewed by the European Commission's Scientific Committee on Consumer Safety (SCCS) in 2010 (SCCS 2010) and reviewed by the US EPA in 2016.

It was classified as a Category 2 mutagen (Muta Cat 2) in accordance with European Union Regulation (EC) No 1272/2008 (EU 2008). The reviews conducted by US EPA (2016a) and SCCS were used to inform the health effects assessment of 2-aminophenol. A search of the literature from the year prior to the US EPA 2016 review to February 2019 was conducted, and the critical studies of 2-aminophenol conducted after the aforementioned reviews were also considered in this assessment.

7.3.2.1 Repeated dose toxicity

Oral studies

In a limited short-term study, male rats (5/group) were fed diets with 0, 83, or 586 mg/kg bw/day 2-aminophenol for 12 days. Effects observed in the high-dose group included abnormal red blood cell morphology and decreased hemoglobin and hematocrit. Histopathologic changes included hyperkeratosis of the non-glandular portion of the stomach, congestion and hypocellularity of the spleen (Eastman Kodak 1992 cited in US EPA 2016a).

In a short-term study (OECD TG 407), both sexes of SD rats (10 sex/group) were administered 2-aminophenol via gavage at 0, 2, 5 or 15 mg/kg bw/day for 30 days. Reduced body weight gain was observed in high-dose males as well as in all treated females. Significantly increased relative thyroid weight was reported in high-dose females. A NOAEL of 5 mg/kg bw/day was determined by the study authors, although this effect was considered questionable by SCCS (2010) due to a lack of histopathological evidence.

In another 30-day study (OECD TG 407), SD rats (10 sex/group) were administered 2-aminophenol via gavage at 0, 20, 80 or 320 mg/kg bw/day for 30 days. Increased bladder urothelium vacuolization in low- and mid-dose males and females and increased renal tubular lesions in mid- and high-dose males were reported. Increased urinary proteins and increased relative kidney and liver weights were reported in both sexes of the high-dose group. A NOAEL was not established (SCCS 2010).

In a limited 90-day study, male and female SD rats (10/group) were orally administered 2-aminophenol at 0 or 50 mg/kg bw/day as a 1% solution in propylene glycol. No exposure related effects in body weight, hematological or biochemistry parameters were observed. Histopathological examination showed bronchopulmonary injuries. However, the association between this effect and exposure to 2-aminophenol could not be confirmed (SCCS 2010).

Dermal studies

Topical application of a hair dye formula containing 0.15% 2-aminophenol in hydrogen peroxide on the skin of New Zealand White rabbits twice per week for 13 weeks at a dosage of 1 mL/kg bw resulted in no treatment-related effects (SCCS 2010).

7.3.2.2 Reproductive and developmental toxicity

Oral studies

2-Aminophenol was tested for teratogenicity in pregnant SD rats. After exposed to 2-aminophenol at 0, 20, 70, 250 mg/kg bw/day via gavage from GD 6 to 15, brown-coloured urine was reported in all treated dams 24 hours after the first administration. In the high-dose group, reduced body weight gain and decreased food consumption were observed in dams; decreased mean body weight and slight ossification retardation were seen in fetuses. Two fetuses from the same litter showed bilateral anophthalmia (absence of both eyes) in the high-dose group. The anomalies in fetuses were considered by SCCS to be maternal toxicity-related health effects. A NOAEL of 70 mg/kg bw/day for maternal and fetal health effects was determined **(**SCCS 2010).

Dermal studies

In a two-generation dermal study (OECD TG 416), 0.5 ml of a hair dye formula containing 0.15% 2-aminophenol was applied onto the clipped skin of Charles River rats (20/dose group) twice per week during growth, mating, gestation and lactation through to weaning, in all generations (F0 to F2). F0 parents were mated twice and the selected offspring of the second mating became F1 parents. F1 parents were mated twice and selected offspring of the second mating became F2 parents. F2 parents mated 3 times thus producing F3a, F3b and F3c litters. No substance-related systemic changes were observed in parents or pups (Burnett and Goldenthal 1988 cited in US EPA 2016a).

7.3.2.3 Genetic toxicity

In in vitro assays, 2-aminophenol induced gene mutation in TA100 with or without metabolic activation. It also strongly inhibited replicative DNA synthesis in Chinese hamster V79 cells and induced sister chromatid exchanges (SCE) in human fibroblasts and lymphocytes (AGDH 2016; SCCS 2010).

In in vivo tests, 2-aminophenol intraperitoneal treatment resulted in micronucleus formation, but not SCE in the bone marrow of Chinese hamsters. In Swiss mice, a single intraperitoneal injection of 2-aminophenol did not induce significant increases in micronuclei formation or chromosome aberration in bone marrow cells. Moreover, 2-aminophenol did not induce unscheduled DNA synthesis in hepatocytes of male rats after being treated via gavage with 400 or 2 000 mg/kg bw of the substance and examined after 4 or 12 hours of exposure. In addition, 2-aminophenol was not mutagenic in the sex-linked recessive lethal test with *Drosophila melanogaster* (SCCS 2010; AGDH 2016).

7.3.2.4 Carcinogenicity

Based on limited studies performed in rats (0.117% in diet, for 9 months) and mice (0.15%, dermal 21 months), SCCS (2010) and US EPA (2016a) state that there is insufficient information to conclude on the carcinogenicity of 2-aminophenol.

7.3.3 Characterization of risk to human health

No exposure to 2-aminophenol is expected for the general population from environmental media or food. Exposure of the general population in Canada to 2-aminophenol occurs predominantly through the use of hair dyes.

2-aminophenol is a Category 2 mutagen. The available data indicate that it is capable of causing DNA damage and inducing weak mutagenicity in vitro. However, no carcinogenic effects were observed in the limited chronic studies. The critical effects identified following short-term oral exposure to 2-aminophenol include effects in the kidney and liver, as well as body weight and thyroid weight changes.

Because limited dermal toxicity studies were available, the estimated dermal exposures were compared to the critical health effect level derived from an oral study. A NOAEL of 70 mg/kg bw/day was established for maternal and fetal health effects (decreased mean body weight in dams, slight ossification retardation, and bilateral anophthalmia observed at 250 mg/kg bw/day) and was used in the risk estimation.

Table 7-8 provides relevant exposure values and effect levels for critical health effects as well as the resultant margins of exposure (MOEs) for the characterization of risk for 2-aminophenol. It was assumed that both dermal and inhalation exposures are involved during the application of hair dyes. Dermal and inhalation exposures were combined given the lack of route-specific health effect studies. However, the predominant route of exposure is expected to be the dermal route.

Table 7-8. Relevant exposure and hazard values for 2-aminophenol, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure[a]	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE
Temporary hair dye (dermal[b]) (per event)	0.0014 – 0.044 mg/kg bw/event	NOAEL = 70	Decreased mean body weight in dams, at 250 mg/kg bw/day (rats, GD 6-15, oral)	1 600 – 50 000
Permanent hair dye (dermal[b]) (per event)	0.013 – 0.16 mg/kg bw/day	NOAEL = 70	Decreased mean body weight in dams at 250 mg/kg bw/day (rats, GD 6-15, oral)	438 – 5 385
Powdered permanent hair dye (dermal[b]) (per event)	0.14 – 0.17 mg/kg bw/event	NOAEL = 70	Decreased mean body weight in dams, at 250 mg/kg bw/day (rats, GD 6-15, oral)	412 – 500

[a] Range includes exposure to all concentrations for all relevant age groups. A 15% dermal absorption value was applied.
[b] The estimated inhalation exposures were insignificant in comparison to the dermal exposures. Therefore, only the dermal exposures are presented.

The MOEs between critical health effects and the estimated exposures from use of temporary, permanent and powdered permanent hair dyes containing 2-aminophenol are considered adequate to address uncertainties in the health effects and exposure databases.

While exposure of the general population to 2-aminophenol is not of concern at current levels, this substance is considered to have a health effect of concern on the basis of its mutagenicity. Therefore, there may be a concern for human health if exposures were to increase.

7.3.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-9. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Limited dermal absorption data for 2-aminophenol is available. Therefore, a factor based on available information was used.	+/-
No environmental monitoring data for 2-aminophenol, so needed to use modeled concentrations for air, water and soil.	+/-
There are no adequate chronic animal studies for oral, inhalation or dermal exposure.	+/-
Only limited information on the carcinogenicity of 2-aminophenol.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.4 MBOCA (CAS RN 101-14-4)

7.4.1 Exposure assessment

7.4.1.1 Environmental media and food

Measured concentrations of MBOCA in environmental media were not identified in Canada. Data for environmental concentrations of MBOCA in the United States are primarily for locations at or near facilities that once produced MBOCA. MBOCA is not currently produced in the United States and these data are for samples taken many years ago (ATSDR 2017b). Outside North America, MBOCA has been detected, but not quantified, in the Sumida River in Japan (Fishbein 1984 cited in ATSDR 1994). Concentration data from other countries are not relevant to Canada as they pertain to areas where MBOCA is manufactured, and MBOCA is not manufactured in Canada.

MBOCA can be released into air from point sources such as manufacturing and processing facilities (OMECP 2019; ATSDR 2017b). Direct release to soil and water is unlikely except through deposition from air releases near processing facilities or through accidental spills (OECD 2013). If released into water, MBOCA is expected to partition to soil and sediment rather than to water given its relatively low water solubility (13.9 mg/L), estimated log K_{OC} (3.75) and the presence of amine groups, which have an affinity for soil organic matter (ATSDR 2017b; HSDB 2012).

Though not manufactured in Canada, MBOCA may be found in areas near processing facilities (OMECP 2019; NPRI 2018). MBOCA has been reported to the National Pollutant Release Inventory (NPRI) by plastic and rubber product manufacturing facilities (NPRI 2018). Total on-site releases ranged from 2.5 to 4 kg from 2013 to 2017 (NPRI 2018; OMECP 2019). On-site releases are expected to be to air (stack or point sources) on the basis of data provided to NPRI in previous years (2003-2013) as well data from the Toxic Releases Inventory (TRI) in the United States, which reported that MBOCA is released into the atmosphere from manufacturing and processing facilities (US EPA 2019). No discharges to surface water or land were reported (NPRI 2018). As a result, ambient air concentrations around facilities that use MBOCA were estimated using the SCREEN 3 model (SCREEN 3 1996). The results from the tier-one air dispersion model, based on distance from the release source, demonstrate that at

100 m (approximate distance from facility to residential area), daily and annual concentrations from production and manufacturing processes to ambient air were approximately 4.95 x 10^{-5} µg/m^3 and 2.47 x 10^{-5} µg/m^3, respectively. Parameters used in the model are outlined in Appendix A (Table A-1). Estimates of daily and annual intake (µg/kg bw/d) of MBOCA are presented in Appendix A, Table A-2 and Table A-3, respectively.

MBOCA binds to and penetrates the roots of plants grown in MBOCA-contaminated soil (ATSDR 2017b). No data were identified on the presence of MBOCA in food in Canada or elsewhere. Given that MBOCA is not manufactured in Canada and that there is no evidence of MBOCA-contaminated soils in Canada, exposure of Canadians to MBOCA from food is not expected.

7.4.1.2 Products available to consumers

MBOCA is used principally as a curing agent and is incorporated into the stable matrices of the cured polymers. Although trace amounts of unreacted MBOCA may be present in products, an ECHA report noted that, during the hot moulding process MBOCA reacts rapidly with the prepolymer and is consumed in the process, leaving virtually no residual MBOCA in the fully cured product (ECHA 2016). Its high molecular weight and low volatility suggest that the rate of migration of any unreacted MBOCA to the surface of the polymer where consumer exposure would occur is expected to be minimal. The Danish EPA analyzed several products available to consumers, including textile fabrics, textile colourants, glass and porcelain colourants, as well as toys and children's products made of foam plastic, for MBOCA (Danish EPA 2003, 2005, 2006). MBOCA was not detected above the limit of detection in any of these products (LOD of 0.5 mg/kg for fabric textiles, 30 mg/kg for textile, glass and porcelain colourants, and 5 mg/kg for children's foam plastic toys) (Danish EPA 2003, 2005, 2006). On the basis of this information, exposure to MBOCA from use of products available to consumers is not expected.

7.4.2 Health effects assessment

MBOCA was reviewed by the US EPA (2006), the IARC (1993, 2010, 2012), the OECD (SIAP 2013), the National Toxicology Program (NTP 2016), ATSDR (1994, 2017b), the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (SCOEL 2013) and the Committee for Risk Assessment (RAC) of ECHA (ECHA 2017). These reviews provided the basis for the health effects characterization in this assessment. A search of the literature one year prior to the ECHA RAC (2017) review to February 2019 was conducted, and the relevant new information is included in this assessment.

MBOCA was classified as a Group 1 carcinogen (carcinogenic to humans) by IARC (2012) based on inadequate evidence in humans, sufficient evidence in laboratory animals, and strong evidence of genotoxic mechanism of action for the carcinogenicity of MBOCA. This classification was reaffirmed by ECHA in 2017. The European Council

(Regulation 1272/2008) determined that MBOCA was a Category 1B carcinogen (may cause cancer) without a specific concentration limit (ECHA 2017). MBOCA is listed as "reasonably anticipated to be a human carcinogen" by NTP (2016).

7.4.2.1 Reproductive and developmental toxicity

The reproductive/developmental health effects of MBOCA were investigated in a combined repeated dose and reproductive/developmental toxicity screening test in rats. Groups of SD rats (12/sex/dose) were administrated MBOCA at 0, 0.4, 2, 10 and 50 mg/kg bw/day via gavage for 42 days in males, and from 14 days before mating to day 4 of lactation (42 to 52 days) in females. Significantly decreased body weight in dams in the late pregnancy period and significantly prolonged pairing days until copulation were observed in dams in the 50 mg/kg bw/day dose group. MBOCA exposure did not affect other reproductive and developmental parameters. Based on increased pairing days until copulation and altered body weight in dams, a parental NOAEL of 10 mg/kg bw/day was determined by the OECD (2013) for this study.

7.4.2.2 Genotoxicity

The genotoxicity of MBOCA has been extensively evaluated in in vivo and in vitro systems. Evidence indicates that MBOCA and its metabolites are mutagenic and were able to induce DNA adduct formation, DNA damage and cell transformation (IARC 2012).

MBOCA and its n-hydroxylated metabolite are mutagenic in *Salmonella typhimurium* strains TA98 and TA100 in the presence and absence of metabolic activation (Health Canada 2010). MBOCA also induced mutations in human lymphoblastoid cells, stimulated prophage induction in *Escherichia coli* and caused aneuploidy in *Saccharomyces cerevisiae.* It induced unscheduled DNA synthesis in cultured mouse hepatocytes, induced transformation in several mammalian cell cultures, and caused sister chromatid exchange in lymphocytes of rats treated with MBOCA in vivo as well as in cultured Chinese hamster ovary cells in vitro. MBOCA was found to interact with DNA to form adducts in urothelial cells and to induce sister chromatid exchange and micronuclei formation in urothelial cells and lymphocytes of exposed workers (IARC 2012).

There is strong mechanistic evidence indicating that the carcinogenicity of MBOCA involves a genotoxic mechanism of action, including metabolic activation, DNA adduct formation, and induction of mutagenic and clastogenic effects (IARC 2012).

7.4.2.3 Carcinogenicity

7.4.2.3.1 Human studies

A previous investigation conducted in 1971 in 203 current or former workers exposed to MBOCA via dermal and inhalation routes did not identify any evidence of urinary tract

abnormalities (urine sediment cytology) or of risk of cancer of any type when compared with 31 never-exposed subjects (Linch et al. 1971 cited in ATSDR 2017b). These results differ from the bladder-cytology surveys conducted in the United States and Taiwan where bladder cancer cases were identified in exposed workers as well as in occupational accident cases associated with MBOCA exposure (Ward et al. 1988, 1990; Mason and Vogler 1990; Chen et al. 2005). However, the causality between MBOCA exposure and the incidence of bladder cancer cannot be determined due to limitations in these studies (IARC 2012). In a cohort of 308 male workers engaged in the manufacture of polyurethane elastomers using MBOCA in the UK (employed for at least 12 months), there was one bladder cancer death (compared with an expected number of 0.18) and 2 bladder cancer registrations (compared with an expected number of 0.61) for the period 1979 to 2007; the expected values were based on national rates (Dost et al. 2009). The limited human carcinogenicity data did not provide a convincing causal association between bladder tumours and exposure to MBOCA (ECHA 2017).

7.4.2.3.2 Animal studies

MBOCA was tested for carcinogenicity in mice, rats and dogs via the oral route. MBOCA induced bladder tumours in dogs, liver tumours in rats and mice, and hemangiosarcoma, lung, Zymbal gland and mammary gland tumours in rats. The critical studies used by international authorities for the derivation of various reference values are discussed below.

In a study in which the dose–response was best characterized, male Charles River CD rats (50 to 100 per group) were administered MBOCA in their diet for 18 months followed by a 32-week observation period. The rats were exposed to MBOCA in protein-adequate diets (27% protein) at 0, 250, 500, or 1 000 ppm (corresponding to 0, 12.5, 25, or 50 mg/kg) or in protein-deficient diets (8% protein) at 0, 125, 250, or 500 ppm (corresponding to 0, 6.25 12.5, or 25 mg/kg bw/day). The dose was corrected to 9.4, 18.8 and 37.5 mg/kg bw/day for lifetime exposure by the US EPA (2006) There was a significant increase in the incidence of lung tumours in all treated groups (in protein-adequate diet group: 1%, 23%, 37% and 70% for the control, low-, mid- and high-dose groups, respectively; in protein-deficient diet group: 0%, 6%, 15% and 26% for the control, low-, mid- and high-dose groups, respectively). At 500 ppm (25 mg/kg bw/day), significant increases in mortality were observed and body weights were markedly decreased in both types of diet groups. The incidence of mammary adenocarcinomas, hemangiosarcomas and hepatocellular carcinomas (at ≥25 mg/kg bw/day) and of Zymbal gland carcinomas (at ≥12.5 mg/kg bw/day) was also reported and the incidences were significant at the highest dose level (50 mg/kg bw/day). Non-neoplastic lesions, organ weight changes or clinical appearance were not reported (Kommineni et al. 1979 cited in ECHA 2017; ATSDR 2017b). Based on the significant increases in the incidence of lung tumours in all treated rats in the lifetime study, the ECHA RAC (2017) calculated the daily doses that are responsible for 25% tumour incidence (T25) induction in the general population from lifetime exposure to MBOCA. The T25s derived from the lowest dose of 9.4 mg/kg bw/day for lung tumours for oral and inhalation routes of exposure are 2.65 mg/kg bw/day and 4.6 mg/m^3, respectively (ECHA 2017). The US

EPA (2006) had derived an additional quantitative risk assessment for cancer to estimate the probability of a person developing cancer from exposure to MBOCA. An oral unit risk estimate of 0.10 (mg/kg bw/day)$^{-1}$ was calculated based on the combined incidence of lung tumours (adenoma, adenocarcinoma, epidermoid carcinoma) in male rats from an 18-month study.

In a chronic study in dogs, six female beagle dogs (1-year old) were administered MBOCA at 0 or 10 mg/kg bw/day by capsule three days per week for six weeks, and then five days per week thereafter for up to nine years. One dog died after 3.4 years of treatment, due to infection which was unrelated to MBOCA treatment. Histopathology revealed nodular hepatic hyperplasia and disruption of liver structure in three of the five treated dogs but not in controls. A statistically significant increase in serum alanine aminotransferase (ALT) in treated dogs also indicated damage to the liver. Urine sediment cytology revealed abnormalities suggestive of neoplasia of the genitourinary system in dogs after 7 years of treatment. Four of the five treated dogs developed transitional cell carcinomas of the urinary bladder, and one developed transitional cell carcinoma and adenocarcinoma of the urethra ($p < 0.025$, Stula et al. 1977 cited in ECHA 2017; ATSDR 2017b). The liver was considered the most sensitive target organ for non-cancer health effects induced by oral exposure to MBOCA. A LOAEL of 10 mg/kg bw/day was determined for liver health effects (US EPA 2006; ATSDR 2017b). Increased incidences of vascular tumours, and urinary bladder, lung and liver tumours were also reported in mice and rats in other chronic dietary or subcutaneous studies. However, the respective effect dose levels derived from these studies are higher than that of the LOAELs reported by Kommineni et al. (1979) or Stula et al. (1977). Thus, the details of those studies were not discussed further in this assessment.

In addition, the evidence study showed that the intermediate duration of exposure (3 months) to MBOCA could induce degeneration and/or dysplasia of liver, stomach, intestine, and kidney and urinary bladder in mice at higher dose levels (at ≥50 mg/kg bw/day via drinking water; at ≥ 100 mg/kg bw/day via dermal application) (Chen et al. 2014 cited in ATSDR 2017b).

7.4.3 Characterization of risk to human health

The general population in Canada is not likely to be exposed to MBOCA except in instances of populations living in the vicinity of facilities using MBOCA for processing and manufacturing. In such instances, those individuals may be exposed from releases to air.

MBOCA is a multi-organ carcinogen with strong evidence of a genotoxic mechanism of action for its carcinogenicity. It induces bladder tumours in dogs, liver tumours in rats and mice, and hemangiosarcoma, lung, Zymbal gland and mammary gland tumours in rats. An oral cancer slope factor of 0.10 (mg/kg bw/day)$^{-1}$, based on the combined incidence of lung tumours (adenoma, adenocarcinoma, epidermoid carcinoma) in male rats derived by the US EPA (2006), was used to derive quantitative cancer risk estimates for MBOCA for the Canadian population.

The lifetime average daily dose (LADD) for MBOCA to which populations living in the vicinity of facilities using MBOCA for processing and manufacturing could be exposed was determined using the intakes shown in Appendix A, Table A-3. The LADD was determined to be 6.3 x 10^{-9} mg/kg bw/day (see Appendix C). The US EPA (2006) recommended the use of age-dependant adjustment factors (ADAFs) when using the oral cancer slope factor derived for MBOCA for the determination of cancer risk to young children. Accordingly, the ADAFs recommended by the US EPA (2005) were considered and adjusted to the Health Canada age groups (see Appendix C, Table C-4). These factors were then applied to the cancer risk calculation for each age group (see Appendix C). The resulting lifetime cancer risk calculated using the cancer slope factor of 0.10 (mg/kg bw/day)$^{-1}$ and applying the appropriate ADAFs to the exposure estimates is 3.0 x 10^{-8}. The lifetime cancer risk value does not represent a concern for human health for residents within the vicinity of facilities using MBOCA for processing and manufacturing.

For non-neoplastic effects, a LOAEL of 10 mg/kg bw/day for the liver health effect from a nine-year oral dog study was identified. A comparison of the highest estimated daily intake of 3.6 x 10^{-8} mg/kg bw/day for one year-olds (see Appendix A, Table A-1) with the LOAEL of 10 mg/kg bw per day results in a MOE of 2.78 x 10^{8}, which is considered adequate to address uncertainties in the health effects and exposure databases.

While exposure of the general population to MBOCA is not of concern at current levels, this substance is considered to have a health effect of concern on the basis of its carcinogenicity. Therefore, there may be a concern for human health if exposures were to increase.

7.4.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-10. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
No environmental monitoring data for MBOCA was identified.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.5 44PD (CAS RN 101-96-2)

7.5.1 Exposure assessment

7.5.1.1 Environmental media and food

No empirical data were identified for 44PD in air, water or soil in Canada or elsewhere. Therefore, ChemCAN (2003) was used to derive potential environmental concentrations of 44PD in Canada using the upper-end import and manufacturing volume data from

Table 4-1 (i.e., 51 176 kg). The estimated concentrations of 44PD in air, water and soil were 0.0332 ng/m^3, 8.17 ng/L, and 0.638 ng/g, respectively, which resulted in negligible daily intakes (i.e. <2.5 ng/kg bw/day) for the general population of Canada. Exposures of the general population of Canada to 44PD through environmental media are expected to be negligible.

There is no indication of the presence of 44PD in food. Exposure to this substance from food is unlikely and is not considered further.

7.5.1.2 Products available to consumers

Products available to consumers that contain 44PD are primarily lawn trimmer motor oils, with concentrations ranging from 0.10% to 2% (Environment Canada 2013; SDSs 2013c, 2005, 2015a). The primary route of exposure to 44PD from use of lawn trimmer motor oil is expected to be dermal.

A range of dermal exposure to 44PD resulting from a DIY lawn trimmer motor oil change was estimated at between 2.29 x 10^{-3} and 4.58 x 10^{-2} mg/kg bw per event. Parameters used in the model are outlined in Appendix B.

7.5.2 Health effects assessment

There are no national or international reviews available for 44PD. The toxicity information of 44PD submitted to ECHA (ECHA c2007-2019b) was used to inform the hazard assessment. A search of the literature to February 2019 was conducted; the critical studies of 44PD were considered in this assessment.

Multiple toxicology studies on 44PD not otherwise identified in the public domain were cited from the Registration, Evaluation, Authorisation and Restriction of Chemicals' dossier on this substance (ECHA c2007-2019b).

7.5.2.1 Repeated dose toxicity

Both sexes of Wistar rats (5 /group) were administered 44PD at 0, 3, 10, or 30 mg/kg bw/day via gavage for 28 days. An increase in absolute and relative liver weights in both sexes and in the relative weights of the kidney in females were observed in the high-dose group. Treatment-related increases in the incidence and severity of hepatocellular histopathological changes in the liver, such as the homogenous appearance of cytoplasm in the periportal hepatocytes, were observed in the mid- and high-dose groups in both sexes. Significantly increased plasma gamma-glutamyltransferase activity and increased total protein, bilirubin, cholesterol and calcium concentrations were observed in the high-dose females. Increased incidences of focal alopecic areas were also reported in the same dose group. A NOAEL of 3 mg/kg bw/day for hepatocellular histopathological changes was determined (ECHA c2007-2019b).

In another short-term study, both sexes of weanling SD rats (10/sex/groups) were administered 44PD at 0, 10, 25, 50, or 100 mg/kg bw/day via gavage for 28 days. Treatment-related elevations in liver enzyme levels, an indication of hepatotoxic effects of the test compound, were seen at all dose levels. Elevated serum glutamic oxaloacetic transaminase (also known as aspartate transaminase (AST)), serum glutamic pyruvic transaminase, (also known as alanine transaminase (ALT)) and gamma glutamyl transpeptidase (GGTP) levels were reported in high-dose groups. In addition, an increase in AST and ALT was observed in males treated with 50 mg/kg bw/day and in both sexes of rats treated with 10 and 25 mg/kg bw/day. An increase in GGTP was also observed in females treated with 50 mg/kg bw/ day. Absolute and relative liver weights were significantly increased in both sexes in all treatment groups except for the lowest dose groups. Microscopic examination revealed hepatocellular periportal degeneration and necrosis in both sexes at all dose levels. Decreased erythropoietic parameters were reported in both sexes of the high-dose groups. A NOAEL could not be determined for this study. A LOAEL of 10 mg/kg bw/day was derived for treatment-related elevations of liver enzymes levels and hepatocellular lesions (Monsanto 1984).

In a limited dermal study, 0 or 90 mg/kg bw/day of 44PD was applied to the clipped dorsal skin of male rats (3/group, strain not specified) 5 days per week for 2 weeks, irritant effects and ulceration of the skin were observed in the treated rats (ECHA c2007-2019b).

7.5.2.2 Reproductive and developmental toxicity

Groups of male and female Wistar Han rats were orally administered 0, 10, 30, or 60 mg/kg bw/day 44PD by gavage (polyethylene glycol as vehicle) in a study submitted to ECHA (2019b). Rats were dosed daily for 14 days before mating and during mating in males and females, and throughout gestation to day 14 post-partum in females, resulting in durations of 29 days in males and approximately 50 to 54 days in females. Thyroid hormone (T4) levels in male rats were decreased (28%) in a statistically significant manner at 60 mg/kg bw/day; T4 levels in male rats at the low- and mid-dose levels were also decreased, but were within historical controls. Female rats were not observed to have thyroid hormone effects after exposure to 44PD. Hepatic effects, including significant increased absolute liver weight in mid-dose male rats and high-dose male and female rats, increased relative liver weight in mid- and high-dose male (24%, 37%, respectively) and female rats (15%, 27%, respectively), and increased incidence of histopathology (diffuse or periportal hepatocellular hypertrophy) in mid-dose male rats and high-dose male and female rats, were observed compared to controls. In addition, a high-dose male rat was sacrificed in extremis on day 21, where the liver effects (periportal hepatocellular necrosis) were considered the target organ of 44PD treatment. Since the liver was identified as the target organ, the study submitter considered that this death was related to treatment with 44PD. Clinical observations (hunched posture, rales, diarrhea, piloerection) and body weight loss (16% in one week) were also observed. No reproductive or developmental effects were observed after treatment to 44PD. On the basis of the observed mortality at 60 mg/kg bw/day in a male rat, a NOAEL of 30 mg/kg bw/day was determined (ECHA c2007-2019b).

In a developmental (teratogenicity) toxicity study, 44PD was administered to pregnant Wister Han rats by oral gavage at 0, 10, 30, or 60 mg/kg bw/day from GD 6 to 20, at which time a Caesarean section was performed. There was significant loss of body weight and food consumption in the high-dose group on day 9 post-coitum, followed by recovery . Relative mean liver weights were around 23% and 37% higher than the mean of the concurrent controls at 30 and 60 mg/kg, respectively. At 60 mg/kg, the mean number of viable fetuses was significantly lower when compared to the concurrent control mean (9.3 vs 11.4). An increased number of early resorptions were reported in two high-dose females, which were considered to be secondary to maternal effects on the dams. A maternal NOAEL of 30 mg/kg bw/day (organ weights and organ/body weight ratios) was determined. A developmental NOAEL of at least 60 mg/kg bw/day (fetal/pup body weight changes and changes in litter size and weights) in the presence of maternal toxicity was determined (ECHA c2007-2019b).

7.5.2.3 Genotoxicity

In vitro tests indicated that 44PD was not mutagenic, in the presence or absence of metabolic activation, in *S. typhimurium* strains TA97, TA98, TA100 or TA1535 and that it did not induce chromosome aberrations or mutagenic response in Chinese hamster V79 cell line. No in vivo genotoxicity studies for 44PD were identified in the registration dossier (ECHA c2007-2019b).

7.5.2.4 Carcinogenicity

There are no chronic toxicity studies identified for 44PD.

7.5.3 Characterization of risk to human health

Exposure of the general population in Canada to 44PD from environmental media is considered to be negligible and exposure to this substance from food is unlikely. Canadians may be exposed to 44PD during a lawn trimmer motor oil change.

44PD is not mutagenic in either bacteria or mammalian cell lines. The primary targets after repeated dietary exposure to 44PD are the liver and red blood cells. Treatment-related elevations in liver enzyme levels, increased incidence and severity of hepatocellular histopathological changes, and altered red blood cell parameters occurred after short-term (i.e., 28 days) oral exposure to 44PD.

Dermal exposure during lawn trimmer motor oil change was estimated, resulting in a per-event exposure dose range of 2.29E-06 to 4.58E-05 mg/kg bw. No suitable mammalian dermal studies showing systemic effects following a similar exposure pattern were identified on which to calculate an MOE for this exposure scenario. However, a number of short-term studies were considered. A NOAEL of 3 mg/kg bw/day for hepatocellular histopathological changes was determined from a 28-day

gavage study in rats, and a LOAEL of 10 mg/kg bw/day was derived for treatment-related elevations of liver enzyme levels and hepatocellular lesions from another 28-day gavage study in rats. In a limited dermal study, irritant effects and ulceration of the skin were observed in rats after a two week exposure to 44PD on the skin. The effects observed in these short-term studies are not likely to occur after infrequent (i.e., 1 to 2 times per year) dermal exposure to 44PD from use of lawn trimmer motor oil.

Therefore, dermal exposures to small amounts of 44PD occurring infrequently as a result of a lawn trimmer motor oil change are not considered to constitute a risk to human health.

7.5.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-11. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
No environmental monitoring data for 44PD was identified.	+/-
There are no reliable short-term animal studies for dermal exposure.	-
There are no reproductive or developmental toxicity studies.	-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.6 Dimethylaniline (CAS RN 121-69-7)

7.6.1 Exposure assessment

7.6.1.1 Environmental media and food

Dimethylaniline was detected in Lake Ontario in 1986 (no further data found) (IARC 1993). No other information on the presence of dimethylaniline in the environment was identified. Therefore, ChemCAN (2003) was used to derive potential environmental concentrations of dimethylaniline in Canada using the upper-end import and manufacturing volume data from Table 4-1 (i.e., 100 100 kg). The estimated concentrations from air, water and soil were 0.0366 ng/m^3, 14.2 ng/L and 0.882 ng/g, respectively, which resulted in negligible daily intakes (i.e., <2.5 ng/kg bw/day) of the general population of Canada to dimethylaniline.

Dimethylaniline may be used as a component in fibreglass reservoirs for holding water used in food processing establishments with the potential for direct food contact. The estimated dietary exposure for the general population to dimethylaniline from this use is negligible (personal communication, email from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated February 2017; unreferenced).

Exposures of the general population of Canada to dimethylaniline through environmental media and food are expected to be negligible.

7.6.1.2 Products available to consumers

Dimethylaniline was identified in three automotive products available to consumers in Canada, with concentrations ranging from 0.1% to 5% (SDS 2015b, 2017, 2019). The primary routes of exposure to dimethylaniline from the use of these automotive products are expected to be dermal and inhalation. Estimated dermal and inhalation exposures were derived using ConsExpo Web (2016) and are presented in Table 7-12. Refer to Appendix B for details on parameters used.

Table 7-12. Estimated dermal and inhalation exposures to dimethylaniline from use of automotive products

Exposure scenario	Concentration range	Estimated inhalation exposure (mg/kg bw/event)	Estimated dermal exposure (mg/kg bw/event)	Total exposure (mg/kg bw/event)
2-component glue (small project)[a]	2.5%	0.031	0.034	0.065
2-component glue (big project)[d]	2.5%	0.33	0.34	0.67
Body filler (small project)[a,c]	1%	0.0086	0.030	0.039
Body filler (big project)[c,d]	1%	0.16	0.030	0.19
Paint primer (spray)	1%	0.23[c]	0.21[e]	0.44

[a] ConsExpo default.
[b] Assumes the whole bottle of adhesive is used (SDS 2019).
[c] Estimates of exposure for mixing and loading did not impact the final exposures.
[d] Assumes half the can of body filler is used, based on professional judgement (SDS 2015b).
[e] Estimates include both the mixing and loading (0.0068 mg/kg bw) and the application (0.2 mg/kg bw) exposures.

7.6.2 Health effects assessment

Dimethylaniline was reviewed by the IARC in 1993 and was determined to be “not classifiable as to its carcinogenicity to humans” (Group 3). However, the European Union Regulation (EC) No 1272/2008 (EU 2008) considered it to be a Category 2 carcinogen. Dimethylaniline was also reviewed by the US EPA IRIS in 1987 and 2002, and by the US EPA Provisional Peer-Reviewed Toxicity Values (PPRTV) program in 2016. These reviews were used to inform the health effects assessment of dimethylaniline. A search of the literature from the year prior to the US EPA PPRTV (2016b) review to February 2019 was conducted. The critical studies of dimethylaniline performed after the aforementioned reviews were also considered in this assessment.

7.6.2.1 Repeated dose toxicity

Oral studies

As part of the carcinogenicity study of dimethylaniline (NTP 1989), a preliminary study was conducted whereby groups of rats and mice were exposed to 0, 94, 188, 375, 750 or 1 500 mg/kg bw/day dimethylaniline by gavage for 14 days. No organ weight, hematology, clinical chemistry or urine analysis was conducted; histologic examination was conducted in animals from the 94 and 375 mg/kg bw/day groups (3 male, 3 female). High mortality was reported in rats and mice administered 750 and 1 500 mg/kg bw/day, while body weights were observed to be reduced in the 375 mg/kg bw/day (15%) and remaining 750 mg/kg bw/day (47%) male rats compared to control. A dose-related incidence in splenomegaly was reported in rats and mice administered doses of 188 mg/kg bw/day or greater. In addition, extramedullary hematopoiesis and increased hemosiderin were observed in male and female rats and mice administered 375 mg/kg bw/day (NTP 1989). A NOAEL of 94 mg/kg bw/day in rats was determined due to the observed splenomegaly at higher doses (US EPA 2016b).

As part of a series of tests conducted in 1979, groups of male rats (5/dose) were administered 0, 10 or 100 mg/kg bw/day dimethylaniline by gavage 13 times over 17 days. The authors reported enlarged spleens, increased absolute spleen weight and splenic congestion in addition to changes in red blood cell morphology at 100 mg/kg bw/day. Additional hematological effects, including slight decreases in erythrocyte, hematocrit and hemoglobin levels, were also reported at 100 mg/kg bw/day. Methemoglobin was not among the hematology parameters measured. No effects were reported for animals administered 10 mg/kg bw/day (Eastman Kodak 1995). An adjusted NOAEL of 7.7 mg/kg bw/day was calculated based on the number of dosing days (13/17 days), and a NOAEL of 10 mg/kg bw/day was determined for splenic effects observed at 100 mg/kg bw/day (US EPA 2016b).

In a subsequent study, 500 mg/kg bw dimethylaniline was administered via gavage to three rats, and methemoglobin levels in blood were evaluated two and four hours after administration. Methemoglobin levels of 34% and 41.7% were reported two and four hours after administration, compared to negative controls of 1.1% and 0.4%. These

were similar to levels observed for m-dinitrobenzene, a positive control (37.2% and 33.8%, respectively) (Eastman Kodak 1995).

Groups of F344 rats and B6C3F1 mice (10/sex/group) were administered dimethylaniline via gavage at doses of 0, 31.25, 62.5, 125, 250 or 500 mg/kg bw/day for 13 weeks. Decreased body weight gain occurred in male rats at equal to or greater than 250 mg/kg bw/day. Neurobehavioural examination identified decreased motor activity in all treated males and in females treated at equal to or greater than 125 mg/kg bw/day. A dose-related increase in the incidence and severity of enlarged spleen as well as splenic hemosiderosis and hematopoiesis were observed in mice and rats at equal to or greater than 31.25 mg/kg bw/ day. Hemosiderosis was observed in livers, testes and kidneys of treated rats and mice at equal to or greater than 125 mg/kg bw/day (Abdo et al. 1990 cited in IARC 1993). A LOAEL of 31.25 mg/kg bw/day was estimated based on the adverse effects in the spleen; no NOAEL was established (US EPA 1987; AGDH 2017b).

Dermal Studies

Undiluted, 6 or 0.03 g/l dimethylaniline (equivalent to 7, 4 or 0.02 mg/kg) (US EPA 2016b) was applied to clipped skin of New Zealand rabbits (2/sex/dose) for 24 hours under occluded conditions. The researchers evaluated rabbits for viability, clinical toxicity, body weight, hematology (hemoglobin, methemoglobin, hematocrit, erythrocyte count) and gross pathology. An increase in methemoglobin levels in male and female rabbits administered undiluted dimethylaniline was reported (4.6 and 8.3 times higher after exposure, respectively) compared to pre-treatment baseline. Although the methemoglobin levels were lower five days after exposure, levels were still higher (2.2 and 3.3 times in male and female rabbits, respectively) compared to baseline. No effects on hemoglobin, hematocrit or erythrocyte count were reported. No hematological or gross pathology results were reported for rabbits administered 0.02 or 4 mg/kg dimethylaniline (BioDynamics 1982). A NOAEL of 4 mg/kg bw/day was determined based on the effects observed for undiluted dimethylaniline.

Inhalation Studies

A subchronic inhalation study in rats (100 days) was identified by the US EPA (2016b), which presented a NOAEC of 0.0055 mg/m^3 based on hematological effects and clinical chemistry and histological observations in the liver, spleen, brain and lungs at 0.3 mg/m^3. However, the original study was not considered to be reliable by the US EPA because of poor reporting of the methods and results (US EPA 2016b).

7.6.2.2 Reproductive and developmental toxicity

In a limited developmental toxicity test, pregnant CD-1 mice (50/dose) were administered dimethylaniline via gavage at 0 or 365 mg/kg bw/day from GD 7 to 14. No significant health effects were observed in dams or pups (IARC 1993). No reproductive toxicity studies were identified for dimethylaniline.

7.6.2.3 Genetic toxicity

Dimethylaniline did not induce gene mutation in *S. typhimurium* strains TA98, TA100, TA1535 or TA1537 in the presence or absence of metabolic activation (IARC 1993; AGDH 2017b). Negative results were also obtained in an unscheduled DNA synthesis (UDS) assay conducted with rat primary hepatocytes (IARC 1993). However, in the presence of metabolic system, dimethylaniline induced gene mutation in mouse lymphoma L5178Y cell, caused micronucleus formation in Chinese hamster lung (CHL) cells, and induced chromosomal aberrations and SCE in Chinese hamster ovary (CHO) cells (IARC 1993; AGDH 2017b).

In in vivo studies in rats and mice, dimethylaniline increased DNA elution rates in liver cells after intraperitoneal administration but not after gavage administration (AGDH 2017b).

7.6.2.4 Carcinogenicity

In a chronic study, F344/N rats (50/sex/group) were administered dimethylaniline at 0, 3 or 30 mg/kg bw/day via gavage for two years. The incidence of splenic hemosiderosis and hematopoiesis was greater than 85% in all treated groups. However, the severity of these effects was significantly higher only in the high-dose groups. The fibrosis and fatty metamorphosis of the spleen in males and chronic focal inflammation of the liver in females were significantly increased in the high-dose group. The statistically significant increase in splenic tumours in high-dose male rats exceeds the occurrence in historical controls (0/50, 0/50, 3/50 in control, low- and high-dose, respectively; based on analyses for sarcoma or combined sarcoma and osteosarcoma, p = 0.01). This observation was considered by NTP (1989) as treatment-related evidence of carcinogenicity. A LOAEL of 3 mg/kg bw/day for non-neoplastic findings was identified based on increased severity of splenic hemosiderosis in male and female rats. No NOAEL was determined. A provisional oral cancer slope factor of 2.7×10^{-2} (mg/kg bw/day)$^{-1}$ for splenic tumours was derived by the US EPA PPRTV program (2016b).

In another carcinogenicity study, groups of B6C3F1 mice (50/sex/ group) were administered dimethylaniline at 0, 15 or 30 mg/kg bw/day via gavage for two years. The marginally increased incidence of forestomach squamous cell papillomas in high-dose females (p=0.042; 2/50, 2/50, and 8/50 in control, low- dose and high-dose, respectively) was considered as “equivocal evidence of carcinogenic activity” by NTP (1989). The mode of action for dimethylaniline-induced carcinogenicity is not clear. The available studies of dimethylaniline provide evidence for some key events leading to tumour formation in the spleen, with both genotoxic and nongenotoxic events being plausible (US EPA 2016b).

7.6.3 Characterization of risk to human health

Exposure of the general population of Canada to dimethylaniline through environmental media and food is expected to be negligible. Canadians may be exposed to dimethylaniline via the use of automotive products available to consumers.

Dimethylaniline has been classified by the European Union as a Category 2 carcinogen (EU 2008), and by the US EPA as part of the PPRTV process as having “suggestive evidence of carcinogenic potential” (US EPA 2016b). Dimethylaniline has mixed genotoxicity results in vitro, where positive results were observed for several studies of clastogenicity in mammalian cells with metabolic activation. Negative results were reported for bacterial mutagenicity and DNA damage. Although a mode of action has not been elucidated for dimethylaniline (US EPA 2016b), evidence suggests that oral administration to rats, considered as being a more sensitive species, results in lesions in the spleen. In addition, these lesions appear to become neoplastic with increased dose and duration of exposure. Given that exposure through environmental media and food is expected to be negligible and because of the intermittent use patterns of the identified products, the cancer risk for dimethylaniline was not characterized.

For the risk estimation of non-cancer endpoints, an adjusted NOAEL of 7.7 mg/kg bw/day for splenic congestion and increased spleen weight at 100 mg/kg bw/day from a short-term oral rat study was used. Male and female rabbits dermally exposed to undiluted dimethylaniline for 24 hours were observed to have increased methemoglobin levels after exposure as well as after 5 days of recovery compared to levels before treatment; no other hematology parameters were affected. A NOAEL of 4 mg/kg bw/day was estimated based on methemoglobin response to undiluted dimethylaniline treatment. The results from this dermal study are considered supportive of the results observed in the oral study, as methemoglobin was not measured as part of the hematology evaluation. These erythrocyte and spleen effects were observed in multiple species, where splenic effects were considered adverse in chronic oral studies in rats and mice. Effect levels are noted to decrease with increased duration of exposure.

Table 7-13 provides relevant exposure values and effect levels for critical health effects as well as the resultant margins of exposure (MOEs) for the characterization of risk for dimethylaniline. It was assumed that both dermal and inhalation exposures are involved during the use of the automotive products. Dermal and inhalation exposures were combined given the lack of route-specific health effect studies.

Table 7-13. Relevant exposure and hazard values for dimethylaniline, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE
2-component glue	0.065 – 0.67 mg/kg bw/event (small project – big project)	NOAEL = 7.7	Splenic congestion and increased spleen weight (rat; oral (gavage); dosed 13/17 study days)	11 – 118
Body filler	0.039 – 0.19 mg/kg bw/event (small project – big project)	NOAEL = 7.7	Splenic congestion and increased spleen weight (rat; oral (gavage); dosed 13/17 study days)	41 – 197
Spray paint primer	0.44 mg/kg bw/event	NOAEL = 7.7	Splenic congestion and increased spleen weight (rat; oral (gavage); dosed 13/17 study days)	18

The calculated MOEs associated with occasional dermal and inhalation contact with dimethylaniline in automotive products for non-cancer health effects are considered potentially inadequate to address uncertainties in the health effects and exposure databases.

7.6.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-14. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Limited environmental monitoring data for dimethylaniline.	+/-
The available developmental toxicity study is limited; no reproductive toxicity study available.	-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk

7.7 Diphenylamine (CAS RN 122-39-4)

7.7.1 Exposure assessment

7.7.1.1 Environmental media and food

No empirical data were identified for diphenylamine in air, water or soil in Canada or elsewhere. Therefore, ChemCAN (2003) was used to derive potential environmental concentrations of diphenylamine in Canada using the upper-end import and manufacturing volume data from Table 4-1 (i.e., 708 100 kg). The estimated concentrations from air, water and soil were 0.262 ng/m^3, 47.9 ng/L, and 7.1 ng/g, respectively. The estimated daily intakes for diphenylamine for the general population of Canada from environmental media ranged from 1.92×10^{-5} µg/kg bw/day for breast-fed infants to 6.30×10^{-3} µg/kg bw/d for formula-fed infants (see Appendix A, Table A-2).

Diphenylamine was identified as a naturally occurring volatile in various food items, including onions, buckwheat, celery, cheese, chicken, citrus fruits, clams, coriander seeds, fenugreek, kiwifruit, lemon balm, potatoes, sweet grass oil, and tea (Nijssen et al. 1963-2018). Quantitative data were only available for onions (23 ppm), cheese (0.06 ppm) and tea (0-1.5 ppm) and were used to estimate potential exposures to diphenylamine from food for the general population of Canada. Exposure to diphenylamine based on its natural occurrence in foods is expected to have a negligible contribution to overall dietary exposure. As a registered pest control product for post-harvest treatment of apples in storage, dietary exposure to diphenylamine is not of concern under the current conditions of use (i.e., anti-scalding products for apples) (Health Canada 2017a; personal communication, emails from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated December 5, 2018 to February 5, 2019; unreferenced).

7.7.1.2 Products available to consumers

Uses of diphenylamine identified in Table 4-2, such as toys, playground and sporting equipment, adhesives and sealants, plastic and rubber materials, inner liners and tubes for tires, are expected to be limited to industrial applications (as stabilizers and/or antioxidants during production and storage of polymers to prevent undesirable polymer chain scission) that would not result in exposure to the Canadian general population (Environment Canada 2009).

Products available to consumers that contain diphenylamine are motor and engine oils (SDS 2009, 2010, 2010b), transmission fluid (SDS 2011, 2015) and high-mileage oil filters (SDS 2014). The primary route of exposure to diphenylamine from use of these products is expected to be dermal. A sentinel scenario for dermal exposure was developed for chainsaw and lawn trimmer motor oils with concentration of diphenylamine ranging from 0.1% to 1.5% (SDS 2009, 2010, 2010b).

A range of dermal exposures to diphenylamine resulting from a DIY gas chainsaw and lawn trimmer motor oil change was estimated at between 0.087 and 1.30 mg/kg bw per event. Parameters used in the model are outlined in Appendix B.

7.7.2 Health effects assessment

Diphenylamine has been reviewed by the US EPA (1998, 2005, and 2011a), the European Commission (EC 2008), the European Food Safety Authority (EFSA 2012), and Health Canada's Pest Management and Regulatory Agency (PMRA) (Health Canada 2017a). These reviews were used to inform the health effects assessment of diphenylamine. A search of the literature from the year prior to the Health Canada (2017) review to February 2019 was conducted, and the critical studies of diphenylamine conducted after the aforementioned reviews were also considered in this assessment.

7.7.2.1 Repeated dose toxicity

The diphenylamine-induced health effects were investigated in 90-day oral studies in rats, mice and dogs, and in a 1-year study in dogs. Effects on the spleen and red blood cells were identified as targets when diphenylamine is administered orally in the three animal species. Diphenylamine was also found to interfere with normal liver function in rats and dogs.

Oral studies

Both sexes of Swiss-derived CD-1 mice (15/group) were administered diphenylamine in the diet at 0, 10, 525, 2 625 or 5 250 ppm for 90 days (equivalent to doses of 0, 1.7, 94, 444 and 926 mg/kg bw/day for males and 0, 2.1, 107, 555, and 1 101 mg/kg bw/day for females). Statistically significant increased incidences of splenic congestion and hemosiderosis occurred in females at 107 mg/kg bw/day and in males at 444 mg/kg bw/day. Dose-related increases in the incidence and severity of the lesions in the spleen and extra-medullary hematopoiesis in the liver were observed. Dose-related alteration in red blood cell parameters and dose-related increases in liver and spleen weights were statistically significant in the top two dose groups compared with controls. Increased absolute kidney weight (males only at 926 mg/kg bw/day) and relative kidney weight (females only at 1 101 mg/kg bw/day) as well as decreased ovary weight in female mice at 107 mg/kg bw/day were observed. Therefore, a NOAEL of 2.1 mg/kg bw/day in female mice for statistically significant increased incidences of congestion and hemosiderosis in the spleen was determined (Botta 1992 cited in EC 2008 and US EPA 2011a).

SD rats (10/group) were administered diphenylamine in the diet at 0, 150, 1 500, 7 500 or 15 000 ppm for 90 days (equivalent to doses of 0, 9.6, 96, 550 and 1 200 mg/kg bw/day for males and 0, 12, 110, 650 and 1 300 mg/kg bw/day for females). Significantly decreased erythrocyte counts and hemoglobin values occurred in the top

two dose groups compared to the controls. The hematocrit values were significantly lower than those of controls in females in the top three doses groups. In males, dose-related increases in absolute and relative liver and spleen weights and in relative kidney and testes weights became significant at the top two dose levels. Dose-related increases in absolute and relative liver weights were also seen in treated females. Histopathological examination revealed an increased incidence of hematopoiesis and pigment in the liver, hematopoiesis, hemosiderosis, and congestion in the spleen, and pigmented kidneys in the top two dose groups in both sexes of rats. Therefore, a NOAEL of 12 mg/kg bw/day in female rats was determined for a significantly decreased hematocrit and red blood cell effects, organ weights and histopathological changes in both sexes at higher doses of diphenylamine (Krohmer 1992a cited in EC 2008).

Beagle dogs (4 sex/group) were administered diphenylamine in gelatine capsule at 0, 10, 25, or 100 mg/kg bw/day for 52 weeks. Hematological examination revealed decreased erythrocyte counts hemoglobin and hematocrit in high-dose males; smaller decreases in these parameters were found in females. The dose-related increase in the platelet count in males and in mean total bilirubin concentration (in both sexes) became statistically significant in the mid- and high-dose groups. A statistically significant increase in mean cholesterol concentration was only observed in high-dose males and females. The blood urea nitrogen concentration was decreased in females in the mid- and high-dose groups. A dose-related increase in absolute liver weights in males was significant only in the high-dose group. There were no treatment-related histopathological changes. A NOAEL of 10 mg/kg bw/day was determined by EC (2008) for altered clinical chemistry parameters in both sexes of dogs (unpublished; Botta 1994c cited in EC 2008 and Botta 1994a cited in US EPA 2011a).

Dermal studies

New Zealand white rabbits (5 sex/group) received repeated dermal applications of diphenylamine on clipped skin (at about 10% of the body surface area) at 0, 100, 500 or 1 000 mg/kg bw/day, 6 hours per day for 21 days under occluded conditions. A NOAEL of 100 mg/kg bw/day for systemic effects was determined based on a dose-dependent increase in the frequencies of dark-red foci in the stomach in mid- and high-dose males and females (Siglin 1992 cited in EC 2008).

In a 90-day dermal study, SD rats were treated with diphenylamine at 0, 500 or 2 000 mg/kg bw/day for five days per week. All treated animals exhibited dermal hyperplasia at the application site. A NOAEL of 500 mg/kg bw/day for systemic toxicity was determined based on an increase in the relative kidney weights in the high-dose males (Mobil Oil Corp 1994 cited in EC 2008).

Because the dark-red foci in the stomach reported in the 21-day rabbit study were not observed in rats at the same dose level in a longer term (90 days) study, the European Commission's Scientific Committee on Health and Environmental Risks (SCHER) selected the NOAEL of 500 mg/kg bw/day for kidney weight effects derived from the 90-day study in rats to characterize the risk from dermal exposures to diphenylamine

(SCHER 2008). A recent draft human health risk assessment conducted by the US EPA also considered the stomach findings in the 21-day rabbit study by Siglin (1992) unrelated to treatment with diphenylamine, as the foci were not observed in other studies, species or routes of exposure (US EPA 2018).

7.7.2.2 Reproductive and developmental toxicity

Pregnant SD rats (25/group) received diphenylamine via gavage at 0, 10, 50 or 100 mg/kg bw/day from GD 6 to 15. Increased weights, size and pigmentation of the spleen occurred in high-dose treated dams. No developmental health effects were seen at any dose level (NOAEL maternal = 50 mg/kg bw/day; unpublished study by Rodwell 1992 cited in US EPA 2011). A similar study conducted in pregnant rabbits did not identify any treatment-related effects at oral doses up to 300 mg/kg bw/day, except for a green discolouration in urine in all treated animals (Edwards et al. 1983 cited in EC 2008 and Edwards et al. 1983b cited in US EPA 2011a).

In a two-generation study, SD rats (28 /group) were administered diphenylamine in their diet at 0, 500, 1 500 or 5 000 ppm (equivalent to doses of 0, 40, 115 or 399 mg/kg bw/day for males and 0, 46, 131 or 448 mg/kg bw/day for females). Enlarged and congested spleens, spleen hemosiderosis, hepatocytic hypertrophy, and pigmentation in kidneys, livers and spleens were reported in the mid- and high-dose parent rats. Decreased litter size in F1 and F2 generations occurred in high-dose groups, but the effect was significant only for the F2 litters. Significantly decreased body weights in F2 pups during lactation were reported in the mid- and high-dose groups. Both paternal and developmental NOAEL values of 40 mg/kg bw/day were determined for gross and histologic effects observed in the spleen, liver and kidney, as well as pup weight effects, respectively. A reproductive NOAEL of 115 mg/kg bw/day in male rats was determined based on decreased litter size (unpublished study by Rodwell 1993 cited in US EPA 2011a).

7.7.2.3 Genotoxicity

Diphenylamine did not induce unscheduled DNA synthesis, DNA single strand breaks, sister chromatid exchange (SCE) or micronucleus formation in in vitro systems. It was not mutagenic to various *S. typhimurium* or *E. coli* strains (US EPA 2011). Although a potential of causing micronuclei formation in human cells was reported by Santovito et al. (2012), diphenylamine is generally unlikely to be mutagenic or genotoxic in the testing systems examined (US EPA 2011a).

Available in vivo genotoxicity studies indicate that diphenylamine did not induce chromosomal aberration or micronucleus formation in rats after oral or dermal exposure. In addition, diphenylamine did not induce SCE or micronuclei formation in mice after oral or intraperitoneal administration (EC 2008).

7.7.2.4 Carcinogenicity

Chronic exposure to diphenylamine via the oral route did not induce treatment-related tumours in animals. The target organs for chronic exposure to diphenylamine are the hematological system, liver, spleen and kidney (Health Canada 2017a; US EPA 2011a). The lowest NOAEL of 2.5 mg/kg bw/day derived from a two -year dog study on the basis of growth retardation and organ weight alterations was used by Health Canada (Health Canada 2017a) for the calculation of an acceptable daily intake value (ADI) for dietary exposure to diphenylamine from pest control products.

In a chronic study, Beagle dogs (2/sex/group) were administered diphenylamine at 0, 0.01, 0.1 or 1.0% (equivalent to 0, 2.5, 25 and 250 mg/kg bw/day) in the diet for two years. After one year of exposure, the mid- and high-dose groups had marked growth retardation and developed dose-dependent changes in red blood cell parameters. At the end of the study, the high-dose groups showed moderate liver damage in a liver function test and a moderate decrease in resistance of erythrocytes to hypotonicity. Increased liver weights along with perilobular fatty changes, increased lipid content, hemosiderosis of the spleen, kidneys and bone marrow, and slightly increased kidney weights were reported in high-dose groups. A NOAEL of 2.5 mg/kg bw/day was determined on the basis of growth retardation and changes in red blood cell parameters at 25 mg/kg bw/day, increased liver and kidney weights, and histopathological changes at 250 mg/kg bw/day (Thomas et al. 1967b cited in EU 2008 and Thomas et al. 1967a cited in US EPA 2011a). Similar health effects occurred in mice at higher dose levels (≥ 370 mg/kg bw/day) after chronic (78 weeks) dietary exposure (Botta 1994c cited in US EPA 2011a).

Albino rats (20/sex/group) were administered diphenylamine at 0, 0.001%, 0.01%, 0.1% 0.5% or 1% in the diet (equivalent to 0, 0.5, 5, 50, 250 and 500 mg/kg bw/day) for two years. Significant growth retardation accompanied by reduced feed consumption occurred in the top two dose groups in both sexes. Slightly reduced hemoglobin levels and erythrocyte counts and increased numbers of circulating normoblasts (red blood cell precursors) were seen in the 500 mg/kg bw/day dose groups. Rats in the 50 and 250 mg/kg bw/day dose groups exhibited signs of dilated renal tubules as well as chronic interstitial nephritis (the effects were not discussed for the highest dose groups). The US EPA did not derive a NOAEL due to limited reporting of study results (US EPA 2011a). In addition, the reported kidney lesions were considered by the author as not being a treatment-related effects (DeEds, short version 1963 cited in EC 2008 and DeEds 1963b cited in US EPA 2011a).

Similar health effects, such as altered hematological parameters and histopathological changes in the spleen, liver, and kidneys were also reported by other chronic oral studies, but at much higher dose levels, and were therefore not discussed in this assessment.

No chronic inhalation or dermal studies were identified. Some occupational studies were available. However, these were limited by the inability to distinguish the effects of exposure to a number of different chemicals in the industry (US EPA 2011a).

7.7.3 Characterization of risk to human health

Exposure of the general population in Canada to diphenylamine may occur from environmental media and from food as a result of its use as an anti-scalding agent in apples and, to a lesser extent, its natural presence in certain food items. Canadians may also be exposed to diphenylamine from the use of motor oils used in gas-powered chainsaws and lawn trimmers.

Diphenylamine is unlikely to be mutagenic or genotoxic and it is not expected to be carcinogenic. The available reproductive and developmental toxicity studies indicate that the observed diphenylamine treatment-induced reproductive and developmental effects occur at levels that cause health effects in parental animals. The primary target organs after short-term and long-term dietary exposure to diphenylamine are the blood system, kidneys, spleen and liver. The lowest NOAEL for chronic exposure was determined to be 2.5 mg/kg bw/day from a two -year study. A NOAEL of 500 mg/kg bw/day from a short-term dermal study based on increases in kidney weights in laboratory animals at the next dose tested was considered the most relevant endpoint for assessment of risk from short-term dermal exposure to diphenylamine.

Table 7-15 provides relevant exposure and hazard values, as well as the resultant MOEs for the determination of risk for diphenylamine.

Table 7-15. Relevant exposure and hazard values for diphenylamine, as well as margins of exposure, for determination of risk

Exposure scenario	Systemic exposure (age group)	Critical effect level (mg/kg bw/day)	Critical health effect endpoint	MOE
Environmental media (daily)	6.30 x 10^{-6} mg/kg bw/day (formula fed infants)	NOAEL = 2.5 mg/kg bw/day	Growth retardation and anemia at 25 mg/kg bw/day (dogs, two years, oral)	> 397 000
Do-it-yourself gas chainsaw and weed eater motor oil change (per event)	0.087 to 1.30 mg/kg bw (adult)	NOAEL= 500 mg/kg bw/day	Increased relative kidney weight in males at 2 000 mg/kg bw/day (rat, 90day, dermal)	>385

The calculated MOEs associated with environmental media and with the occasional uses of diphenylamine-containing gas chainsaw and lawn trimmer motor oils are considered adequate to address uncertainties in the health effects and exposure databases. In addition, based on an analysis conducted by the Pest Management Regulatory Agency, potential dietary exposure from use of diphenylamine in pest control products is not expected to be of concern (Health Canada 2017a).

7.7.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-16. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
Limited environmental monitoring data for diphenylamine.	+/-
Uncertainty in regards to whether presence of diphenylamine in certain food items is indeed as a result of naturally occurrence.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7.8 2-Naphthyl anthranilate (CAS RN 63449-68-3)

7.8.1 Exposure assessment

7.8.1.1 Environmental media and food

No environmental media data were identified on the presence of 2-naphthyl anthranilate in Canada or elsewhere. It is not manufactured or imported in Canada in quantities greater than 100 kg (see section 4.0) and, given its physical and chemical properties, exposure to this substance from environmental media is not expected.

2-Naphthyl anthranilate may be used as a flavouring agent in baked goods, chewing gum, frozen dairy, gelatins/puddings, non-alcoholic beverages, hard candy and soft candy (Burdock 2010).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated a group of 19 anthranilate derivatives, including 2-naphthyl anthranilate, for use as food flavouring agents (JECFA 2006b). As part of that evaluation, it estimated the per capita intake of 2-naphthyl anthranilate from its use as a food flavouring agent to be 2 µg/day for the US population using a maximized survey-derived daily intake (MSDI) approach that is based on annual production volumes reported by the food industry in poundage surveys (Lucas et al. 1999; NAS 1982 as reported in JECFA 2006b). The estimated per capita intake for European countries is 1.3 µg /capita/day (EFSA 2011). In the absence of data on the actual use, if any, of 2-naphthyl anthranilate as a food flavouring agent in foods sold in Canada, the JECFA per capita intake estimate for the US population is an acceptable estimate of possible Canadian dietary exposure to this substance from this use in food.

7.8.1.2 Products available to consumers

2-Naphthyl anthranilate was not identified in any products available to consumers in Canada.

7.8.2 Health effects assessment

As a food flavouring agent, the safety of 2-naphthyl anthranilate was previously reviewed by JECFA (WHO 2006a) and EFSA (2008, 2011) as part of the anthranilate derivatives group, based on the assumption that the substances within this group should have some metabolic and biological behaviour in common. A search of the literature from the year prior to the EFSA (2011) review to February 2019 was conducted. No toxicity studies were identified for 2-naphthyl anthranilate. The relevant information for anthranilate derivatives obtained from the aforementioned international review by JECFA was used to inform the health effects assessment of 2-naphthyl anthranilate.

As an anthranilic acid ester, 2-naphthyl anthranilate is expected to be readily absorbed, in either unchanged or hydrolyzed form. Once absorbed, the unchanged esters are hydrolysed hydrolyzed in the liver to form their corresponding alcohols and carboxylic acids (anthranilic acid, N-methylanthranilic acid, N-ethylanthranilic acid or N,N-dimethylanthranilic acid). These anthranilic acid derivatives are then rapidly excreted in the urine (WHO 2006a). According to WHO (2006a), all the food flavouring agents in this group are expected to be metabolized to innocuous products.

The available LD_{50} values for anthranilate derivatives indicate that the oral acute toxicity of this group of substances is low (WHO 2006b).

Limited information of 10 substances in the anthranilate derivatives group indicate that the food flavouring agents in this group present no significant genotoxic potential (WHO 2006b).

There were no carcinogenicity studies available for the anthranilate derivatives group. The information of anthranilic acid, an analogue of anthranilate derivative, was discussed by WHO (2006b), and the substance was determined by the committee as not carcinogenic.

7.8.3 Characterization of risk to human health

For 2-naphthyl anthranilate, chemical-specific empirical hazard data were lacking. The exposure of 0.03 µg/kg bw per day to 2-naphthyl anthranilate that was derived by JECFA for the US population is a suitable estimate of possible average lifetime exposure for the Canadian population from use as a food flavouring agent. Given the lack of hazard information and the low exposure estimates, the threshold of toxicological concern (TTC)-based approach was deemed to be relevant and was adopted accordingly (Health Canada 2016). The TTC value of 0.0015 mg/kg bw/day was assigned on the basis that the chemical structure of 2-naphthyl anthranilate is a Cramer Class III substance (OECD QSAR Toolbox 2016) and given the overall negative genotoxicity. Therefore, as exposure was less than the TTC value, 2-naphthyl anthranilate was not considered to be a concern for human health at current levels of exposure.

7.8.4 Uncertainties in evaluation of risk to human health

The key sources of uncertainty are presented in the table below.

Table 7-17. Sources of uncertainty in the risk characterization

Key source of uncertainty	Impact
No empirical hazard data for 2-naphthyl anthranilate.	+/-

+ = uncertainty with potential to cause over-estimation of exposure/risk; - = uncertainty with potential to cause under-estimation of exposure risk; +/- = unknown potential to cause over or under estimation of risk.

7. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to the environment from NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, dimethylaniline, diphenylamine and 2-naphthyl anthranilate. It is proposed to conclude that the eight substances in the Aromatic Amines Group 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.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that dimethylaniline meets the criteria under paragraph 64(*c*) of CEPA as it is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of the information presented in this draft screening assessment, it is proposed to conclude that NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, diphenylamine and 2-naphthyl anthranilate 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 proposed to conclude that dimethylaniline meets one or more of the criteria set out in section 64 of CEPA and that NDPhA, P1NA, 2-aminophenol, MBOCA, 44PD, diphenylamine and 2-naphthyl anthranilate do not meet any of the criteria set out in section 64 of CEPA.

It is also proposed to conclude that dimethylaniline meets the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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Appendix A. Estimates of air concentrations around point source facilities and daily intake by various age groups within the general population of Canada

The simple terrain option in the SCREEN3 model was selected and input parameters in to the model are outlined in Table A-1 below.

Table A-1. Parameters used in SCREEN3 to estimate air concentrations around point source facilities that use MBOCA in production and manufacturing processes

Variables	Inputs
Source type	Area
Emission rate (g/m2.s)[a]	$0.73x10^{-11}$
Source release height (m)[b]	2.5
Effective emission area[b]	135m x 90m
Receptor height (m)[c]	1.74
Adjustment factor for yearly exposure[d]	0.2
Adjustment factor for daily exposure[d]	0.4
Urban/rural option	Urban
Anemometer height[e]	10m
Momentum and buoyancy fluxes[e]	0.00 m^4/s^2
Meteorology[e]	1 (full meteorology)
Minimum and maximum distance to use[f]	10 – 1 000m

[a] Estimated based on quantities reported by facilities under NPRI, assuming continuous release (NPRI 2018)
[b] Professional judgement based on aerial photo analysis
[c] Curry et al (1993)
[d] US EPA (1992)
[e] Default value in SCREEN3 (1996).
[f] Terrain height of 0 m above stack base was used for the distances.

Based on aerial photo analysis, residential area was estimated to be 100 m away from source facility. The modelled air concentration at 100 m is 0.1237E-03 µg/m^3. Daily and yearly exposures were calculated as shown below, assuming continuous emission of MBOCA throughout the calendar year (NPRI 2018):

Daily exposure = 0.1237E-03 * 0.4 = 0.00004948 (4.95E-05) µg/m^3.

Yearly exposure = 0.1237E-03 * 0.2 = 0.00002474 (2.47E-05) µg/m^3.

Assumptions for various age groups within the general population of Canada:

- 0–5 months: Assumed to weigh 6.3 kg (Health Canada 2015), to breathe 3.7 m^3 of air per day (US EPA 2011b [modified]), and to ingest 21.6 mg of dust per day (Wilson and Meridian 2015 [modified]). It is assumed that no soil ingestion occurs due to typical caregiver practices.
    - Exclusively for breast -fed infants, assumed to consume 0.744 L of breast milk per day (Health Canada 2018a), and breast milk is assumed to be the only dietary source.
    - Exclusively for formula-fed infants, assumed to drink 0.826 L of water per day (Health Canada 2018a), where water is used to reconstitute formula. See footnote on drinking water for details.
- 6–11 months: Assumed to weigh 9.1 kg (Health Canada 2015), to breathe 5.4 m^3 of air per day (US EPA 2011b [modified]), to drink 0 L of water per day (Health Canada 2017b), to ingest 7.3 mg of soil per day, and to ingest 27.0 mg of dust per day (Wilson and Meridian 2015 [modified]).
- 1 year: Assumed to weigh 11.0 kg (Health Canada 2015), to breathe 8.0 m^3 of air per day (US EPA 2011b [modified]), to drink 0.36 L of water per day (Health Canada 2017b), to ingest 8.8 mg of soil per day, and to ingest 35.0 mg of dust per day (Wilson and Meridian 2015 [modified]).
- 2–3 years: Assumed to weigh 15 kg (Health Canada 2015), to breathe 9.2 m^3 of air per day (US EPA 2011b [modified]), to drink 0.43 L of water per day (Health Canada 2017b), to ingest 6.2 mg of soil per day, and to ingest 21.4 mg of dust per day (Wilson and Meridian 2015 [modified]).
- 4–8 years: Assumed to weigh 23 kg (Health Canada 2015), to breathe 11.1 m^3 of air per day (US EPA 2011b [modified]), to drink 0.53 L of water per day (Health Canada 2017b), to ingest 8.7 mg of soil per day, and to ingest 24.4 mg of dust per day (Wilson and Meridian 2015 [modified]).
- 9–13 years: Assumed to weigh 42 kg (Health Canada 2015), to breathe 13.9 m^3 of air per day (US EPA 2011b [modified]), to drink 0.74 L of water per day (Health Canada 2017b), to ingest 6.9 mg of soil per day, and to ingest 23.8 mg of dust per day (Wilson and Meridian 2015 [modified]).
- 14–18 years: Assumed to weigh 62 kg (Health Canada 2015), to breathe 15.9 m^3 of air per day (US EPA 2011b [modified]), to drink 1.09 L of water per day (Health Canada 2017b), to ingest 1.4 mg of soil per day, and to ingest 2.1 mg of dust per day (Wilson and Meridian 2015 [modified]).
- ≥19 years: Assumed to weigh 74 kg (Health Canada 2015), to breathe 15.1 m^3 of air per day (US EPA 2011b [modified]), to drink 1.53 L of water per day (Health Canada 2017b), to ingest 1.6 mg of soil per day, and to ingest 2.6 mg of dust per day (Wilson and Meridian 2015 [modified]).
- Negligible exposures are defined as <2.5 ng/kg bw/day.

Table A-2. Estimates of daily intake (µg/kg bw/d) of MBOCA

Age categories	Ambient air[a]	Indoor air[b]	Total intake
0 to 5 months (breast milk-fed)	3.63E-6	2.54E-5	2.91E-5
0 to 5 months (formula fed)	3.63E-6	2.54E-5	2.91E-5
6 to 11 months	3.67E-6	2.57E-5	2.94E-5
1 year	4.50E-6	3.15E-5	3.60E-5
2 to 3 years	3.79E-6	2.66E-5	3.03E-5
4 to 8 years	2.98E-6	2.09E-5	2.39E-5
9 to 13 years	2.05E-6	1.43E-5	1.64E-5
14 to 18 years	1.59E-6	1.11E-5	1.27E-5
Greater than or equal to 19 years	1.26E-6	8.83E-6	1.01E-5

[a,b] Estimated to be 4.95×10^{-5} µg/m^3 daily exposure using SCREEN 3 (1996) and the 2017 NPRI release (stack and point source) volume data (3 kg). The concentration decreases as distance from the release source increases.

Table A-3. Estimates of yearly intake (µg/kg bw/d) of MBOCA

Age categories	Ambient air[a]	Indoor air[b]	Total intake
0 to 5 months (breast milk-fed)	1.82E-6	1.27E-5	1.45E-5
0 to 5 months (formula fed)	1.82E-6	1.27E-5	1.45E-5
6 to 11 months	1.84E-6	1.28E-5	1.47E-5
1 year	2.25E-6	1.57E-5	1.80E-5
2 to 3 years	1.90E-6	1.33E-5	1.52E-5
4 to 8 years	1.49E-6	1.04E-5	1.19E-5
9 to 13 years	1.02E-6	7.16E-6	8.19E-6
14 to 18 years	7.93E-7	5.55E-6	6.34E-6
Greater than or equal to 19 years	6.31E-7	4.42E-6	5.05E-6

[a,b] Estimated to be 2.47x10-5 µg/m^3 yearly exposure using SCREEN 3 (1996) and the 2017 NPRI release (stack and point source) volume data (3 kg). The concentration decreases as distance from the release source increases.

Table A-4. Estimates of daily intake (µg/kg bw/d) of diphenylamine

Age categories	Ambient air[a]	Drinking water[b]	Soil[c]	Total intake
0 to 5 months (breast milk-fed)	1.92E-5	N/A	N/A	1.92E-5
0 to 5 months (formula fed)	1.92E-5	6.28E-3	N/A	6.30E-3
6 to 11 months	1.94E-5	4.02E-3	5.70E-6	4.05E-3
1 year	2.38E-5	1.57E-3	5.68E-6	1.60E-3
2 to 3 years	2.01E-5	1.37E-3	2.93E-6	1.40E-3
4 to 8 years	1.58E-5	1.10E-3	2.69E-6	1.12E-3
9 to 13 years	1.08E-5	8.44E-4	1.17E-6	8.56E-4

14 to 18 years	8.40E-6	8.42E-4	1.60E-7	8.51E-4
Greater than or equal to 19 years	6.68E-6	9.90E-4	1.54E-7	9.97E-4

Abbreviations: N/A, not applicable.

[a] Estimated to be 2.62 x 10^{-4} µg/m^3 using ChemCAN (2003) and the upper-end volume data from Table 4-1 (i.e., 708 100 kg). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[b] Estimated to be 4.79 x 10^{-2} µg/L using ChemCAN (2003) and the upper-end volume data from Table 4-1 (i.e., 708 100 kg).

[c] Estimated to be 7.10 ng/g using ChemCAN (2003) and the upper-end volume data from Table 4-1 (i.e., 708 100 kg).

Appendix B. Parameters used to estimate human exposures from use of products

Exposure estimates were calculated based on default body weights of 6.3 kg (0 to 5 months old), 9.1 kg (6 to 11 months old), 11 kg (1 year old), 15 kg (2 to 3 years old), 23 kg (4 to 8 years old), 42 kg (9 to 13 years old), 62 kg (14 to 18 years old) and 74 kg (19 years and older) (Health Canada 2015b). The estimated exposure parameters are described in Tables B-1 to B-5.

Table B-1. Dermal and oral exposure parameter assumptions for NDPhA in textiles

Exposure scenario	Assumptions
Full body textile (amortized daily oral)	Maximum reported concentration: > 100 ppm (or > 100 mg/kg) (Ecology 2018) Estimated daily oral exposure to aromatic amine = (Conc x SA x AW x M x F x MP)/BW Age group: Infant Surface area of object mouthed (SA): 20 cm^2 (Zeilmaker et al. 2000) Frequency (F): 1x/day Area weight of textile (AW): 20 mg/cm^{2a} (US EPA 2012) Migration fraction (M): 0.0005 (BfR 2007)[b] Combined market penetration rate and likelihood of wearing a colour formulated with a dye containing the substance of interest on a given day (MP): 0.1[c] BW: body weight (kg) Conversion factor (kg/mg): 0.000001
Full body textile (acute dermal)	Maximum reported concentration: > 100 ppm (or > 100 mg/kg) (Ecology 2018) Estimated acute dermal exposure to Aromatic Amine = (Conc x SA x AW x M x F x SCF)/BW Age group: 0 to 5 months, 6 to 11 months, 1 year, 2 to 3 years, 4 to 8 years, 9 to 13 years, 14 to 18 years, 19 years and older Total surface area (SA): 3 500 cm^2 (0 to 5 months), 4 500 cm^2 (6- to 11-month-olds), 5 300 cm^2 (1-year-olds), 6 500 cm^2 (2- to 3-year-olds), 8 900 cm^2 (4- to 8-year-olds), 13 400 cm^2 (9- to 13-year-olds), 17 200 cm^2 (14-to 18-year-olds), 18 700 cm^2 (19 years and older) (Health Canada 2018b) Area weight of textile (AW): 20 mg/cm^{2a} (US EPA 2012) Skin contact factor (SCF): 1 Dermal absorption (DA): 1

Exposure scenario	Assumptions
	Frequency (F): 1x/day Migration fraction (M): 0.005[b] (BfR 2007) BW: body weight (kg) Conversion factor (kg/mg) = 0.000001
Full body textile (chronic dermal)	Maximum reported concentration: >100 ppm (or > 100 mg/kg) (Ecology 2018) Estimated daily oral exposure to aromatic amine = (concentration x SA x AW x M x F x SCF x MP)/BW Age group: 0 to 5 months, 6 to 11 months, 1 year, 2 to 3 years, 4 to 8 years, 9 to 13 years, 14 to 18 years, 19 years and older Total surface area (SA): 3 500 cm^2 (0 to 5 months), 4 500 cm^2 (6- to 11-month-olds), 5 300 cm^2 (1-year-olds), 6 500 cm^2 (2- to 3-year-olds), 8 900 cm^2 (4- to 8-year-olds), 13 400 cm^2 (9- to 13-year-olds), 17 200 cm^2 (14- to 18-year-olds), 18 700 cm^2 (19 years and older) (Health Canada 2018b) Area weight of textile (AW): 20 mg/cm^{2a} (US EPA 2012) Skin contact factor (SCF): 1 Frequency (F): 1x/day Dermal absorption (DA): 1 Migration fraction (M): 0.0005[b] (BfR 2007) Combined market penetration and likelihood of wearing a colour formulated with a dye containing the substance of interest on a given day (MP): 0.1[c] BW: body weight (kg) Conversion factor (kg/mg): 0.000001

[a] The area weight of textile corresponds to “cotton”

[b] The migration of dyes from textiles varies considerably depending on the type of fibre, type of dye used, dye load, dyeing technology, colour intensity and after treatment process. The exposure from textiles is partly dictated by the amount of dye that migrates from textile material onto human skin (ETAD 1983) or via mouthing. The “Textiles” Working Group (BfR 2007) uses a peak initial migration of 0.5% to estimate exposure to dyes from newly bought unwashed garments, and the chronic migration rate is assumed to be one tenth of the value measured for the first migration to reflect exposure after initial washes. It is assumed that the sweat migration rate is similar to the salivary migration rate. This is consistent with observations of leaching behaviours of dyes from textiles reported by Zeilmaker et al. (1999). Accordingly, the fraction of dye that migrates from a textile material per day was assumed to be 0.0005 for estimating both dermal and oral exposures on a chronic basis.

[c] The assumed combined adjustment factor to account for market penetration rate and the likelihood of wearing fabric containing NDPhA on a given day of 0.1 (10%) is considered to be conservative. The market penetration rate of any particular textile dye in the Canadian marketplace is relatively low (e.g., given the number of potential dyes available), and in the case of NDPhA it was reported as a contaminant in dyes. The portion of this 10% fraction attributed to the assumed likelihood of wearing fabric coloured with a dye containing NDPhA on a given day is based on professional judgement.

Table B-2. Dermal and oral exposure parameter assumptions for NDPhA in marker ink

Exposure scenario	Assumptions
Markers – per event exposure	Concentration: 1 000 – 5 000 ppm (or 1 000 – 5 000 mg/kg) (Ecology 2018) Scenario: Method for characterizing exposure for various ink scenarios (2009 personal communication from Art and Creative Materials Institute to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Intake = [concentration of substance in ink (w/w) x estimated amount of ink per exposure x fraction absorbed]/BW Concentration of substance in ink: 0.1%, 0.5% Estimated amount of ink per exposure: 50 mg Fraction absorbed: 1 BW: body weight (kg)
Markers – daily exposure	Concentration: 1 000 – 5 000 ppm (or 1 000 – 5 000 mg/kg) (Ecology 2018) Scenario: Method for characterizing exposure for various ink scenarios (2009 personal communication from Art and Creative Materials Institute to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) Intake = [(concentration of substance in ink (w/w) x ink laydown rate(µg/cm) x ink line/day)/1000]/BW Concentration of substance in ink: 0.1%, 0.5% Ink laydown rate: 100 µg/cm Ink line/day: 25 cm BW: body weight (kg) Frequency: daily exposure for the lifetime of child or adult

Table B-3. Dermal exposure parameter assumptions for P1NA, 44PD, and diphenylamine in DIY products

Exposure scenario	Assumptions
DIY products (adult) – per event exposure	Concentration: P1NA[a]: 0.01-3% (Environment Canada 2013; SDSs 2013, 2013b, 2007). 44PD[b]: 0.10-2% (Environment Canada 2013; SDSs 2013c. 2005, 2015) Diphenylamine[c]: 0.1-1.5% (SDS 2009, 2010, 2010b)

	Scenario: Motor oil; lubricants scenario (US EPA 1986a,b)[d] Intake = (concentration x SA x film thickness x density)/BW Concentration: 0.01%–3% Surface area: 12 cm^2 (surface area of fingertips of 2 fingers and 2 thumbs) Film thickness: 0.01588 cm Density: 0.889 g/cm^3 (DIY grease application, DIY transmission fluid top-up and motor oils), 1 g/cm^3 (DIY lubricant application) BW: body weight (kg)

[a] DIY grease, lubricant and transmission fluids.
[b] DIY lawn trimmer motor oil.
[c] DIY gas chainsaw and lawn trimmer motor oil.
[d] Exposure factors taken from the US EPA's Versar Manual and based on a thin film approach (US EPA 1986a,b).

Table B-4. Dermal exposure parameter assumptions for 2-aminophenol in hair dyes

Exposure scenario	Assumptions
Temporary hair dye (dermal)[a]	Concentration: 0.1 – 1% (Personal communication, emails from CPSD, HC, to ESRAB, HC, September 2018; unreferenced) Exposed area: 305 cm^2 (4- to 8-year-olds), 350 cm^2 (9-to 13-year-olds), 370 cm^2 (14-to 18-year-olds), 585 cm^2 (19+ years) Loading: Instant application Weight fraction substance: 0.1% - 1% Product amount: 3.4 g (Bremmer 2006) Absorption model: Fixed fraction Absorption fraction: 0.5
Permanent hair dye (dermal)[a]	Concentration: 0.1% – 10.5%[c] (Personal communication, emails from CPSD, HC, to ESRAB, HC, September 2018; unreferenced) Exposed area: 370 cm^2 (14-to 18-year-olds), 585 cm^2 (19 + years) Loading: Instant application Weight fraction substance: 0.1% – 10.5% Product amount (liquid hair dye): 132.6g (Ramirez-Martinez et al. 2015) Product amount (powder hair dye): 66.3 g (based on product label and professional judgement) Absorption model: Fixed fraction Absorption fraction: 0.5

[a] Cosmetic exposures were estimated using ConsExpo Web (2016).
[b] Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.
[c] This 10.5% concentration is reported in a powder hair dye that will be diluted to approx. 1.1% prior to application. (0.21 oz of powder is mixed with 2 oz of water prior to application according to product label).

Concentration = (m_{powder}/m_{water})*0.105 = (0.21 oz/2 oz)*0.105 = 0.011 = 1.1%

Table B-5. Dermal and inhalation exposure parameter assumptions for dimethylaniline in automotive products

Exposure scenario	Assumptions
2-component adhesive (inhalation)	Maximum concentration: 5% (SDS 2019) Scenario: Two-component glue from Do-It-Yourself Products Fact Sheet (RIVM 2007a) Age group: 19+ Exposure to vapour, evaporation model Exposure duration: 240 minutes Product amount: 20 g, 215 g[b] (SDS 2019) Weight %: 2.5% (substance is only in one of the components) Room volume: 90 m^3[c] Ventilation rate: 1.5/hr Inhalation rate: 15.1 m^3/day Application temperature: 25°C Mass transfer coefficient: 10 m/hr Release area: 0.05 m^2 (small project), 1 m^2 (big project) Emission duration: 8 min (small project), 50 min (big project)
2-component adhesive (dermal)	Maximum concentration: 5% (SDS 2019) Scenario: Two-component glue from Do-It-Yourself Products Fact Sheet (RIVM 2007a) Age group: 19+ Exposed area: 43 cm^2 Loading: Instant application Weight %: 2.5% (substance is only in one of the components)Product amount: 0.1 g (small project), 1 g (big project, maximum amount as per Appendix A.2 in RIVM 2007)
Body filler (inhalation)	Maximum concentration: 1% (SDS 2015b) Age group: 19+ Scenario: Application: two-component filler from Do-It-Yourself Products Fact Sheet (RIVM 2007a)

	Exposure to vapour, evaporation model Exposure duration: 240 minutes Product amount: 200 g(ref), 1500 g[d] (SDS 2015b) Room volume: 90 m^3[c] Ventilation rate: 1.5/hr Inhalation rate: 15.1 m^3/day Application temperature: 25°C Mass transfer coefficient: 10 m/hr Release area: 0.005 m^2 (small project), 0.1 m^2 (big project) Emission duration: 30 min (small project), 30 min (big project)
Body filler (dermal)	Maximum concentration: 1% (SDS 2015b) Age group: 19+ Scenario: Application: two-component filler from Do-It-Yourself Products Fact Sheet (RIVM 2007a) Exposed area: 22 cm^2 Loading: Instant application Weight fraction substance: 1% Product amount: 0.2 g
Paint primer (spray) (inhalation)	Maximum concentration: 1% (SDS 2017) Age group: 19 years+ Scenario: Mixing and Loading: two-component paint from Paint Products Fact Sheet (RIVM 2007b) Exposure to vapour, evaporation model Exposure duration: 5 minutes Product amount: 800 g[e] (SDS 2017) Room volume: 90 m^3[c] Ventilation rate: 1.5/hr Inhalation rate: 15.1 m^3/day Application temperature: 20°C Mass transfer coefficient: 10 m/hr Release area mode: Constant Release area: 0.0095 m^2 Emission duration: 5 min Scenario: Application: Pneumatic spraying from Paint Products Fact Sheet (RIVM 2007b)

	Exposure to spray, instantaneous release Exposure duration: 25 minutes Product amount: 800 g[e] Room volume: 90 m^3[c] Ventilation rate: 1.5/hr Inhalation rate: 15.1 m^3/day
Paint primer (spray) (dermal)	Maximum concentration: 1% (SDS 2017) Age group: 19+ Scenario: Mixing and Loading: two-component paint from Paint Products Fact Sheet (RIVM 2007b) Exposed area: 2 cm^2 Loading: Instant application Weight fraction substance: 1% Product amount: 0.05 g Scenario: Application: Pneumatic spraying from Paint Products Fact Sheet Loading: Constant rate Weight fraction substance = 1% Contact rate: 110 mg/min Release duration: 13.3 min

[a] Unless specified, the defaults come from the relevant ConsExpo Fact Sheet for the scenario presented.
[b] Assumes the whole bottle of adhesive is used.
[c] Changed ConsExpo default of 34 m^3 to 90 m^3 as estimate of two car garage (90 m^3 is the default garage volume used in US EPA Consumer Exposure Model v. 2.0 and consistent with values in Batterman et al. (2007); this garage size allows sufficient space to work on automobile) .
[d] Assumes half the can of body filler is used, based on professional judgement.
[e] Based on professional judgement (assuming about 1 L of paint needed, product needs to be mixed at a 4:1 ratio with the catalyst (label instructions), it is assumed that about 800 g of product contains substance of interest).

Appendix C: Lifetime average daily dose calculation

For the purpose of estimating the risk of cancer from exposure to NDPhA and MBOCA, a lifetime average daily dose (LADD) from environmental media and food and from dermal and/or oral exposure to markers (oral/dermal) and textiles, was calculated using the following equation (Health Canada 2013):

LADD = exposure rate x exposure duration / Lifetime

where,

Exposure rate = daily intake in mg/kg bw/day

Exposure duration = exposure duration during life stage (years)

Lifetime = years in a lifetime = 80 years

NDPhA

The low and high end estimates of systemic exposure to NDPhA from daily exposure to markers (oral/dermal) are shown in Table C-1. The low and high end estimates of systemic exposure to NDPhA from daily exposure to textiles (oral/dermal) are shown in Table C-2.

Table C-1. Estimated exposure for NDPhA from markers (details in Appendix B)

Age group	0 to 5 months[a]	6 to 11 months[a]	1 year	2 to 3 years	4 to 8 years	9 to 13 years	14 to 18 years	19 years and older
Markers (mg/kg bw/day)	0	0	2.27E-04 - 1.14E-03	1.67E-04 - 8.33E-04	1.09E-04 - 5.43E-04	5.95E-05 - 2.98E-04	4.03E-05 - 2.02E-04	3.38E-05 - 1.69E-04

[a] Markers are not expected to be used by children under 1 years old

$LADD_{low}$ = (0 × 0.5/80) + (0 × 0.5/80) + (2.27E-04 × 1/80) + (1.67E-04 × 2/80) + (1.09E-04 × 5/80) + (5.95E-05 × 5/80) + (4.03E-05 × 5/80) + (3.38E-05 × 61/80)

= 4.58E-05 mg/kg bw/day

$LADD_{high}$ = (0 × 0.5/80) + (0 × 0.5/80) + (1.14E-03 × 1/80) + (8.33E-04 × 2/80) + (5.43E-04 × 5/80) + (2.98E-04 × 5/80) + (2.02E-04 × 5/80) + (1.69E-04 × 61/80)

= 2.29E-04 mg/kg bw/day

Table C-2. Estimated exposure for NDPhA from Textiles (details in Appendix B)

Age Group	0 to 5 months	6 to 11 months	1 year	2 to 3 years	4 to 8 years	9 to 13 years	14 to 18 years	19 years and older
Full body textiles (mg/kg bw/day)	5.56E-05	4.95E-05	4.82E-05	4.33E-05	3.87E-05	3.19E-05	2.77E-05	2.53E-05
Mouthing of textile objects (mg/kg bw/day)	3.17E-07	2.20E-07	1.82E-07	1.33E-07	N/A	N/A	N/A	N/A

Abbreviations: N/A, not applicable

Dermal

LADD = (5.56E-05 × 0.5/80) + (4.95E-05 × 0.5/80) + (4.82E-05 × 1/80) + (4.33E-05 × 2/80) + (3.87E-05 × 5/80) + (3.19E-05× 5/80) + (2.77E-05 × 5/80) + (2.53E-05 × 61/80)

= 2.78E-05 mg/kg bw/da

Oral

$LADD_{high}$ = (3.17E-07× 0.5/80) + (2.1978E-07 × 0.5/80) + (1.81818E-07 × 1/80) + (1.33333E-07 × 2/80) + (0 × 5/80) + (0× 5/80) + (0 × 5/80) + (0 × 61/80)

= 8.96E-08 mg/kg bw/day

MBOCA

The estimates of yearly intake from environmental media as shown in Table A-3 were used to derive a lifetime average daily dose for populations living near facilities that use MBOCA for processing and manufacturing.

LADD from environmental media (air):

LADD: (1.45E-05x0.5/80) + (1.46E-05x0.5/80) + (1.79E-05x1/80) + (1.52E-05x2/80) + (1.19E-05x5/80) + (8.18E-06x5/80) + (6.34E-06x5/80) + (5.05E-06x61/80)

= 6.29E-6 µg/kg bw/day or 6.29E-9 mg/kg bw/day

The US EPA (2006) recommended the use of age-dependant adjustment factors (ADAFs) when using the oral cancer slope factor derived for MBOCA for the determination of cancer risk to young children. Accordingly, the ADAFs recommended by the US EPA (2005) were considered and adjusted to the Health Canada age groups (see Table C-4). These factors were then applied to the cancer risk calculation for each age group and used to derive lifetime cancer risk (see Table C-5).

Table C-4. Age-dependent adjustment factors (ADAFs) used in the determination of cancer risk to Canadians from exposure to MBOCA

Life stage	Age (years)	ADAF
Infant	0 to 5 months	10
Infant	6 to 11 months	10
Toddler	1 year	10
Toddler	2 to 3 years	3
Child	4 to 8 years	3
Pre-teen	9 to 13 years	3
Teenager	14 to 18 years	1.8[a]
Adult	19+ years	1

[a] $ADAF_{14–18} = (ADAF_{14–15} \times D_{14-15}/D_{14-18}) + (ADAF_{16-18} \times D_{16-18}/D_{14-18}) = 1.8$, where Di = exposure duration (years) [$ADAF_{14–18} = (3 \times 2/5) + (1 \times 3/5) = 1.8$]

Table C-5. Age-specific cancer risks used in the calculation of lifetime cancer risk.

Age-group	Age-specific cancer risk[a]
0 to 5 months	9.06E-11
6 to 11 months	9.15E-11
1 year	1.79E-8
2 to 3 years	4.56E-9
4 to 8 years	3.57E-9
9 to 13 years	2.46E-9
14 to 18 years	1.14E-9
19+ years	5.05E-10
Lifetime cancer risk[b] =	**3.04E-8**

[a] Age-specific cancer risk = [oral slope factor $(mg/kg\ bw/day)^{-1}$ x ADAF x exposure estimate (mg/kg bw/day) x averaging $time_{age\ group}$]; Example for infants 0 to 5 months old = 0.1 $(mg/kg\ bw/day)^{-1}$ x 10 x (1.45E-8 mg/kg bw/day x 0.5/80) = 9.06E-11

[b] Lifetime cancer risk = sum of all age-specific risk calculations