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Canada

Screening Assessment

Methanone, diphenyl-

(Benzophenone)

Chemical Abstracts Service Registry Number 119-61-9

Environment and Climate Change Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of Environment and the Minister of Health have conducted a screening assessment of methanone, diphenyl-, herein referred to as benzophenone. Benzophenone was identified as a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA. The Chemical Abstracts Service Registry Number (CAS RN[1]) for this substance is 119-61-9.

Benzophenone occurs naturally in the environment and is also synthetically manufactured. It is used in Canada in a wide range of applications, including cosmetics, paints and coatings, stains, adhesives and sealants, pest control products, inks, toners, and colourants. It may also be used in the inks employed in some food packaging applications and as a flavouring agent in foods. According to information reported in response to a survey under section 71 of CEPA, less than 1000 kg of benzophenone were reported to be manufactured in Canada in 2008, and between 35 000 kg and 135 000 kg were reported to be imported into Canada that same year.

The ecological risk of benzophenone was 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, benzophenone is considered unlikely to be causing ecological harm.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from benzophenone. It is concluded that benzophenone does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is 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.

Benzophenone has been reviewed internationally by the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). IARC

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classified benzophenone as Group 2B (“possibly carcinogenic to humans”) with sufficient evidence in experimental animals for the carcinogenicity of benzophenone. Chronic exposure to benzophenone via the oral route caused cancer in rats and mice. Benzophenone was non-genotoxic in both *in vitro* and *in vivo* bioassays. For non-cancer effects, the critical effect following oral administration in laboratory studies was effects on kidneys and maternal effects.

The general population of Canada may be exposed to benzophenone from indoor air and dust, food, and baby bottles. Products available to consumers, including cosmetics, stains, paints and coatings, are also sources of general population exposure in Canada.

A comparison of estimated levels of exposure to benzophenone associated with environmental media and food, including exposure to benzophenone from baby bottles, and critical effect levels results in margins of exposures that are considered adequate to address uncertainties in the health effects and exposure data. However, a comparison of estimated levels of exposure to benzophenone associated with the use of certain products available to consumers (i.e., nail polishes, exterior and interior paint, and stains) and critical effect levels results in margins of exposure that are considered inadequate to account for uncertainties in the health effects and exposure datasets.

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

Therefore, it is concluded that benzophenone meets one or more of the criteria set out in section 64 of CEPA.

It has been determined that benzophenone 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 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 methanone, diphenyl-, herein referred to as benzophenone, to determine whether this substance presents or may present a risk to the environment or to human health. Benzophenone was considered a priority for assessment as it met categorization criteria under subsection 73(1) of CEPA 1999 (Environment Canada, Health Canada [modified 2017]).

The ecological risk of benzophenone was 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.

Benzophenone was reviewed internationally through the International Agency for Research on Cancer (IARC), and an IARC monograph is available. These assessments undergo rigorous review and endorsement, and Health Canada and Environment and Climate Change Canada consider them to be reliable. A toxicological evaluation of benzophenone was also conducted by the Scientific Panel of the European Food Safety Authority (EFSA 2009, 2017). The IARC monograph, as well as the EFSA review, were both used to inform the health effects characterization in this screening assessment.

This 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 March 2019. Empirical data from key studies as well as some results from models were used to reach conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

Benzophenone has been detected in vaping products (also known as electronic cigarettes), which may represent an additional source of exposure to benzophenone. The assessment of risk to the general population from this use, including risk relative to that associated with conventional cigarettes, and possible options to mitigate risk associated with these products, would be addressed through a separate legislative and regulatory framework.

This 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 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. The human health portions of this screening assessment have undergone external peer review and consultation. Comments on the technical portions relevant to human health were received from Theresa Lopez, Jennifer Flippin and Joan Garey (TetraTech Inc.). Additionally, the draft of this screening assessment (published August 4, 2018) was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

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

2. Identity of substance

This screening assessment focuses on the evaluation of benzophenone. The Chemical Abstracts Service Registry Number (CAS RN[3]), *Domestic Substances List* (DSL) name and common name and/or abbreviations for benzophenone are presented in Table 2-1. Various known or novel benzophenone derivatives, generally designated as benzophenone -1 through benzophenone -12, as well as other less known derivatives, are not evaluated in this assessment.

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

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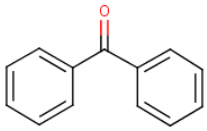
Table 2-1. Substance identities

CAS RN	DSL name (common name, abbreviations, other names)	Chemical structure and molecular formula	Molecular weight (g/mol)
119-61-9	Methanone, diphenyl- (benzophenone; Ph2CO; BZPh; diphenyl ketone; diphenylmethanone)	 $C_{13}H_{10}O$	182.22

3. Physical and chemical properties

Benzophenone is an aromatic ketone. It is moderately soluble in water and freely soluble in organic solvents, and it is a semi-volatile organic compound (EFSA 2009). A summary of the physical and chemical properties of benzophenone is presented in Table 3-1. Additional physical and chemical properties are presented in ECCC (2016b).

Table 3-1. Physical and chemical property values (at standard temperature and pressure) for benzophenone

Property	Value	Key reference(s)
Physical state	White crystals with flowery odour	IPCS 2010
Boiling point (°C)	304.5	IARC 2013
Melting point (°C)	48.5	IARC 2013; ECHA 2014
Vapour pressure (Pa)	0.257	EFSA 2009; ECHA 2014
Water solubility (mg/L)	137	EFSA 2009
log K_{ow} (dimensionless)	3.18	LOGKOW 2010, as cited in IARC 2013

4. Sources and uses

Benzophenone occurs naturally in the environment (i.e., in a limited number of fruits and plants) and is also synthetically manufactured (IARC 2013).

Benzophenone was included in a survey issued pursuant to a CEPA section 71 notice (Canada 2009). In 2008, less than 1000 kg of benzophenone were reported to be manufactured in Canada and 35 000 to 135 000 kg were reported to be imported into

Canada.[4] Non-confidential uses for benzophenone reported in the survey include its function as an additive in paints and coatings, adhesives and sealants, as a fragrance ingredient, as a photosensitive substance in inks, toners and colourants, as a laboratory substance for medical devices and as an industrial photoinitiator.(Environment Canada 2009).

According to notifications submitted under the *Cosmetic Regulations* to Health Canada, benzophenone is used in certain cosmetic products in Canada such as nail polishes, fragrances, body cleansers, makeup, and hair products (personal communication, emails from Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2016 to March 2019; unreferenced). It is not included on the List of Prohibited and Restricted Cosmetic Ingredients (Health Canada 2015).

In Canada, benzophenone has also been identified as a component in some printing inks used in a limited number of food packaging materials that have no direct contact with food. It may also be used as a food flavouring agent. The *Food Chemicals Codex* (FCC) indicates that benzophenone functions as a flavouring agent (FCC USP 2016). It is also listed in Fenaroli's Handbook of Flavor Ingredients (Burdock 2010). The European Union permits benzophenone to be used as a flavouring agent in food (EU Food Flavourings Database 2019), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that there were no safety concerns from current intake of benzophenone when used as a flavouring agent (WHO 2001). The substance was previously permitted to be used a food flavouring agent in the United States (as specified in the Code of Federal Regulations 21 CFR 172.515), but in 2018, the US Food and Drug Administration (US FDA) granted a petition for a ban on certain synthetic food flavourings, including benzophenone, by amending the food additive regulations to no longer authorize the use of these substances as synthetic flavouring substances for use in food. While the FDA's scientific analysis has determined that benzophenone does not pose a risk to public health under the conditions of its intended use, the substance is being removed from the food additive regulation under the Delaney Clause, which requires that the FDA cannot approve the use of any food additive that has been found to induce cancer in humans or animals at any dose. (US FDA 2016, 2017, 2018). No definitive information is available concerning the potential use of benzophenone as a food flavouring agent in Canada (personal communication, emails from the Food Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated October and December 2016; unreferenced). Benzophenone is listed in the Natural Health Products Ingredients Database with a non-medicinal role for oral use as flavour enhancer only, with a tolerable daily intake of 0.03 mg/kg bw/day consistent with EFSA (2009, 2017).

[4] Values reflect quantities reported in response to a survey conducted under a CEPA section 71 notice (Environment Canada 2009). See survey for specific inclusions and exclusions (schedules 2 and 3).

Although benzophenone is currently listed in the Licensed Natural Health Products Database as being present in a limited number of currently licensed natural health products (NHPs), according to communications with the associated licence holders, it is rather benzophenone derivatives (i.e., benzophenone -1, benzophenone -2, or benzophenone -3) that are present in these products (LNHPD 2018; NHPID 2019; personal communication, email from Natural and Non-prescription Health Products Directorate, Health Canada, to ESRAB, Health Canada, dated September 2017; unreferenced). Benzophenone is also used as a formulant in pest control products in Canada (personal communication, email from Pest Management Regulatory Agency, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, dated September 2016; unreferenced).

Publicly available safety data sheets (SDSs) indicate that benzophenone may also be present in exterior and interior paints (SDS 2015, 2019) as well as in stains for decks, deck crack fillers, and auto-related cleaning products available to the general population of Canada (SDS 2014, 2018).

Internationally, in addition to aforementioned uses, benzophenone is used in the synthesis of benzophenone derivatives. Benzophenone is added to plastic packaging or contents to prevent the UV photo-degradation of packaging plastics or its contents (NTP 2006; HSDB 2010, as cited in IARC 2013). Benzophenone may be present in or has been demonstrated to migrate from low density polyethylene (LDPE) films for food packaging (Maia et al. 2016; Paseiro-Cerrato et al. 2016), adult plastic toys (Nilsson et al. 2006), and baby bottles (Mertens et al. 2016; Onghena et al. 2016; Simoneau et al. 2012). Benzophenone has been detected in black tattoo inks (Lehner et al. 2011) and e-cigarette liquids (Hutzler et al. 2014). It has also been identified as being used in air care products, cleaning products, industrial and automotive chemicals, polishes, and floor maintenance products (CPID 2019).

5. Environmental fate and behaviour

5.1 Environmental persistence

According to models used in ERC (ECCC 2016b), benzophenone is expected to persist in air, but is not expected to persist in water, sediment or soil.

5.2 Potential for bioaccumulation

Given low K_{ow} and low bioconcentration factors (ECCC 2016b), benzophenone is not expected to significantly bioaccumulate in organisms.

6. Potential to cause ecological harm

6.1 Characterization of ecological risk

The ecological risk of benzophenone was 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 scientific literature, from available empirical databases (e.g., OECD QSAR Toolbox 2014), and from responses to a survey issued pursuant to section 71 of CEPA, or they were generated using selected (quantitative) structure-activity relationship ([Q]SAR) 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 and 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 based on 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 under-classification 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 in empirical or modelled 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 2014). 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 analysis. Error in 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 benzophenone and the hazard, exposure and risk classification results are presented in ECCC (2016b).

On the basis of low hazard and low exposure classifications according to information considered under ERC for benzophenone, this substance was classified as having a low potential for ecological risk. It is therefore unlikely that this substance is resulting in concerns for the environment in Canada.

7. Potential to cause harm to human health

7.1 Exposure assessment

7.1.1 Environmental media and food

Environmental media

Limited environmental monitoring data in Canada were identified. Benzophenone was included in a study by the National Research Council (NRC) of Canada on indoor air quality and emissions from building materials and furnishings used in Canadian homes (Won and Lusztyk 2011). Benzophenone was detected in dust from 49 of 50 homes from the Quebec City field study, where concentrations ranged from 0.50 to 225.85 µg/g, with an arithmetic mean of 10.4 µg/g (Won and Lusztyk 2011). Although indoor air samples were also collected from these homes, benzophenone was not analyzed in air (Won and Lusztyk 2011). However, as a semi-volatile organic compound, it is expected to be present in indoor air given the range of indoor sources of benzophenone and its presence in dust. Benzophenone was measured in an indoor air monitoring survey conducted by the Japanese Ministry of Environment (Japanese Ministry of Environment 2006, as cited in IARC 2013), with concentrations ranging from approximately 0.96 to 98 ng/m^3 (see ‘Products available to consumers’ section for assessment of air exposures).

Although no data were identified on levels of benzophenone in Canadian drinking water, it has been measured along with several organic waste contaminants in raw and finished drinking water in the United States (mean of 0.26 µg/L, in finished drinking water; n=1/15; 2001–2002) (Loraine and Pettigrove 2006). Benzophenone has also been detected in drinking water elsewhere, such as Japan, where concentrations of up to 8.8 µg/L were measured (Shinohara et al. 1981, as cited in IARC 2013). Finally, a study in South Korea detected benzophenone in soil samples collected in April and May 2003, with concentrations ranging from 0.82 to 16.55 µg/kg dry weight, with a mean of 4.55 µg/kg (97% detection frequency) (Jeon et al. 2006).

Food

No Canadian data were identified on the levels of benzophenone that may be present in foods. However, several dietary sources have been identified in the international literature. Benzophenone dietary sources include its natural occurrence in some food, its use as a food flavourant, its migration from food packaging materials, and its presence in drinking water (as discussed above) and fish, as well as its migration from baby bottles (Mertens et al. 2016; Onghena et al. 2016; Simoneau et al. 2014).

Benzophenone is reported to occur naturally in some foods, including wine (muscat) grapes, tropical fruits, and black teas. It may also be used as a food flavouring agent (IARC 2013). On the basis of a comparison of production volumes, it has been determined that consumption of benzophenone as a food flavouring agent may be greater than that from foods that naturally contain benzophenone (WHO 2002). Internationally, the JECFA estimated the per capita intake of benzophenone as flavouring agent in the United States at 11 µg/day (International Organization of the Flavor Industry 1995, cited in WHO 2002; Lucas et al. 1999, cited in WHO 2002). IARC (2013) used the single portion exposure technique developed by the JECFA and estimated intakes of 6 µg/day (based on surveyed, refined levels of use provided by industry to the EU Commission in 2008), 40 µg/day when applied to data from the Council of Europe (2000) and 170 µg/day (based on use levels reported by the U.S. Flavor and Extract Manufacturers Association in 1994). In the United States, the average levels of benzophenone used as a food flavouring agent ranged from 0.57 ppm in non-alcoholic beverages to 1.57 ppm in baked goods; the maximum levels ranged from 1.28 ppm in non-alcoholic beverages to 3.27 ppm in frozen dairy (Burdock 2010).

In Canada, benzophenone has been identified as having limited uses in some food packaging materials, but only in those for which there is no direct contact with food. Internationally, benzophenone is used as a photoinitiator in UV-cured inks (at 5% to 10%) that are applied to the external face of paperboard food packaging (EFSA 2009, 2017; IARC 2013). Benzophenone has been shown to migrate either directly or through the vapour phase to food. More recently, two studies have attempted to improve the prediction of benzophenone migration from low density polyethylene (LDPE) film packaging. Results of modelling benzophenone migration into real foods showed that diffusion and partition coefficients were higher than previously predicted (Maia et al.

(2016) and that the most reliable predictor was log K_{ow} of foods (i.e., preference for migration into high-fat foods) (Paseiro-Cerrato et al. 2016).

In 2000, 2006 and 2011, the United Kingdom Food Safety Agency (UK FSA) conducted three comprehensive surveys of foodstuffs packaged in printed plastic, printed paper or board. Benzophenone was detected in 14%, 17% and 11%, respectively, of the 350 foods sampled for each survey (UK FSA 2011). The 2006 results showed that benzophenone was more frequently detected in foods packaged in printed paper and board (20%) than in printed plastics (3%). The UK FSA generated a range of potential dietary intakes using the 2006 data for “high-level consumers” ranging from 1.2 to 1.5 µg/kg bw/day for a 60 kg adult (UK FSA 2006, as cited in IARC 2013). While estimates were not derived for children, this age group may have greater exposure to packaged foods because infants and children consume considerably more food per kilogram of bodyweight than adults, and young children in particular receive a limited variety of dietary products. Also, because small packaging sizes, which have a larger surface-to-volume ratio, are especially marketed to children, higher migration per kilogram of food is possible (Foster 2010; Muncke 2011). In the most recent UK FSA survey (2011), benzophenone was detected in a small number (11%) of food items packaged in heavily printed carton board, including several brands of breakfast cereals, pancakes, chocolate and candy, fries, chicken products and fish cakes, with concentrations ranging from <10 to 2460 µg/kg for foods likely to be consumed by children (UK FSA 2011). Although benzophenone has only been identified in North America as a component of inks used on the exterior of cans or polyethylene containers that do not have direct contact with the food, data from the UK FSA (2011) survey of food items in which benzophenone was measured were used as a conservative approach to estimate potential dietary exposures from all potential food sources for Canadians.

Additional data exist on the presence of benzophenone in food products from other countries, such as cake (12 000 µg/kg) in Spain (Rodriguez-Bernaldo de Quiros et al. 2009, as cited in IARC 2013) and breakfast cereals in Belgium (up to 4210 µg/kg) (CS AFSCA Belgium 2009, as cited in IARC 2013). In a study by Koivikko et al. (2010, as cited in IARC 2013) in the EU, results appeared to show that multilayer material within the packaging can limit or prevent migration. This has also been demonstrated by Pastorelli et al. (2008, as cited in IARC 2013). The EU Standing Committee for Food therefore endorsed a specific food migration limit of 0.6 mg/kg for the sum of benzophenone and 4-methylbenzophenone and advised EU ink and carton board industry associations that printing inks containing benzophenone are not suitable for printing of food packaging unless a functional barrier is present that blocks their transfer into food by direct contact and via the gas phase (EU 2009, as cited in IARC 2013).

Benzophenone has also been shown to migrate from baby bottles, purchased in Belgium, made of materials used as substitutes for polycarbonate (Mertens et al. 2016; Onghena et al. 2016) as well as from those available in the EU market originating from several countries, including Canada (although the specific details for the Canadian samples were not provided) (Simoneau et al. 2012).

In the Belgium study, 24 baby bottles considered representative of the market were sterilized according to the manufacturer's recommendations (i.e., filled with boiling water and left for 10 minutes). The bottles were then filled with a formula simulant at 70°C for 2 hours as per the conventional "hot fill conditions" prescribed in EU Regulation 10/2011(EU 2011). This method also required that the migration test be carried out three times using fresh food simulant to mimic the repetitive use of baby bottles (Mertens et al. 2016; Onghena et al. 2016). Benzophenone was detected in 4 bottles (polypropylene and silicone materials), with average benzophenone concentrations of the third migrations ranging from 9 to 97 µg/kg formula, which was below the EU-specific migration limit of 600 µg/kg set for repeat-use plastics (Mertens et al. 2016; Onghena et al. 2016). A subset of 6 bottles was further analyzed for a variety of duration tests (e.g., microwave, steam sterilization, and dishwater tests) (Onghena et al. 2016). Of these 6 bottles, benzophenone was only detected in the silicone bottle, at concentrations ranging from <3.6 µg/kg (ninth migration during the microwave test) to 58 µg/kg (first migration during the cook sterilization test). The highest concentration for the tenth repetition of any treatment was 22 µg/kg for the dishwater cleaning treatment. In general, peak benzophenone migrations occurred during the early migrations of tests, i.e., when the bottles were new.

In the EU study, a total of 277 baby bottles purchased from 26 EU countries, Canada, Switzerland and the United States were analyzed (Simoneau et al. 2012). Using the protocols prescribed in EU Regulation 10/2011(EU 2011), first migration results were presented as a screening method. Benzophenone migration was associated with bottles made of polypropylene, silicone polyamide (PA) and polyethersulphone (PES). Benzophenone concentrations ranged from 1 to 286 µg/kg, with an average of 43 µg/kg, for the polypropylene bottles (39/149 detects) and from 11 to 637 µg/kg, with an average of 184 µg/kg, for the silicone bottles (5/5 detected) and were 2 µg/kg for the PA bottles (2/28 detects). The authors noted that the higher concentrations in one brand of PES bottles and in silicone bottles could be a result of the paper and cardboard instruction leaflets placed inside the bottles.

Estimated intakes

Intakes for adults and children were derived using Canadian and international data to inform exposure for the general population of Canada. Total intakes from environmental media (dust, indoor air and drinking water) and food, based primarily on monitoring data, were found to be 1.1 µg/kg bw/day for adults and 4.5 µg/kg bw/day for toddlers (details presented in Appendix A). Conservative exposure intakes associated with the migration of benzophenone from baby bottles resulted in oral intakes ranging from 1.5 to 51 µg/kg bw/day for 0 to 1-month-old infants (details presented in Appendix B).

7.1.2 Products available to consumers

Benzophenone is used in a range of products available to Canadian consumers, including cosmetics, exterior and interior paints, and stains (see Sources and Uses

section). According to notifications submitted to Health Canada under the *Cosmetic Regulations*, benzophenone is present in cosmetics (e.g., nail polish, fragrances and body cleansers). In the aforementioned NRC study, benzophenone was detected in emissions from a single sample material, i.e., water-based interior paint, out of 58 materials tested, and air concentrations in the small-scale environmental chamber were found to be 11.7 µg/m^3 (Won and Lusztyk 2011). Exposure estimates related to the use of cosmetics, stains and paint were derived using ConsExpo exposure modelling (RIVM 2006) on the basis of expected use patterns by the general population of Canada (see Table 7-1). These estimated exposures were derived for sentinel products which represent the highest exposures when compared to similar products. Estimated exposures to benzophenone in air care products, cleaning products, polishes and floor maintenance products, were lower than those derived for fragrance and body cleansers. The exposure estimates were determined for various durations (per event and chronic scenarios), age groups (adults and children), and routes (dermal and inhalation).

Benzophenone is expected to be readily absorbed through all routes of exposure (IARC 2013). The dermal absorption of benzophenone was determined in an *in vivo* study in monkeys to be 69% of the dose applied to occluded skin within 24 hours. Under unoccluded conditions, dermal absorption was reduced to 44%, presumably due to evaporation (Bronaugh et al. 1990, as cited in IARC 2013). The dermal absorption value of 44% for unoccluded conditions was applied to the exposure estimates and is deemed to be more representative of the dermal scenarios considered in this assessment than the occlusion-based values. Given the potential for evaporation, both dermal and inhalation exposures may occur simultaneously, and estimates of exposure via the dermal and inhalation routes have been combined in order to derive overall estimates of exposure. The details and default parameters applied to each of the exposure scenarios are provided in Appendix C.

Table 7-1. Estimated exposures to benzophenone from the use of products available to consumers

Product scenario (duration)[a]	Conc. %[b]	Age group	Dermal exposure estimate (mg/kg bw/day or mg/kg/event)[c,d]	Inhalation exposure estimate (mg/kg bw/day or mg/kg/event)[c,e]	Combined exposure estimate (mg/kg bw/day or mg/kg/event)
Nail polish (per event)	5	Adult	0.072	0.0047	0.076
		Teen	0.085	0.0055	0.091
		Child	0.043	0.0059	0.049
Fragrance (daily)	0.3	Adult	0.010	0.00016	0.010
Body cleanser (daily)	0.3	Adult	0.0029	Not quantified	0.0029
		Teen	0.0024		0.0024

Product scenario (duration) [a]	Conc. %[b]	Age group	Dermal exposure estimate (mg/kg bw/day or mg/kg/event)[c,d]	Inhalation exposure estimate (mg/kg bw/day or mg/kg/event)[c,e]	Combined exposure estimate (mg/kg bw/day or mg/kg/event)
Paint (per event)	0.3	Adult	0.067	0.00122	0.068
Stain (per event)	0.3	Adult	0.067	Not quantified	0.067

Abbreviation: Conc, concentration

[a] Intakes for "per-event" scenarios are presented as mg/kg per event, and "daily" scenarios are based on mg/kg/day.

[b] Concentrations for cosmetics from personal communications (emails from the Consumer and Hazardous Products Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada dated September 19, 2016, May 25, 2017 and March 25, 2019; unreferenced); concentrations for paint from SDS (2015, 2019); concentrations for stain from SDS 2018.

[c] Only estimates associated with the upper-bound concentration are presented.

[d] Assuming 44% dermal absorption

[e] Assuming 100% absorption for inhalation

7.2 Health effects assessment

Benzophenone has been reviewed by IARC (2013) and EFSA (2009, 2017). These reviews provide a basis for the health effects characterization in this screening assessment. IARC (2013) evaluated the risk of cancer from benzophenone exposure and concluded that "there is sufficient evidence in experimental animals for carcinogenicity of benzophenone" based on chronic oral studies in rats and mice, and it classified the substance as "possibly carcinogenic to humans" (Group 2B). Targeted literature searches were conducted from one year prior to the IARC monograph publication date (July 2013) to May 2018. No health effects studies that could impact the risk characterization (i.e., result in different critical endpoints or lower points of departure than those stated in IARC (2013) and EFSA (2009, 2017)) were identified. There are no data available on the health effects of inhalation exposure.

Toxicokinetics and metabolism

Benzophenone can be absorbed following inhalation, oral, and dermal exposure (IARC 2013). The metabolites of benzophenone in laboratory animals following dietary administration are benzhydrol and 4-hydroxybenzophenone, probably with the sulfate and glucuronide conjugates, which may undergo enterohepatic circulation (Jeon et al. 2008; Nakagawa et al. 2000; Nakagawa and Tayama 2002; Robinson 1958). In rabbits, benzhydrol was excreted in the urine at 41% to 61% of the administered benzophenone in the diet (NTP 2006), while in rats, only 1% of the orally administered benzophenone was excreted in the urine as 4-hydroxybenzophenone, as detected in enzyme-treated urine samples (NTP 2000). Clearance of benzophenone appears to be more rapid in mice than in rats, as when mice received six times more benzophenone than rats via single intravenous or gavage administration, the area under the plasma concentration versus time curve (AUC) of benzophenone was significantly lower in mice than in rats

(NTP 2006). The peak levels of benzophenone and its metabolites in plasma were reached approximately 4 hours after single dosing via gavage in rats, and the elimination half-life of the parent compound was approximately 19 hours (Jeon et al. 2008). Details on dermal absorption studies are provided in section 7.1.2.

The metabolites 4-hydroxybenzophenone and 3-hydroxybenzophenone are also formed by UV or sunlight irradiation of aqueous solutions of benzophenone (IARC 2013).

Carcinogenicity and genotoxicity

The primary targets of benzophenone exposure following oral administration in rats and mice are the liver, kidney, and hematopoietic system (EFSA 2009, 2017; IARC 2013).

Carcinogenicity studies were conducted in rats and mice via the oral route of exposure in diet by NTP (2006). Animals were exposed for 105 weeks at 0, 15, 30, and 60/65 mg/kg bw/day (male/female) for F344/N rats and at about 0, 35/40, 70/80, and 150/160 mg/kg bw/day (male/female) for B6C3F1 mice (NTP 2006). The survival of high-dose male rats was significantly lower than that of the control group, whereas the survival of exposed females was similar to that of the controls. In male rats, there was a positive trend in the incidence of renal tubule adenoma (significant in the mid- and high-dose groups) accompanied by significantly increased incidences of renal tubule hyperplasia, and a dose-dependent enhancement of the severity of nephropathy was observed in all treatment groups. In female rats, significantly enhanced severity of nephropathy was observed in mid- and high-dose groups. Significantly increased incidence of hepatocytic centrilobular hypertrophy was reported in all exposed groups of rats. The incidences of mononuclear cell leukemia increased significantly in mid- and high-dose male rats (both groups exceeded the historical control ranges). In female rats, the incidence of mononuclear cell leukemia was significantly increased only in the mid-dose group compared to the controls (incidences in all dose groups, including control group, exceeded historical control values). A marginal increase in the incidence of histiocytic sarcoma in high-dose female rats was also reported (exceeded historical control). However, both the mononuclear cell leukemia and histiocytic sarcoma observed in female rats were considered by NTP (2006) as equivocal evidence of carcinogenic activity of benzophenone. Survival of exposed groups of mice was similar to that of the control groups, except for the high-dose females, which had decreased survival rate at the end of the study. The incidences of hepatocellular adenoma in mid- and high-dose groups were increased in both sexes of mice. However, the differences from the controls were significant only in male mice (exceeded the historical control ranges). A positive trend in the incidence of histiocytic sarcoma in female mice was observed, and the significantly increased incidence was reported in the mid-dose group (exceeded the historical control range). The incidences of nephropathy in exposed female mice and the severity of nephropathy in exposed male mice were significantly increased. Female mice in all exposed groups had increased incidences of spleen hematopoietic cell proliferation.

As EFSA (2009, 2017) considered benzophenone to be non-genotoxic, it used both the cancer and non-cancer kidney effects observed in male rats in the carcinogenicity study to derive the benchmark dose for a 10% increase in effect ($BMDL_{10}$). The lowest $BMDL_{10}$ value for non-cancer kidney effects was 3.1 mg/kg bw/day, and the lower end of the range of $BMDL_{10}$ for kidney cancer was determined as 19 mg/kg bw/day. As a result, the BMDL 3.1 mg/kg bw/day was adopted by EFSA (2009, 2017) as the most appropriate point of departure for their tolerable daily intake calculation.

Limited reports of dermal studies on the potential carcinogenicity of benzophenone performed with female Swiss mice (Stenbäck and Shubik 1974) and New Zealand White rabbits (Stenbäck 1977) were identified. Benzophenone dissolved in acetone at 0%, 5%, 25% and 50% was applied twice a week at 0.02 mL on 1-inch squares of dorsal skin of mice for 120 weeks or to the inner ears of rabbits for 160 weeks (application conditions not specified). In mice, similar numbers of skin tumours were seen in both treated and control animals. IARC (2013) concluded that dermal application of benzophenone was not carcinogenic in the skin of mice. In rabbits, benzophenone had no effect on the incidences of cancer or non-cancer lesions. The authors therefore concluded that the studies did not identify carcinogenic potential or non-cancer effects of benzophenone via dermal exposure. This conclusion for mice was supported by IARC (2013), but the rabbit study was not addressed in the IARC review. EFSA (2009, 2017) stated that “the negative results obtained with benzophenone in carcinogenicity studies by dermal application are in line with the presumed non-genotoxic mode of action of this compound.” It should be noted that histological examinations were conducted only on skin samples and grossly observed tumours or lesions in both dermal studies. As well, the authors provided only limited information on the results as well as on administered doses, although it was noted that the tested doses of the compound may have been too low in the rabbit study. In addition, the number of rabbits tested in each dose group was small (n=5), limiting the power of this study to detect toxicological effects.

Benzophenone induced cancer on multiple sites in both rats and mice in oral chronic studies. However, the mode of action of carcinogenicity of benzophenone in the oral studies is uncertain. Given the results of the NTP bioassay and the evidence of effects on the endocrine system (see below), IARC (2013) suspected that multiple mechanisms, such as the generation of reactive oxygen species and interference with endocrine system via multiple receptors, might be involved in the carcinogenicity of benzophenone. In addition, the pathogenesis of benzophenone-induced renal tubule cancer has not been determined by NTP (2006). While IARC (2013) considered that the short survival of high-dose male rats was attributable to the increased severity of chronic progressive nephropathy (CPN), it did not conclude that CPN was a mechanism for renal tumour development.

In vitro, benzophenone was not mutagenic in *Salmonella typhimurium* strains (TA98, TA100, TA1535 or TA1537) or in mouse lymphoma L5178Y/tk+/- cells in the presence or absence of metabolic activation (NTP 2006). Neither benzophenone nor its metabolites benzhydrol or 4-hydroxybenzophenone induced *umu* gene expression in

S. typhimurium strain TA1535 in the presence or absence of metabolic activation from rat, mouse or human sources. However, in the same studies, *umu* gene expression was elicited in the presence of recombinant human cytochrome P450s (Takemoto et al. 2002).

In vivo, benzophenone did not increase the frequency of micronuclei in erythrocytes from bone marrow or from peripheral blood in mice after intraperitoneal injections at 200 to 500 mg/kg bw/day for 3 days or after dietary exposure at 200 to 4200 mg/kg bw/day for 14 weeks (NTP 2006) (i.e., doses greater than those associated with tumour development in the long-term studies in mice and rats).

Considering the information summarized above, EFSA (2009, 2017) concluded that benzophenone has no genotoxic potential.

However, a study showed that the combination of benzophenone and sunlight caused DNA damage in a human keratinocyte cell line in the Comet assay (Amar et al. 2015).

Short-term and sub-chronic toxicity

Benzophenone was administered in the diet of both sexes of Sprague-Dawley (SD) rats at 0, 20, 100 and 500 mg/kg bw/day. The low-dose group was treated for 90 days, while the mid- and high-dose groups were treated for 28 days (Burdock et al. 1991). Treatment-related changes, including altered hematological and clinical biochemistry endpoints, increased liver and kidney weights, and increased hepatocellular hypertrophy, occurred in both sexes of rats at mid- and high-dose levels. A no-observed-adverse-effect level (NOAEL) of 20 mg/kg bw/day was derived from this study by the Danish EPA (2015). Increased liver and kidney weights, increased hepatocellular hypertrophy, and renal tubular changes were also reported in F344 rats in a 14-week feeding study at the lowest dose level tested of 75 mg/kg bw/day or higher (NTP 2000).

Reproductive and developmental toxicity

The NTP conducted several range-finding developmental toxicity studies with benzophenone in rats and rabbits in which effects on the fetus were only observed in the presence of maternal toxicity (NTP, 1992, 1993, 1999, as cited in NTP 2004). In follow-up studies, benzophenone was administered by gavage to rats on gestational days (GD) 6 to 19 at doses of 0, 100, 200, or 300 mg/kg bw/ day (NTP 2002, as cited in NTP 2004), or to rabbits on GD 6 to 29 at 0, 5, 25, or 45 mg/kg bw/day (NTP 2004). In rats, maternal liver and kidney weights were significantly increased in all dose groups, accompanied by a reversible decrease in body weight. Decreased fetal body weight was noted at the highest dose, and what were considered “mild developmental delays with a high probability of recovery during early postnatal development” were observed at all doses. The maternal toxicity lowest-observed-adverse-effect level (LOAEL) was reported as 100 mg/kg bw/day (no NOAEL was established). In rabbits, dose-related increases in the incidences of abortion or early delivery were reported in the mid- and high-dose groups, along with dose-related reductions in maternal body weight (not

reversed) and fetal body weight. The LOAEL was considered to be 25 mg/kg bw/day for maternal toxicity and early termination of pregnancy and the NOAEL was determined to be 5 mg/kg bw/day.

No reproductive toxicity or effects on the endocrine system were observed in a two-generation study in which both sexes of SD rats were exposed to benzophenone in diet at 0, 6/9, 29/40 and 130/170 mg/kg bw/day (male/female) (Hoshino et al. 2005; Yamasaki et al. 2005). However, in both sexes of F0 and F1 parents, inhibition of body weight gain and food consumption, significantly elevated renal weights and changes in renal tubules, and significantly increased hepatic weight and centrilobular hepatocytic hypertrophy were observed in mid- and high-dose groups. Although increased centrilobular hepatocytic hypertrophy in low-dose parents was noted, it was not accompanied by hepatic weight increase and was therefore considered by EFSA (2009, 2017) as a vital adaptive change. The inhibition of body weight gain in offspring was observed in both sexes of F1 and F2 generations in the high-dose groups in this study.

There are no human studies available for benzophenone. A prospective cohort investigation on 4-hydroxybenzophenone, a major metabolite of benzophenone, found that male parental urine 4-hydroxybenzophenone levels were associated with reduced fecundity (Buck Louis et al. 2014) and a slight excess in male births (Bae et al. 2016). Other cohort studies found no association of urinary 4-hydroxybenzophenone concentration with the incidence of endometriosis, uterine leiomyoma, or semen quality (Kunisue et al. 2012; Pollack et al. 2015; Buck Louis et al. 2015). However, it is unclear if benzophenone was the source of 4-hydroxybenzophenone in the urine of the human subjects as the source was not indicated.

The *in vivo* estrogenic activity of benzophenone and its metabolite, 4-hydroxybenzophenone, has been confirmed in multiple uterotrophic assays (IARC 2013; ECHA 2015). In ovariectomized rats, increased uterine weights were reported after benzophenone administration for 3 days at 400 mg/kg bw/day by gavage (Nakagawa and Tayama 2002) or at 300 mg/kg bw/day by intraperitoneal injections (Suzuki et al. 2005). In immature female rats, however, only the metabolite 4-hydroxybenzophenone was found to cause uterine weight increases after subcutaneous injections (Nakagawa and Tayama 2001; Hayashi et al. 2006). Evidence suggests that the estrogen-like effects of benzophenone may be due to its metabolite 4-hydroxybenzophenone (Nakagawa and Tayama 2001, 2002; IARC 2013).

In *in vitro* assays, the metabolite 4-hydroxybenzophenone elicited estrogenic and anti-androgenic activity (IARC 2013, ECHA 2015). Benzophenone itself showed no estrogenic activity in earlier assays (Nakagawa et al. 2000; Yamasaki et al. 2002; Hayashi et al. 2006; Suzuki et al. 2005). Recent studies showed that benzophenone was able to induce high responses on estrogen receptors of human ovarian and breast cancer cell lines (Simon et al. 2016) and to decrease the thyroid peroxidase activity of a human follicular thyroid cancer cell line (Song et al. 2011, 2012).

7.3 Characterization of risk to human health

Chronic exposures from environmental media (dust, indoor air and drinking water) and food for the general population of Canada were conservatively estimated on the basis of Canadian and/or international data to be 0.0011 mg/kg bw/day for adults and 0.0045 mg/kg bw/day for toddlers. Exposure intakes associated with the migration of benzophenone from baby bottles resulted in oral intakes ranging from 0.0015 to 0.051 mg/kg/d for 0- to 1-month-old infants. Exposure intakes for products used by consumers were also derived for cosmetics, stains and paints as representative scenarios. All estimates are presented in Table 7-2.

Benzophenone was found to be non-genotoxic both *in vitro* and *in vivo*. Chronic oral exposure to benzophenone induced kidney adenoma and leukemia in male rats, liver tumours in male and possibly female mice (not statistically significant in females), and histiocytic sarcomas in female mice. Effects in the kidney were considered the most sensitive non-cancer endpoints.

$BMDL_{10}$ values of 3.1 mg/kg bw/day for non-cancer kidney effects and 19 mg/kg bw/day for kidney cancer were derived by EFSA (2009, 2017) as points of departure from the oral carcinogenicity study and were used to characterize the risk posed by chronic oral exposure to benzophenone in this screening assessment.

Dermal studies on the carcinogenicity of benzophenone were performed on mice and small groups of rabbits and showed no carcinogenic potential. However, the quality of the studies could not be verified given the limited information provided in the published reports, and the extent of the histological examinations appears to have been limited. Thus, to characterize risk from daily dermal exposure, the $BMDL_{10}$ values of 3.1 and 19 mg/kg bw/day from the chronic oral carcinogenicity study were used.

To characterize risk of benzophenone associated with short-term dermal exposure, the NOAEL of 5 mg/kg bw/day for maternal health effects associated with early termination of pregnancy and reductions in maternal body weight from the oral developmental toxicity study was used for adults and teens, and the NOAEL of 20 mg/kg bw/day from the 28-day oral toxicity study was used for children, teens and adults in light of the absence of short-term toxicity investigations. A dermal absorption value of 44% for benzophenone, determined in monkeys under unoccluded conditions, was applied to the dermal estimates for route-to-route extrapolation from the dermal to oral route (see section 7.1.2).

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

Source	Age group	Route	Exposure estimate (mg/kg bw/day or mg/kg bw/event)[a]	Oral critical effect level (mg/kg bw/day)	Margins of exposure (MOE)
Environ-mental media and food (daily)	Toddler Adult Toddler Adult	Oral	0.0045 0.0011 0.0045 0.0011	3.1 (non-cancer kidney effects) 19 (kidney cancer)	688 2 800 4 210 17 200
Baby bottles	Infants	Oral	0.0015-0.051	20 (non-cancer kidney and liver effects)	393–13 500
Nail polish (per event)	Adult Teen	Dermal and inhala-tion	0.076 0.091	5 (maternal toxicity in developmental study) 20 (non-cancer kidney and liver effects)	55–65 220–263
Nail polish (per event)	Child	Dermal and inhala-tion	0.049	20 (non-cancer kidney and liver effects)	409
Fragrance (daily)	Adult	Dermal and inhala-tion	0.01	3.1 (non-cancer kidney effects) 19 (kidney cancer)	310 1 900
Body cleanser (daily)	Adult	Dermal	0.0029	3.1 (non-cancer kidney effects) 19 (kidney cancer)	1 069 6 552
Body cleanser (daily)	Teen	Dermal	0.0024	3.1 (non-cancer kidney effects) 19 (kidney cancer)	1 292 7 917
Interior paint (per event)	Adult	Dermal and inhala-tion	0.068	5 (maternal toxicity in developmental study)	74

Source	Age group	Route	Exposure estimate (mg/kg bw/day or mg/kg bw/event)[a]	Oral critical effect level (mg/kg bw/day)	Margins of exposure (MOE)
Exterior paint and stain (per event)	Adult	Dermal	0.067	5 (maternal toxicity in developmental study)	75

[a] Only estimates associated with the upper-bound concentration are presented for products available to consumers.

The calculated margins of exposure (MOEs) associated with environmental media and food, including exposure to benzophenone from baby bottles, are considered adequate to address uncertainties in the health effects and exposure datasets. For products used by consumers, the potential dermal and inhalation exposures were combined to quantitatively characterize the risk of using products available to consumers containing benzophenone. The calculated MOEs associated with the nail polishes and exterior and interior paint as well as stain use scenarios are considered inadequate to address uncertainties in the health effects and exposure datasets.

7.4 Uncertainties in evaluation of risk to human health

Although there are some uncertainties in the health effects dataset (e.g., no inhalation study available, limited details available for chronic dermal studies, and unknown mode of action of carcinogenicity), there is high confidence that carcinogenicity and renal and liver effects are critical endpoints for benzophenone. There is also some uncertainty regarding the metabolism of dermally absorbed benzophenone and the extrapolation of the critical effect levels from oral studies to dermal route of exposure. However, the extrapolation from oral to dermal is considered appropriate. There is also uncertainty regarding the hazard potential of benzophenone via dermal route of exposure in combination with sunlight exposure, which may lead to the generation of more toxic metabolites. There is uncertainty in the exposure dataset including the parameters used in the models as well as the potential for aggregate exposures.

8. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to the environment from benzophenone. It is concluded that benzophenone does not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as it is 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 screening assessment, it is concluded that benzophenone 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.

Therefore, it is concluded that benzophenone meets one or more of the criteria set out in section 64 of CEPA.

It has also been determined that benzophenone 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 daily intake (µg/kg bw/day) of benzophenone for various age groups within the general population of Canada

Table A-1. Estimates of daily intake (µg/kg bw/day) of benzophenone for various age groups within the general population of Canada

Route of Exposure	0–6 mo[a] (breast milk fed)[b]	0–6 mo[a] (formula fed)[c]	0–6 mo[a] (not formula fed)[d]	0.5–4 yr[e]	5–11 yr[f]	12–19 yr[g]	20–59 yr[h]	≥60 yr[i]
Indoor air[j]	0.02	0.02	0.02	0.05	0.04	0.02	0.02	0.02
Drinking water[k]	NA	0.03	0.01	0.01	0.01	0.01	0.01	0.01
Food[l]	NI	NI	1.30	3.85	3.04	1.90	1.07	0.71
Dust[m]	1.14	1.14	1.14	0.60	0.23	0.01	0.01	0.01
Total	**1.17**	**1.20**	**2.48**	**4.51**	**3.31**	**1.94**	**1.11**	**0.74**

Abbreviations: N/A = not applicable; NI = data not identified in the literature; mo = months; yr = years.

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day (Health Canada 1998), and to ingest 38 and 0 mg of dust and soil per day, respectively (Wilson et al. 2013).

[b] No breast milk monitoring data for benzophenone was identified.

[c] Exclusively for formula-fed infants, assumed to drink 0.8 L of water per day (Health Canada 1998), where water is used to reconstitute formula. No monitoring data on benzophenone in formula were identified; therefore, dietary intakes are only those from water. See footnote on drinking water for details.

[d] Exclusively for not formula-fed infants, assumed to drink 0.7 L of water per day (Health Canada 1998), and approximately 50% of non-formula-fed infants are introduced to solid foods by 4 months of age, and 90% by 6 months of age (NHW 1990).

[e] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day, to consume 54.7 g of fish per day (Health Canada 1998), and to ingest 41 and 14 mg of dust and soil per day, respectively (Wilson et al. 2013).

[f] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day, to consume 89.8 g of fish per day (Health Canada 1998), and to ingest 31 and 21 mg of dust and soil per day, respectively (Wilson et al. 2013).

[g] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day, to consume 97.3 g of fish per day (Health Canada 1998), and to ingest 2.2 and 1.4 mg of dust and soil per day, respectively (Wilson et al. 2013).

[h] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day, to consume 111.7 g of fish per day (Health Canada 1998), and to ingest 2.5 and 1.6 mg of dust and soil per day, respectively (Wilson et al. 2013).

[i] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day, to consume 72.9 g of fish per day (Health Canada 1998), and to ingest 2.5 and 1.5 mg of dust and soil per day, respectively (Wilson et al. 2013).

[j] No Canadian indoor air monitoring data were identified; therefore, Japanese indoor air monitoring data (maximum of 98 ng/m^3) were used as a conservative approach for deriving upper-bounding estimates of daily exposure from indoor air. No outdoor air monitoring data were identified.

[k] US treated drinking water monitoring data (0.26 µg/L; mean, Loraine and Pettigrove 2006) were used for deriving estimates of daily intake from drinking water exposure.

[l] No Canadian monitoring data for food packaging material were identified; therefore, food monitoring from the UK FSA 2011 comprehensive survey were used for deriving conservative estimates of daily intake of benzophenone based on food items and ingestion rates from the 1970–1972 Nutrition Canada Survey (Health Canada 1998). Given these are measurement data, it is assumed that these values would account for benzophenone from all potential sources (i.e., flavouring agent, packaging, natural occurrence (lesser extent) and environmental presence).

[m] Canadian dust monitoring data (maximum of 225.8 µg/g; Won and Lusztyk 2011) were used for deriving upper-bounding estimates of daily intake for dust exposure via ingestion.

[n] NA

Appendix B. Estimates of daily intake of benzophenone for infants from baby bottles

Peak concentrations of benzophenone in simulated formula were associated with the use of new baby bottles and appeared to decrease considerably with repeated use or migrations (Onghena et al. 2016; Simoneau et al. 2012). While new baby bottles may be introduced at any time during infancy, a scenario was developed for early infancy, i.e., 0–1 month of age, as a conservative approach by assuming (1) that concentrations of benzophenone in formula would be observed up to the highest average reported in the literature (184 µg/kg) based on the first migration of new bottles at 70°C for 2 hours (Simoneau et al. 2012) and (2) that this age group would be strictly bottle-fed. Maintaining concentrations associated with the first migration from new bottles for all feedings during an entire month is expected to be a conservative approach given the frequency of use (average meals per day) for this age group (US EPA 2008) relative to migration patterns (decreasing concentration) with repeated use.

Table B-1. Benzophenone intake estimates for infants associated with benzophenone migration from baby bottles

Infant age groups	BW (kg)	Range of average conc (µg/kg)	Average ingestion rate (kg/day)	Max ingestion rate (kg/day)	Lower intake (average ingestion + lower conc) (µg/kg bw/day)	Upper intake (max ingestion + upper conc) (µg/kg bw/day)
0 to 1 month[a]	3.9	9–184[b]	0.644	1.08	1.5	51

Abbreviations: BW = body weight; conc = concentration; max = maximum.

[a] Based on average female infant weight of 3.9 kg (NCHS 2000) and an average formula intake of 644 g/day and maximum formula intake of 1080 g/day (INSPQ 2001).

[b] Range of average concentrations from early migrations from baby bottles reported in Mertens et al. 2016 and Simoneau et al. 2012.

Appendix C. Parameters and details on scenarios for products used by consumers

Exposures were estimated for different age groups on the basis of Health Canada's exposure factors for the general population of Canada (Health Canada 1998):

Children (5–11 years): 31.0 kg; inhalation rate of 14.5 m^3/day
Teenagers (12–19 years): 59.4 kg; inhalation rate of 15.8 m^3/day
Adults (20–59 years): 70.9 kg; inhalation rate of 16.2 m^3/day

Exposure scenarios were derived using ConsExpo Web (2016), and defaults and assumptions are presented in Table C-1. For cosmetics and paint scenarios, all assumptions and defaults were based on several references and ConsExpo default assumptions (RIVM 2006). An overall retention factor of 1 was used unless otherwise specified, and frequencies are based on per day events unless otherwise specified.

Table C-1. Details of exposure scenarios

Product and conc.	Age group	Dermal scenario	Inhalation scenario
Nail polish[a] 5%	Adult Teen	Product amount on skin = 0.23 g (0.16 g on skin from 2 colour coats, and 0.07g from 1 top coat)	Product amount applied (total, 2 colour coats, 1 top coat) =1.13 g Exposure/Application duration = 53 min Release area[b] = 78.8 cm^2
Nail polish[a] 5%	Child	Product amount on skin = 0.06 g (2 colour coats)	Product amount applied = 0.27 g Exposure duration = 35 min Release area[b] = 17.6 cm^2
Fragrance[c] 0.3%	Adult	Product amount on skin = 0.33 g Frequency (x/day) = 1.7	Product amount applied = 0.33 g Frequency (x/day) = 1.7
Body cleanser[d] 0.3%	Adult Teen	Product amount on skin = 11 g (both adults and teens) Frequency (x/day) = 1.4 (adults) , 1.0 (teens) Retention factor = 0.01	Not quantified[e]
Interior paint[f] 0.1–0.3%	Adult	Contact rate = 30 mg/min Release duration = 120 min	Exposure duration = 132 min Product amount = 3750 g Release area = 15 m^2 Application duration = 120 min

Product and conc.	Age group	Dermal scenario	Inhalation scenario
			Inhalation rate = 36.7 m^3/day (Light exercise)
Exterior paint[f] 0.1–0.3%	Adult	Contact rate = 30 mg/min Release duration = 120 min	Exterior use, therefore inhalation is not considered[g]
Stain 0.1–0.3%	Adult	Contact rate = 30 mg/min Release duration = 120 min	Exterior use, therefore inhalation is not considered[g]

[a] For adults, teenagers and children, the product amount on skin assumes the product is applied to fingernails and toenails, and that absorption only occurs on the skin around the nails (not through nail). Product amounts are based on Ficheux et al. (2014), and exposed area is based on Ficheux et al. (2014) and RIVM (2006). The evaporation mode of release and the default mass transfer coefficient of 10 m/hr, with a molecular weight matrix of 124 g/mol, with increasing area over time, were selected for inhalation, and all other defaults were as per RIVM (2006) for nail polish.

[b] The release/surface area accounts for the area for the fingers and toes and the area for each coat (drying between coats) (based on information from Ficheux et al. (2014) and professional judgment.

[c] Frequency and product amount are based on Loretz et al. (2006).

[d] Frequency and product amount are based on Loretz et al. (2006) for adults and Ficheux et al. (2015) for teens.

[e] Due to short product use duration and subsequent wash-off, inhalation exposure is not expected to be significant.

[f] Defaults based on ConsExpo's "Brush/roller painting, waterborne wall paint" default scenario (RIVM 2007). The evaporation mode of release and the default mass transfer coefficient of 10 m/hr, with a molecular weight matrix of 120 g/mol, and increasing area over time, and all other defaults are as per the ConsExpo default scenario for inhalation. The modelled mean event concentration in air for this scenario was found to be 25.7 µg/m^3, which is higher than that of 11.7 µg/m^3 measured in the air chamber from the NRC study (Won and Lusztyk 2011).

[g] The predicted concentration in outdoor air was not estimated. Weather conditions, which can be highly variable and affect ventilation rate as well as temperature, and an undefined room volume (infinitely large) prevent the quantification of reasonable outdoor inhalation exposures (RIVM 2007b).