Environment Canada Environnement Canada

Screening Assessment

1,1'-Biphenyl

Chemical Abstracts Service Registry Number 92-52-4

Environment Canada
Health Canada

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Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of 1,1'-biphenyl, Chemical Abstracts Service Registry Number (CAS RN) 92-52-4. 1,1'-Biphenyl (henceforth referred to as biphenyl) had been identified as a priority for assessment based on human health concerns.

Results from a survey conducted under the authority of section 71 of CEPA 1999 for the year 2000 indicate that biphenyl was not manufactured in Canada, although 10,000 to 100,000 kg of biphenyl were imported into Canada. In Canada, biphenyl is mainly used in the chemical industry as an intermediate in the production of heat transfer fluids. Based on information presented in the available scientific and technical literature, biphenyl has also been used as a dye carrier for textiles, in copying paper, as a solvent in chemical and petrochemical industries and as a fungistat in packaging for citrus fruits. Also, biphenyl has been detected in coal tar-derived creosotes, which have a wide application in wood preservation. Until the mid-1970s, biphenyl was used principally as an intermediate in the production of polychlorinated biphenyl (PCBs); however, this use has since ceased because of the prohibition of the manufacture of PCBs.

Biphenyl occurs from both natural and anthropogenic sources. Biphenyl is found naturally in coal tar, crude oil and natural gas. The primarily anthropogenic source is incomplete combustion of biomass, coal, mineral oil, fossil fuels, incinerators and burning of agricultural waste. Other emission sources include motor vehicle exhaust, residential and industrial heating devices, and cigarette smoke.

Biphenyl is expected to be found throughout Canada given its numerous natural and anthropogenic sources. Industrial uses of biphenyl could result in releases to surface waters. Biphenyl is not routinely monitored by Canadian provincial or federal regulatory agencies. Water concentrations have been measured, primarily from municipal drinking water supplies. No reports were found which presented data for the concentration of biphenyl in Canadian soil. Biphenyl was measured in sediment samples collected between the early 1980s and 1990. To supplement these limited older data, environmental concentrations in air, water, and soil were estimated based on National Pollutant Release Inventory data for 2008.

Based on experimental and modelled data, biphenyl is not considered to be persistent in air, water, or soil, but it is somewhat persistent in sediment.

Biphenyl has moderate potential to bioaccumulate in aquatic organisms. Based on experimental acute and chronic toxicity studies for aquatic and terrestrial species at different trophic levels, biphenyl has the potential to harm aquatic organisms at low concentrations. However, the results of conservative risk quotient (RQ) analyses indicate that predicted biphenyl concentrations near sources of exposure are unlikely to pose a risk to aquatic organisms. Similarly, a conservative RQ analysis for soil indicates that biphenyl is unlikely to pose a risk to soil-dwelling organisms in Canada.

Based on the information presented in this screening assessment, there is low risk of harm to organisms or the broader integrity of the environment from this substance. It is concluded that biphenyl does not meet the criteria under paragraph 64(*a*) or (*b*) of CEPA 1999 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 effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

The general population exposure to biphenyl is estimated to be low from environmental media and food. Exposure from consumer products is not expected to be of concern.

Long-term dietary exposure to biphenyl has been reported to cause tumours of the urinary bladder in male rats and hepatocellular adenoma or carcinoma in female mice. The critical non-cancer effects for biphenyl include histopathological changes in the urinary bladder and/or kidney in rat or mice. Investigations of the genotoxicity potential of biphenyl in several *in vivo* and *in vitro* studies have provided mixed results.

Available information indicates that long-term high-dose exposure to biphenyl causes the induction of bladder tumours in male rats by a non-genotoxic mechanism or mechanical irritation secondary to formation of bladder calculi. Similarly, biphenyl-induced hepatocarcinogenicity in female mice has been attributed to induction of peroxisome proliferation, which also reflects a non-genotoxic mechanism and may not be a relevant mode of action for humans.

The margins of exposure between critical effect levels and the upper-bounding total daily intake estimates are considered to be adequate to address uncertainties related to health effects and exposure.

Based on the information available, it is concluded that biphenyl does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as it is 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.

Conclusion

Based on available information for environmental and human health considerations, it is concluded that biphenyl does not meet any criteria set out in section 64 of CEPA 1999.

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1 Introduction

A screening assessment was undertaken for biphenyl, Chemical Abstracts Service Registry Number (CAS RN) 92-52-4. Biphenyl was identified as a priority for assessment on the basis of its high potential for human exposure prior to the completion of the categorization of substances on the Domestic Substances List (DSL). However, during categorization, biphenyl was only identified as inherently toxic to non-human organisms.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999 (Canada 1999). Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution[1].

A 2005 State of the Science Report for a Screening Health Assessment for biphenyl was posted on the Health Canada website in 2005 (Health Canada 2005). This screening assessment includes an update of the State of the Science with respect to human health aspects, along with consideration of ecological aspects.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from literature searches, up to November 2013 for ecological sections of the document and up to September 2011 for human health sections of the document. A US EPA draft toxicological review of biphenyl, published in 2011 (United States Environmental Protection Agency (EPA) 2011), was also considered in this screening assessment. In addition, an industry survey was conducted in 2000 through a Canada Gazette Notice issued under authority of Section 71 of CEPA 1999. This survey collected data on the Canadian manufacture and import of the DSL substances (Environment Canada 2001). Key studies were critically evaluated; modelling results may have been used to reach conclusions.

[1]A determination of whether one or more of the criteria of section 64 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 consumer products. A conclusion under CEPA 1999 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA 1999 or other Acts.

The approach taken in the ecological screening assessment is to examine various supporting information and develop conclusions based on a weight of evidence approach as required under Section 76.1 of CEPA 1999.

Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards. Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances programs at Health Canada and Environment Canada, with input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA) and Gradient Consulting. Comments on the ecological and human health sections of the draft of this screening assessment were received from member countries of the Organization for Economic Cooperation and Development (OECD) as part of the OECD Cooperative Chemicals Assessment Programme. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and outcome of this screening assessment remain the responsibility of Health Canada and Environment Canada.

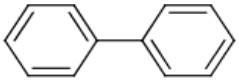
The critical information and considerations upon which the assessment is based are summarized below.

2 Substance Identity

Substance Name

For the purposes of this assessment, the substance 1,1'-biphenyl is referred to as biphenyl in this report.

Table 2-1: Substance identity for biphenyl

Chemical Abstracts Service Registry Number (CAS RN)	**92-52-4**
DSL name	**1,1'-Biphenyl**
Other names [1]	1,1'-biphenyl; bibenzene; Carolid AL; dibenzene; biphenyl; E 230; NSC 14916; phenylbenzene; Tetrosin LY; lemonene; PHPH; xenene, CP 390; MCS 1572; and Phenador-X
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Aromatic hydrocarbons
Major chemical subclass	Neutral aromatics
Chemical formula	$C_{12}H_{10}$
Chemical structure	
Smiles	C1=C(C=CC=C1)C2=CC=CC=C2
Molecular mass	154.21 g/mol

[1] National Chemical Inventories NCI 2009; Fisher Scientific Limited 2003; National Library of Medicine 2003; RTECS 2003

3 Physical and Chemical Properties

Physical and chemical properties that are relevant to the environmental fate of biphenyl are presented in Table 3-1.

Table 3-1: Physical and chemical properties of biphenyl

Property	Type	Value	Reference
Melting point (°C)	Experimental	69	CRC 2000
Boiling point (°C)	Experimental	256.1	CRC 2000
Density (g/mL at 20°C)	Experimental	1.04	CRC 2000
Vapour pressure (Pa at 25°C)	Experimental	1.19	ChemIDplus 1993—
Henry's Law constant	Experimental	28	CRC 2000

($Pa \cdot m^3/mol$)			
Water solubility (mg/L at 25°C)	Experimental	7.48	Yalkowsky and He 2003
Log K_{ow} (dimensionless)	Experimental	4.01	de Bruijn *et al.* 1989
Log K_{oc} (dimensionless)	Modelled	3.71	KOCWIN 2010

Abbreviations: K_{oc}, organic carbon partition coefficient; K_{ow}, octanol–water partition coefficient.

4 Sources

Biphenyl is known to be found both in nature and from anthropogenic sources. Biphenyl occurs naturally in coal tar, crude oil and natural gas (IPCS 1999). According to data submitted in response to a survey conducted under section 71 notice of CEPA 1999, no companies in Canada reported manufacturing biphenyl in a quantity greater than or equal to the reporting threshold of 10 000 kg for the 2000 calendar year. However, it was reported that this substance was imported into Canada in the range of 10 000–100 000 kg in the same year (Environment Canada 2001).

5 Uses

According to data submitted under section 71 of CEPA 1999, biphenyl is mainly used in the chemical industry as an intermediate in the production of heat transfer fluids. High temperature heat transfer fluids are used in chemical manufacturing processes to heat or cool reaction mixtures. The total reported uses of biphenyl under section 71 for the year 2000 were in the range of 10 000 to 100 000 kg (Environment Canada 2001).

Based on information presented in the available scientific and technical literature, biphenyl has been used globally as a heat transfer agent, fungistat in packaging of citrus fruit, dyeing assistant for polyesters organic synthesis, and also for plant disease control and the manufacture of benzidine (Lewis 1997).

The major uses of biphenyl, identified when the DSL was compiled in 1984-86, were: antifreeze/coolant/de-icer, solvent/carrier, preservative, formulation component, functional fluid i.e. hydraulic dielectric or other additives. Other use codes reported were for: catalyst/accelerator/initiator/activator; fragrance/ perfume/deodorizer/flavouring agent; and finishing agent.

Coal tar pitch, in which biphenyl is naturally present, is used in the manufacture of pavement sealants. Additionally, biphenyl has been detected in coal tar-derived creosotes (IPCS 1999); creosotes have a wide application as a wood preservation agent (Dow 2009, HSDB 2009, IPCS 1999). Also, biphenyl is a by-product in the manufacture of high octane motor and aviation fuels (UK Marine SAC (2001)).

In Canada, biphenyl is considered a List 3 formulant under the PMRA List of Formulants but it is not registered as an active ingredient under the *Pest Control Products Act* (PMRA 2007, 2008). Biphenyl is found as a component in a hydrocarbon solvent and in some pesticide fragrances in trace amounts (2009 email from Pest Management Regulatory Agency, Health Canada, to Risk Assessment Bureau, Health Canada; unreferenced). This substance is not currently listed on Health Canada's Cosmetic Ingredient Hotlist, which is an administrative tool used to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene (a) the general prohibition found in section 16 of the *Food and Drugs Act* or (b) a provision of the Cosmetic Regulations. Based on notifications submitted under the Cosmetic Regulations to Health Canada, biphenyl is not used in cosmetic products in Canada (2008, emails from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Biphenyl is not listed in the Drug Product Database as a medicinal ingredient in pharmaceuticals or veterinary drugs (DPD 2011). Biphenyl is listed in the Natural Health Products Ingredients Database (NHPID) as an acceptable non-medicinal ingredient to be used as an antifungal preservative in natural health products (NHPID 2011). The NHPID specifies an acceptable daily intake of 0.05 mg/kg-body weight (bw) per day (adopted from JECFA 1964) for oral administration (NHPID 2011). However, biphenyl is not listed in the Licensed Natural Health Products Database to be present in any currently licensed natural health products in Canada (LNHPD 2011).

The use of biphenyl in consumer products is not identified in information submitted in response to the Section 71 notice (Environment Canada 2001), nor was it listed in the US household product database (HPD 2009). However, biphenyl which exists as a natural component of coal-tar pitch and leftover residue from coal tar distillation was identified in coal tar-based driveway sealants from local retail stores in Canada (Zhu 2007) and may be a source of consumer exposure.

6 Releases to the Environment

Biphenyl is not manufactured in Canada, and its release into the environment may occur from industrial processing of the chemical intermediate, incomplete combustion of organic matter, such as from internal combustion engines, mineral oil and coal combustion, power generation, incinerators, burning of agricultural wastes and wood. Biphenyl is a by-product, notably in the manufacture of high octane motor and aviation fuels. It is also present in exhaust gas of vehicles, as well as emissions from residential heating and cigarette smoke (IPCS 1999, Brandt et al. 2002, Strandberg et al. 2006). Fugitive emissions or venting during the handling, transport or storage of biphenyl could also be a source of biphenyl in ambient air.

In information gathered through a survey conducted under section 71 of CEPA 1999 with respect to biphenyl, companies reported no release of this substance in 2000 (Environment Canada 2001). However, under the National Pollutant Release Inventory (NPRI), industrial facilities in Canada reported a release of 4400 kg and 3800 kg of biphenyl, exclusively to air, in the years 2007 and 2008, respectively (Environment Canada 2009a). On-site releases from the chemical industries sector accounted for 93% of the total emission and the rest was contributed from petroleum and coal products refining and manufacturers.

Additional releases from other sources such as smaller industries and residential wood combustion are also expected to contribute to the total annual releases of biphenyl to the environment. It is estimated that a total of 110,000 kg of biphenyl are released to air through the domestic combustion of wood in Canada (US EPA, 1995; Canadian Facts 1997). Those emissions and those from small industries across the country are not accounted for through the NPRI.

Industrial uses of biphenyl could result in releases to surface waters. Although biphenyl is not routinely monitored by Canadian provincial or federal regulatory agencies, some water sampling has been done, primarily from municipal drinking water supplies.

Biphenyl could end up in soil from the application of sewage sludge to agricultural land. Some biphenyl in Sewage Treatment Plant (STP) influent is removed and does end up in the sewage sludge.

7 Environmental Fate

The environmental distribution of biphenyl was predicted using Level III fugacity modelling (EQC 2003), which indicates that biphenyl will largely reside in the medium to which it is released (Table 7-1). Available release information presented above indicates that biphenyl releases are mostly to air. The results of

the Level III fugacity modeling indicate that if released only to air, biphenyl will remain predominantly in that medium, with small amounts of biphenyl expected to partition to water and soil. The input parameters for the EQC fugacity modelling are shown in Appendix A.

Table 7-1: Results of the Level III fugacity modelling for biphenyl (EQC 2003)

Substance released to	Air	Water	Soil	Sediment
Air (100%)	92.0	5.8	1.50	0.7
Water (100%)	2.3	86.6	negligible	11.1
Soil (100%)	negligible	negligible	100	negligible

8 Persistence and Bioaccumulation Potential

8.1 Environmental Persistence

Based on the empirical and modelled data presented below, biphenyl is not expected to persist for long periods in air or water. Biphenyl is not expected to persist for long periods in sediment or soil under aerobic conditions. Biphenyl is expected to persist for longer periods in sediment and soil under anaerobic conditions.

Air

In air, biphenyl reacts with photochemically produced hydroxyl radicals. One study reports a calculated half-life of approximately 1.5 days at 25ºC, assuming an OH concentration of 1.5×10^6 molecules/cm^3 (Leifer 1993). The predicted value for the atmospheric oxidation half-life of biphenyl (AOPWIN 2010) is 1.58 days, using a rate constant of 6.8×10^{-12} cm^3/molecule-sec (see Table 8-1). This half-life compares favourably with the experimental value.

Biphenyl is not expected to react with other photo-oxidative species in the atmosphere, such as ozone, nor is it likely to degrade via direct photolysis. Therefore, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for biphenyl. With a half-life of 1.5 days via reactions with hydroxyl radicals biphenyl is considered not persistent in air.

The short half-life in air means that biphenyl will not be widely distributed in the atmosphere and will have a low residence time in that environmental compartment.

The Transport and Persistence Level III (TaPL3) model (TaPL3 2003) was used to estimate the Characteristic Travel Distance (CTD) defined as the maximum distance traveled in air by 63% of the substance. Beyer et al. (2000) have proposed CTD's of >2000 km as representing high long-range atmospheric transport potential (LRATP), 700-2000 km as moderate LRATP, and <700 km as low LRATP. Based on the CTD estimate of 391 km, the long-range atmospheric transport potential of biphenyl is considered to be low. This means that biphenyl is not expected to be transported through the atmosphere a significant distance from its emission sources.

The Organisation for Economic Co-operation and Development (OECD) POPs Screening Model can also be used to help identify chemicals with high persistence and long-range transport potential (Scheringer et al. 2006). The OECD model is a global model that compartmentalizes the earth into air, water and soil. This model is "transport-oriented" rather than "target-oriented" as it simply identifies the CTD without indicating specifically where a substance may be transported to (Fenner et al. 2005). Klasmeier et al. (2006) have suggested that a threshold of 5098 km, based on the model's CTD estimate for PCB-180, can be used to identify substances with high long-range-transport potential. PCB-180 is empirically known to be found in remote regions. The CTD calculated for biphenyl using the OECD model is 394 km indicating that biphenyl has a low potential for transport in air from emission sources.

The OECD POPs Screening Model also calculates the transfer efficiency (TE), which is the percentage of emission flux to air that is deposited to the surface (water and soil) in a remote region (TE % = D/E x 100, where E is the emission flux to air and D = the deposition flux to surface media in a target region). The TE for biphenyl was calculated to be 0.0482%, which is well below the boundary of 2.48 (PCB-28)) established based on the model's reference substances empirically known to be deposited from air to soil or water. The low TE means that biphenyl is unlikely to be deposited from the atmosphere onto the Earth's surface.

In addition, the log K_{oa} and log K_{aw} values for biphenyl also indicate that it will have a low Arctic contamination potential (ACP) when examined using chemical partitioning space plots as described by Wania (2003, 2006).

Water

In surface water, biphenyl can be considered both readily and inherently biodegradable, according to experimental results (see Table 8-1).

A test for the ready biodegradability of biphenyl was conducted according to OECD test guideline 301 C (modified MITI test I), and found 66% Biological Oxygen Demand (BOD) after 14 days of incubation (ECHA 2007-2013a). Analysis of test material using gas chromatography and UV-VIS spectroscopy indicated primary biodegradation by 84 and 91%, respectively, after 14 days of incubation. Although this study is regarded, on the European Chemicals Agency (ECHA) website, as the key study for the biodegradation of biphenyl in water, some concerns led to it being classified as reliable with restrictions. Specifically, the substance concentration was far above the maximal water solubility of biphenyl, and no information was given on how the substance was mixed with the test medium and to what extent the substance was dissolved in the test medium. It is noted that "[most] likely the microorganisms were only exposed to a concentration approaching the maximal water solubility, the rest of the added test substance forming an undissolved layer in the test recipient, from which the substance gradually dissolved because of continuous biodegradation of dissolved substance." (ECHA 2007-2013a).

In a study for the inherent biodegradability of biphenyl, pre-adapted activated sludge microorganisms were exposed to 20 mg/L biphenyl for 43 days (Sturm test (cfr. ASTM D5209-91)) (ECHA 2007-2013b). Monitoring of CO_2 evolution indicated that biphenyl is ultimately degraded by 88% after 43 days and around 69% after 28 days. The results are generally consistent with Quantitative Structure-Activity Relationship (QSAR) modelling of the ultimate degradability of the biphenyl structure (BIOWIN 2010,DS TOPKAT c2005-2009), which indicate that biphenyl is readily biodegraded (see Table 8-2). However, the modelling results (BIOWIN 2010) only exceed the model thresholds (Environment Canada 2009b) for ready biodegradation slightly indicating that biphenyl is still a fairly stable compound. All model results are in agreement on this point.

In a study using natural lake water, biodegradation of biphenyl was examined during 10 days in a natural lake water/sediment system with naturally present microorganism (ECHA 2007-2013c). Analysis of trapped $^{14}CO_2$ indicates ultimate biodegradation of 37.8% in the low dose treatment (0.077 mg/L). The half-life of biphenyl was estimated to be 6-10 days in the lake water/sediment system. Given the low exposure duration (10 days), results of this test can be used in a weight-of-evidence approach. It should also be noted that, given its high volatility and its capacity for aerobic biodegradation, anaerobic biodegradation is expected to play a less important role in the elimination of biphenyl from natural sediment/water systems.

A river die-away study was performed in a closed test system using microorganisms present in natural river water (ECHA 2007-2013d). Evolution of

$^{14}CO_2$ was greater than 70% after 28 days, indicating that biphenyl is readily degradable in natural river water.

Estimated half-lives for the primary biodegradation of biphenyl in water range from 1.58 days in a die-away test with river water (Tittabawassee River, Midland, Michigan (Bailey et al. 1983)) to 2.8 months in clean seawater (Reichardt et al. 1981). These results indicate that biphenyl is fairly quickly degraded by microbial activity in natural river water, and to a slightly lesser extent, in marine waters.

In groundwater, calculated biphenyl half-life values ranged from 3 days to 14 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life (Howard et al. 1991).

In addition to biodegradation, the half-life of biphenyl in water might be affected by processes such as sedimentation, bioturbation and desorption. Biphenyl does not contain functional groups expected to undergo hydrolysis.

In addition to the experimental data for the degradation of biphenyl, a QSAR-based approach (Environment Canada 2007) was also applied using degradation models and results are shown in Table 8-2 below. Results from the BIOWIN degradation sub-models 3, 4, 5, and 6 (BIOWIN 2010) indicate that biphenyl biodegrades relatively fast and, therefore, the half-life of biphenyl in water would be < 182 days. The ultimate degradation predictions from DS TOPKAT (DS TOPKAT c2005-2009) and Catalogic (2013) support this conclusion.

Overall, available data suggest that biphenyl has a relatively fast rate of ultimate biodegradation and likely undergoes rapid primary transformations in the environment under aerobic conditions. A first-order mineralization half-life of approximately 17 days for water calculated using Catalogic (2013) based on the experimental 28 day BOD of 66% (ECHA 2007-2013a) was used for modelling the environmental distribution of biphenyl.

Table 8-1: Experimental data for the degradation of biphenyl in air and water

Medium	Fate Process	Test / Guideline	Degradation Value	Degradation Endpoint	Reference
Air	Oxidation	–	1.5 d	Half-life	Leifer 1993
Surface water	Aerobic biodegradation	OECD 301C	66 %	14 day BOD	ECHA 2007-2013a
Water	Aerobic	Sturm test	88 %	43 day CO_2	ECHA

	biodegradation (Inherent biodegradability)	(cfr. ASTM D5209-91		evolution	2007-2013b
Natural lake water/ sediment system	Aerobic biodegradation	–	37.8 %	10 day CO_2 evolution	ECHA 2007-2013c
Natural river water	Aerobic biodegradation	Similar to OECD 309	61 % - 78 %	30 day CO2 evolution (concs. from 0.78 µg/L to 1.27 µg/L)	ECHA 2007-2013d

Table 8-2: Modelled data for the degradation of biphenyl in air and water

Medium	Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Air	Atmospheric oxidation	AOPWIN 2010	$t_{½}$ = 1.58 days (12 hr. days)	< 2
Air	Ozone reaction	AOPWIN 2010	n/a [a]	n/a
Water	Hydrolysis	HYDROWIN 2010	n/a [a]	n/a
Water	Biodegradation (aerobic)	BIOWIN 2010 Submodel 3: Expert Survey (ultimate biodegradation)	2.90 [b] "biodegrades relatively fast"	< 182
Water	Biodegradation (aerobic)	BIOWIN 2010 Submodel 4: Expert Survey (primary biodegradation)	3.64 [b] "biodegrades fast"	< 182
Water	Biodegradation (aerobic)	BIOWIN 2010 Submodel 5:	0.34 [c] "biodegrades	< 182

		MITI linear probability	relatively fast"	
Water	Biodegradation (aerobic)	BIOWIN 2010 Submodel 6: MITI non-linear probability	0.33 [c] "biodegrades relatively fast"	< 182
Water	Biodegradation (aerobic)	DS TOPKAT c2005-2009 Probability	0.57 [c] "biodegrades relatively fast	< 182
Water	Biodegradation (aerobic)	Catalogic 2013 % BOD	t½ = 17 days (based on expt. BOD = 66%) "biodegrades relatively fast"	< 182

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; n/a, not applicable; $t_{½}$, half-life.
[a] Model does not provide an estimate for this type of structure.
[b] Output is a numerical score from 0 to 5.
[c] Output is a probability score.

Sediment and Soil

Biphenyl is expected to adsorb to suspended sediments. A sediment half-life of 333 days is reported in a 394-day mesocosm study with seawater (Pruell and Quinn 1985), however this surface layer concentration decrease is attributed to partitioning rather than biodegradation. There was a lack of decrease deeper in the sediment or in less contaminated sediment over the same time period.

Based on the above, the rate of biodegradation in sediment is expected to be slower under anaerobic conditions.

In soil, the main removal process for biphenyl appears to be biodegradation, with a calculated primary half-life value of 1.5 to 7 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life (Howard et al. 1991).

A 1992 study on the biodegradation of biphenyl in soil was conducted in a soil/groundwater system obtained from a site historically contaminated with hydrocarbons. (ECHA 2007-2013e) The biodegradation of biphenyl was studied in a mixture with phenol and this might have affected the test results. Although

the biphenyl test was conducted in a closed system with radiolabeled biphenyl, no mass balance was presented; however up to 90% of applied radioactivity was evolved as $^{14}CO_2$, so it could be assumed that recovery was acceptably high. A half-life of biphenyl in soil between 1.5 and 3.5 days was reported when nitrogen and phosphorus were added to the soil. However, it is unclear whether this refers to primary or ultimate biodegradation. Additionally, the study is missing some details about the methods used, leading it to be classified as reliable with restrictions.

The half-life of biphenyl was estimated to be 6-10 days in a natural lake water/sediment system with naturally present microorganism (ECHA 2007-2013c). It should also be noted that, given its high volatility and its capacity for aerobic biodegradation, anaerobic biodegradation is expected to play a less important role in the elimination of biphenyl from natural sediment/water systems.

In summary, the rate of aerobic biodegradation of biphenyl in soil is expected to be approximately the same as the rate of biodegradation of biphenyl in surface water, based on limited data. The rate of biodegradation of biphenyl in soil, like sediments, is expected to be slower under anaerobic conditions.

8.2 Potential for Bioaccumulation

The highest log K_{ow} of 4.01 (de Bruijn *et al.* 1989) indicates that biphenyl is expected to be bioavailable in water, resulting in practically all uptake in aquatic biota occurring directly from water.

Experimental bioconcentration factor (BCF) values range from approximately 1900 for rainbow trout (*Oncorhynchus mykiss*) (ECHA 2007-2013f) to 2422 for the eastern oyster (*Crassostrea virginaca*) (ECHA 2007-2013g). Other reported BCF values are typically below 600. A BCF of 427 appears in the BCFBAF model validation training set (BCFBAF 2010). Based on the experimental and modelled results, biphenyl is expected to have some potential to bioaccumulate in organisms.

9 Potential to Cause Ecological Harm

9.1 Ecological Effects Assessment

Experimental acute and chronic toxicity studies for aquatic and terrestrial species at different trophic levels are summarized in Appendices C and G. Critical toxicity values (CTVs) for each taxa were selected based on the lowest toxicity values identified. Chronic toxicity values were preferred over acute toxicity values

because the expected ongoing releases of biphenyl to the various media can result in long-term exposures in the near-field.

The CTV chosen to represent effects in aquatic organisms is an acute 48-hour LC_{50} of 0.36mg/L for *Daphnia magna,* taken from Gersich et al. (1989). For this assessment, the acute LC_{50} was chosen to represent the CTV because it is based on a concentration-response curve and not subject to the weaknesses of hypothesis-based values such as an MATC (Moore and Caux 1999).

No experimental toxicity data were found for benthic (sediment-dwelling) organisms. Therefore, no CTV was identified for benthic organisms.

The CTV selected to represent effects on soil organisms is an EC_{50} for lettuce (*Lactuca sativa*) (Hulzebos et al. 1993). The authors studied the effects of biphenyl on the growth of *Lactuca sativa* in soil and in nutrient solution. For the test of biphenyl in soil, the soil was collected in agreement with the specifications of OECD Guideline 208. The biphenyl was either dissolved in acetone and/or mixed with quartz sand before being mixed with the soil using quartz sand as a carrier. After 7 and 14 days, shoots were harvested by cutting them off at the soil level; the fresh weight of each plant was determined immediately after harvesting. The EC50, for reduction in growth (i.e. reduced biomass) in soil after 7 days, was reported as 54 mg/kg soil (wet weight). This value was based on the nominal concentration of biphenyl in soil.

No experimental studies were found for effects on other soil-dwelling organisms. Ecotoxicity predictions were obtained for the earthworm using the neutral organics structure-activity relationship (SAR) in the ECOSAR model (ECOSAR 2012). There is good domain applicability for the use of this SAR: the number of substances (N) in the training set is 8 and the logkow ranges from 1.5-5.3. So this SAR covers biphenyl as a non-ionizable neutral organic with a logkow within the range of bioavailability according to the SAR's logkow range. Consequently, the CTV chosen to represent effects on soil-dwelling organisms, other than plants,is the 14 day LC50 of 165.92 mg/kg (dry weight) for the earthworm.

For effects on terrestrial wildlife from inhalation, the CTV was selected as the lowest LOEC (5 mg/m^3) reported in a sub-chronic inhalation study involving rats, rabbits and mice (Deichmann et al. 1947; see Appendix G).

9.2 Ecological Exposure Assessment

Biphenyl is expected to be found throughout Canada given its numerous natural and anthropogenic sources.

There are no recent monitoring data for biphenyl concentrations in Canadian air, water, soil and sediment. Concentrations of biphenyl have been measured in Canadian air, primarily in industrial areas of Ontario in 1982-83 and 1991, in the Canadian north in 1988, and in outdoor and indoor air in Ontario in 2003. Water concentrations have been measured, primarily in municipal drinking water in the Toronto area, in a few studies in the Great Lakes area and in one or more municipalities between the 1970s and the1980s. Biphenyl was measured in sediment samples collected between 1979 and 1982 in the St. Lawrence Seaway. No reports were found which presented concentration data for biphenyl in Canadian soil.

Given the age of the monitoring studies, and to supplement empirical data, predicted environmental concentrations (PECs) were estimated using data from the National Pollutant Release Inventory (NPRI) for 2008 (Environment Canada 2009a). Conservative estimates of local exposure in the vicinity of potential sources of release to air, water and sediment were determined. For soil, a biosolids application scenario was developed and the Ontario Ministry of Environment (MOE) guidelines were used for biosolids application rates to agricultural land (MOE 1996).

Canadian monitoring data and model results, by environmental media, are described below and summarized in Table 9-1.

Air

Biphenyl is not routinely analysed in federal or provincial ambient air quality monitoring programs. In a review of the existing scientific literature, four studies identified biphenyl in ambient air at four locations in Canada (Zhu et al. 2005; Foster et al. 1991; Patton et al. 1991; and Hoff and Chan 1987). The highest measured concentrations of biphenyl in other countries ranged from 36 to 220 ng/m^3 in Glendora, California, in August 1986 (Arey et al*.* 1989).

The SCREEN3 air dispersion model (SCREEN3 1995) was used to estimate a current conservative concentration of biphenyl in air (Appendix B). NPRI release data from 2008 (Environment Canada 2013b), along with guidance from the European Commission (2003) were used as model inputs. The highest volume released to air (1600 kg) was reported from one facility in Kingston, Ontario, where biphenyl was used as a textile manufacturing aid, and, therefore, releases would be on-going fugitive gas emissions. The release from this facility accounted for 45.7 % of the total reported volume of releases in Canada for 2008. The SCREEN3 calculations give a concentration of biphenyl in air of 265

µg/m^3 (0.265 mg/m^3) at 100 metres from the source. This distance represents an average distance between an emission source and the border of an industrial site (European Commission, 2003).

Based on calculations recommended for estimating long-term exposures from short term exposures (US EPA 1992), the predicted 90 day average air concentration for biphenyl in Canada is 53.33 µg/m^3. The selection of a 90-day exposure period was based on the exposure duration in the critical mammalian toxicity study.

In addition to the point source described above, additional sources, such as residential wood combustion, might also contribute to the concentration of biphenyl in air. Information in a recent report (Great Lakes Commission 2004) indicates that a total of approximately 12,151 kg of biphenyl was released to air from residential wood combustion sources in Illinois, Minnesota, Ontario and Wisconsin. Given the difficulty in modeling air concentrations in an area of this size, and because Foster et al*.* (1991) collected ambient samples from around the Great Lakes area and found a maximum biphenyl concentration in air of 2.1 ng/m^3, that concentration can be assumed to represent the background concentration of biphenyl in air from all sources, including those identified in the Great Lakes Commission report mentioned above.

Therefore, in the area described above, which is 100 metres from the facility in Kingston, Ontario, the biphenyl concentration in air, based on releases from the facility, and also from other sources in the Great Lakes region, was estimated to be 53.33 µg/m^3. This predicted concentration is greater than the historical biphenyl concentrations measured in Canadian air, so this value was selected for risk assessment to be the conservative PEC of biphenyl in air. This value is also higher than concentrations of biphenyl in air reported in the literature for locations outside of Canada.

Water

Biphenyl is routinely monitored in Toronto drinking water. The method detection limit is 0.6 µg/L and, for 2008, the number of detectable results was zero (City of Toronto 2009). Four studies prior to 1987 identified biphenyl in surface water, with the primary focus being in the Great Lakes and in drinking water from several municipalities in eastern Ontario (Benoit et al. 1979a; 1979b; Williams et al. 1982; LeBel et al. 1987). No biphenyl concentrations in marine water were identified.

To estimate a more recent concentration of biphenyl in Canadian surface water, a PEC was derived using NPRI release data for 2008 (Environment Canada 2009a). A company in Mississauga, Ontario, reported that they disposed of 368 kilograms of biphenyl off-site to a municipal sewage treatment plant (STP). It is assumed that these disposals occurred on a daily basis when the company was in operation (assuming 250 days/year operation) for an average discharge to the STP of 1.472 kilograms of biphenyl per day. Using this discharge rate, and the Mississauga Clarkson STP effluent flow rate (129,000,000 L/d), a conservative PEC of 0.00134 mg/L or 1.34 μg/L of biphenyl in water was derived without considering removal by the STP and dilution by the receiving water (Lake Ontario).

Sediment

Two studies were found that contain information about biphenyl concentrations in Canadian sediments. Sediment concentrations ranged from 'detected' (detection limit not stated) in the Saguenay Fjord (Smith and Levy 1990) to 390 µg/kg in the St. Clair River, an area where, traditionally, some of the highest concentrations of organic contaminants in Canadian sediment are found (OME 1991).

In other countries, the maximum reported sediment concentration was 17 mg/kg from Buffalo, New York, U.S.A. (US EPA 2001). No further information on the number of samples collected or the range of concentrations at this location were identified. This value was found in a database containing over 4,100 values for biphenyl concentrations in sediment from the United States. Of these, 24 samples had a biphenyl concentration of greater than 1 mg/kg while only one sample had a biphenyl concentration of greater than 10 mg/kg. In general, concentrations of biphenyl in sediment ranged from non-detected to 410 µg/kg (Malins et al*.* 1985).

For marine sediment specifically, the detectable concentrations of biphenyl ranged from 'detected' in the Saguenay Fjord, Canada, (Smith and Levy 1990) to 60 µg/kg in the Beaufort Sea (Fowler and Hope 1984) and 410 µg/kg in Puget Sound (Malins et al*.* 1985). The sample with 410 µg biphenyl/kg was taken from an area adjacent to a "hot spot" that fit the profile of a commercial sample of creosote; this sample result was considered by the authors to be unusually high, although no further information was provided (Malins et al*.* 1985).

A conservative assumption could be made that sediment pore water has the same biphenyl concentration as surface water. In reality, sediment pore water should be lower than the surface water concentration because some biphenyl will have partitioned from water to sediment.

If released to water, biphenyl is expected to sorb to suspended particulates, as indicated by its moderate K_{ow} and high K_{oc} values. Simple equilibrium partitioning (EqP), based on the K_{oc}, can be used to predict the concentration of biphenyl in sediment from the concentration in overlying surface water. The equation is:

$$PEC_{sediment} = PEC_{water} \times K_{oc} \times f_{oc}$$

Where:
$PEC_{sediment}$ = Predicted Environmental Concentration of biphenyl in sediment (µg/kg);
PEC_{water} = Predicted Environmental Concentration of biphenyl in water (µg/L);
K_{oc} = Partition coefficient for suspended sediment (L/kg);
f_{oc} = Fraction of organic carbon in sediment (%).

US EPA (2000) identified f_{oc} values ranging from 0.03 to 0.05 for bottom sediments. An f_{oc} of 0.03 was considered appropriate for this assessment.

Using conservative predictions for the surface water concentration (1.34 µg/L), the log K_{oc} ((3.71) (Montgomery 1991) which translates to a K_{oc} of $5.13 \times 10^{3)}$, and using an f_{oc} of 0.03, the resulting PEC for biphenyl in sediment is 206 µg/kg (dry weight).

Soil

No data pertaining to biphenyl concentrations in Canadian soil were found.

In other countries, the highest reported biphenyl concentration in soil was 5,000 mg/kg in a Kentucky, U.S.A. roadside ditch. This value, however, is not considered reliable because no other details or reference for the study were provided (US EPA 1984). Studies from coal-tar contaminated soils, landfills, contaminated sites, and from disposal areas for oil and gas production wastewater in the U.S. have identified concentrations of biphenyl ranging from ‘non-detectable’ to 10,000 µg/kg, with the majority of detectable concentrations ranging between 5 µg/kg and 900 µg/kg (Aamot et al. 1996; Yu et al. 1990; Eiceman et al. 1986; Davani et al. 1985; Ehrlich et al. 1982).

Biphenyl in STP influent is calculated to be removed at 42.9 % by sorption to sludge (Environment Canada 2013c). Since the application of the resulting biosolids to agricultural land is a possibility, an exposure scenario involving biosolids-amended soil was developed.

No data on biphenyl concentrations in Canadian biosolids were found. For the conservative soil exposure scenario, a dry weight concentration of biphenyl in biosolids is calculated for the Mississauga, Ontario site (see Appendix D for calculations). According to Ontario Ministry of Environment guidelines (MOE 1996), the maximum allowable rate for biosolid application to agricultural lands is 8 tonnes per hectare per 5 years. Assuming that the biosolids are incorporated into the top 20 cm of the soil and assuming a standard bulk density of dry soil (1200 kg/m^3 (Williams 1999)), the soil mass is 2400 tonnes/hectare. Using a conservatively estimated biphenyl concentration in biosolids of 10.27 mg/kg dry weight (see Appendix D) and assuming that biphenyl-containing biosolids is applied to agriculture land for 10 years and that no loss of the biphenyl occurs, the soil concentration is calculated as follows:

Soil biphenyl concentration after 10 years of biosolids application

= (10.27 mg/kg dry wt. × 8 tonnes/ha × 2) / (2400 tonnes/ha)

= 0.068 mg/kg dry wt. soil

This value will be used as the PEC for exposure to soil-dwelling organisms.

Table 9-1: Environmental concentrations of biphenyl in Canada

Medium	Sampling location	Concentration	Sampling date/ NPRI Reporting period	Reference
Air	Along the Niagara River, New York State	0.49 ng/m^3 - 9.6 ng/m^3 (particulate) 0.69 ng/m^3 -22 ng/m^3 (vapour)	1982-83	Hoff and Chan 1987
Air	Alert, Northern Ellesmere Island, Canada	0.49-2.4 ng/m^3 1.2 ng/m^3 (mean) (n=10)	1988	Patton et al. 1991
Air	Port Stanley, Point Petre and Dorset Ontario	0.9 ng/m^3 (mean excluding Nds) 0.1 ng/m^3 (low) 2.1 ng/m^3 (high) 31% Nd (n=39)	1991	Foster et al. 1991
Air	Ottawa, Ontario	0.2 µg/m^3 (maximum)	2003	Zhu et al. 2005
Air (Modelled)	Kingston, Ontario	265 µg/m3 (1-hour average) 53.33 µg/m3 (90-day average)*	No date	Environment Canada 2010a
Water (Modelled)	Mississauga, Ontario	1.34 µg/L	2006	Conservative estimate from this assessment
Water	Toronto drinking water	Nd (µg/L) (n=14; MDL=0.6 µg/L)	2008	City of Toronto 2009
Sediment	Artificial islands in Beaufort Sea	Nd-60 µg/kg (dry weight) (n=5)	1981-1982	Fowler and Hope 1984
Sediment	St. Clair River,	Nd - 390 µg/kg	-	OME 1991

	Ontario			
Sediment (Modelled)	Mississauga, Ontario	206 µg/kg (dry weight).	-	Conservative estimate from this assessment
Soil (Modelled)	Mississauga, Ontario	0.068 mg/kg	-	Conservative estimate from this assessment

Notes:
Nd = non-detect
n = number of samples
MDL = method detection limit

* Derived by interpolating between factors recommended in US EPA (1992) for estimating long-term from short-term exposure. A 90-day period was chosen to correspond to the duration of the critical mammalian inhalation toxicity study.

9.3 Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on weight-of-evidence approach and using precaution as required under CEPA 1999. Lines of evidence considered include results from conservative risk quotient calculations, as well as information on persistence, bioaccumulation, ecotoxicity, sources, fate of the substance and its presence and distribution in the environment.

9.3.1 Risk Quotient Analysis

A risk quotient (RQ) analysis, integrating PECs with known adverse environmental effects, was performed for each compartment. For the analysis, a conservative critical toxicity value (CTV) was first selected for different species in all compartments. A predicted no-effect concentration (PNEC) was derived for each endpoint from the CTV by applying an assessment factor of between 10 and 100 to account for species variability, extrapolation of results from laboratory to field, and, as required, from acute to chronic toxicity. For all environmental media, the PNEC was estimated on the basis of the most sensitive species identified in the literature, with preference for chronic over acute studies. The results of the risk quotient analyses are presented in Table 9-2. The RQs for all media are less than 1.

9.3.2 Risk to Pelagic Organisms

Based on conservative estimates, and assuming a 368 kg/yr release of biphenyl from the Mississauga facility, the PEC of biphenyl in surface water is 0.0013 mg/L.

The most sensitive organism to biphenyl is *Daphnia magna*, a freshwater invertebrate, with an acute LC50 of 0.36 mg/L (Gersich et al. 1989). This value has been selected in this assessment as the CTV for aquatic organisms. Dividing the CTV by an assessment factor of 100 (10 to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity, and 10 to account for extrapolation from acute to chronic effects) gives a PNEC of 0.0036 mg/L.

Therefore, the conservative risk quotient (PEC/PNEC) for pelagic organisms is 0.37 (0.00134 mg/L / 0.0036 mg/L). This result indicates that biphenyl in Canadian surface water is unlikely to pose a risk to aquatic organisms.

9.3.3 Risk to Benthic Organisms

Data on the concentration of biphenyl in Canadian sediment are limited.

Exposure of sediment-dwelling benthic organisms to biphenyl could occur from the surface water, i.e., sediment pore water, or via the sediment alone. Organisms are exposed to both simultaneously. The Equilibrium Partitioning (EqP) approach estimates the exposure in pore water, not the ingestion of the solid phase, that causes toxicity. In other words the amount adsorbed to sediment (mg/kg) equates to a sediment pore water concentration that is the main route of exposure, not the sediment itself. Based on conservative estimates, the PEC for sediment porewater is selected to be the same as the PEC in surface water, i.e., 0.00134 mg/L.

No acute or chronic toxicity studies involving freshwater or marine benthic organisms were identified in the literature. Assuming similar toxicity as for pelagic organisms, biphenyl would be unlikely to pose a risk to benthic organisms.

9.3.4 Risk to Soil Organisms

The modelled PEC for biphenyl in Canadian soil is 0.0.68 mg/kg (dry weight).

The most sensitive plant species identified is lettuce (*Lactuca sativa*), with a 7-day EC50 (reduction in growth) of 54 mg/kg soil dw (Hulzebos et al. 1993). This EC50 has been selected in this assessment as the CTV for plants. Dividing the CTV by an assessment factor of 100 (to account for interspecies and intraspecies variations in sensitivity, and extrapolation from acute to chronic effects), gives a PNEC of 0.54 mg/kg dw. Therefore, the risk quotient for plants is 0.13.

Since no experimental data were identified for soil invertebrates, the model ECOSAR (US EPA 2000) is used to estimate an LC50 for earthworms. Using this LC_{50} as a CTV for soil invertebrates and dividing by an assessment factor of 100 to account for interspecies and intraspecies variations in sensitivities and extrapolation from acute to chronic effects) gives a PNEC of 1.78 mg/kg. Therefore, the risk quotient for soil invertebrates is 0.038. It is therefore unlikely that biphenyl poses a risk to soil invertebrates.

9.3.5 Risk to Terrestrial Organisms: Inhalation Exposure

Based on 2008 NPRI data for the facility in Kingston, Ontario reporting the largest release of biphenyl to air (Environment Canada 2009a) and based on the calculated 90-day average concentration of biphenyl in air, the most conservative modelled PEC, at 100 m from the facility, is 0.053 mg/m^3.

For inhalation exposure, the mouse was found to be the terrestrial mammal that is the most sensitive to sub-chronic inhalation of biphenyl (Deichmann et al. 1947), with an 87-day inhalation LOEC of 5 mg/m^3 (respiratory difficulty). This LOEL was selected as the CTV for terrestrial mammal inhalation exposure. Dividing the CTV by an assessment factor of 10 to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity, gives a PNEC of 0.5 mg/m^3.

Therefore, the conservative risk quotient for terrestrial mammals for inhalation exposure is 0.11. Consequently, it appears that biphenyl is unlikely to pose a risk to terrestrial mammals through inhalation exposure.

Table 9-2: Calculation of risk quotients

Media	Organism	CTV	Reference	PNEC	PEC	Reference	RQ
Water	Daphnid *(Daphnia*	0.36 mg/L	Gersich *et. al.* 1989	0.0036 mg/L	0.00134 mg/L	Modeled using NPRI 2008 release data	0.37

Media	Organism	CTV	Reference	PNEC	PEC	Reference	RQ
	magna)					(Environment Canada 2009a)	
Soil	Earthworm	178 mg/kg	ECOSAR model (US EPA 2000)	1.78 mg/kg	0.068 mg/kg	Calculated using STP model (Environment Canada 2013c) and OMOE guidelines for biosolids application	0.038
Soil	Lettuce (*Lactuca sativa*)	54 mg/kg dw	Hulzebos et al. 1993	0.54 mg/kg dw	0.068 mg/kg	Calculated using STP model (Environment Canada 2013c) and OMOE guidelines for biosolids application	0.13
Air	Mouse	5 mg/m^3 (inhala-tion)	Deichmann et al. 1947	0.5 mg/m^3	0.053 mg/m^3 (90-day average)	SCREEN3 model using NPRI release data (Environment Canada 2009a)	0.11

Notes:
dw = dry weight
bw = body weight

9.4 Consideration of Lines of Evidence and Conclusion

Biphenyl is not manufactured in Canada. Biphenyl is imported into Canada and used in significant quantities - between 10 000 and 100 000 kg in calendar year

2000 - for use in the chemical industry as an intermediate in the production of heat transfer fluids. Biphenyl releases are mainly to air, from the industrial activities specified above. However, releases to water and soil (from STP sludge application) could also occur.

Once in the environment, biphenyl is expected to partition mainly to the compartment into which it is released. Some biphenyl released to water will partition to sediment. Biphenyl has low persistence in air is not subject to long-range transport in this medium. Biphenyl is readily and inherently biodegradable in surface water. Biphenyl also has low persistence in soil, and probably low persistence in sediment, via aerobic biodegradation. It is expected that biphenyl will persist for longer periods under anaerobic conditions, such as in deeper sediments. Given biphenyl's lack of persistence in all media, exposure is most likely to occur near sources of release. Biphenyl is bioavailable and has some potential for bioaccumulation: the highest reliable BCF values range from 1900 to 2422).

For inhalation exposure, the mouse was found to be the terrestrial mammal that is the most sensitive to sub-chronic inhalation of biphenyl, with an 87-day inhalation LOEC of 5 mg/m^3 (respiratory difficulty); using this LOEL the conservative risk quotient for terrestrial mammals for inhalation exposure is 0.11. Therefore, it appears that biphenyl is unlikely to pose a risk to terrestrial mammals through inhalation exposure. Biphenyl can be hazardous to aquatic organisms at low concentrations (LC_{50} < 1 mg/L). However, the results of conservative risk quotient (RQ) analyses, indicate that predicted biphenyl concentrations near sources of exposure are unlikely to pose a risk to aquatic organisms. Similarly, a conservative RQ analysis for soil indicates that biphenyl is unlikely to pose a risk to soil-dwelling organisms in Canada. Assuming similar toxicity as for pelagic organisms, biphenyl is unlikely to pose a significant risk to sediment-dwelling organisms.

Therefore, based on the information available, it is concluded that biphenyl does not meet the criteria under paragraph 64 (*a*) or 64(*b*) of CEPA 1999 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.

9.5 Uncertainties in Evaluation of Ecological Risk

For this assessment, environmental concentrations are modelled due to the limited recent Canadian monitoring data available. Model selection, inputs,

release scenarios, specific site information and meteorology data can all affect the final exposure values.

Uncertainty also exists with respect to the quantities of biphenyl released from wood preservation facilities, from areas potentially contaminated sites and from landfill discharges. Additional sources of biphenyl that were not included in the assessment might be important, e.g., residential wood combustion, forest fires, and by-products of fossil fuel manufacture and use, although monitoring data might have accounted for these diffuse sources. Nonetheless, the use of conservative exposure scenarios is considered to be sufficiently protective.

No studies were found for the toxicity of biphenyl to sediment-dwelling organisms. Few studies deal with the effects of biphenyl on terrestrial organisms other than rats and mice. During the external review process, questions were raised about the reliability of the mouse study from which the CTV for air inhalation was taken, but in the absence of other suitable inhalation data, this study was used. Soil invertebrate exposure to biphenyl has not been studied.

10 Potential to Cause Harm to Human Health

10.1 Exposure Assessment

10.1.1 Environmental Media and Food

Although exposure to biphenyl may occur from ingestion of contaminated food or water, the most likely route of exposure is expected to be inhalation of air. Upper-bounding estimates of intake of biphenyl for each age group in the general population of Canada are presented in Appendix D. The upper-bounding estimate of daily intake for the general Canadian population ranges from 0.32 µg/kg body weight (kg-bw) per day for adults aged 60+ years to 0.95 µg/kg-bw per day for children aged 0.5–4 years, with indoor air being the major source of exposure.

10.1.2 Ambient Air, Indoor Air and Personal Air

The indoor air levels of biphenyl were reported in a few studies. In a retrospective analysis of chromatograms obtained from an air quality survey of volatile organic compounds (VOCs) conducted in 74 randomly selected residences in Ottawa, Ontario, during the winter of 2002 and 2003, in which biphenyl was quantified, indoor air concentrations ranged from not detected to a maximum of 1.7 µg/m^3,with an average of 0.2 µg/m^3, whereas outdoor air concentration ranged from non-detected to a maximum of 0.2 µg/m^3 with an average close to the field blank of 0.05 µg/m^3 (Zhu et al. 2005). In another earlier 1991 study of aliquot

composites of stored extracts of indoor air samples from selective 757 Canadian homes, biphenyl was detected at concentrations of about 1 µg/m^3 (Otson et al.1994). This information on the concentration of biphenyl in Canadian air is semi-quantitative and limited due to lack of concurrent measurement of standard samples. Indoor air samples collected from 10 child day care centres in the spring of 1997 in Durham, North Carolina contained biphenyl at a maximum concentration of 0.05 µg/m^3 (Wilson et al. 2001). Environmental monitoring of biphenyl in the departure area of an Italian Airport revealed concentrations ranging from 0.02 to 1.6 µg/m^3, with an average concentration of 0.35 µg/m^3 (Lavicoli et al. 2006).

With respect to outdoor air in Canada, biphenyl was found to be present at lower concentrations. In the same 2002 VOCs study in Ottawa mentioned above, the maximum concentration of biphenyl detected in ambient air was 0.2 µg/m^3 (Zhu et al. 2005). Outdoor air samples taken along the Niagara River in Southern Ontario in September 1982 were reported to contain biphenyl at a mean concentration of 0.007 µg/m^3, whereas a slightly higher level of 0.02 µg/m^3 was detected in those collected in January1983 (Hoff 1987). Outdoor air samples measured at ten child day care centres in Durham, North Carolina found biphenyl level ranged from 0.003 to 0.016 µg/m^3 with a mean of 0.009 µg/m^3 (Wilson et al. 2001).

Levels in indoor air are likely attributed to cigarette smoke and emissions from residential heating devices (CICAD 1999).

10.1.3 Drinking Water

Biphenyl was analyzed in drinking water samples from plants and distribution sites in the City of Toronto collected between January and December 2008 and samples were all detected at or below the detection limit of 0.6 µg/L (City of Toronto 2009).

10.1.4 Soil and Dust

Since no monitoring data of biphenyl in soil were identified, the upper-bounding intake estimate from soil was not quantified.

10.1.5 Food and Beverages

Biphenyl was reported to have been used as fungistat in packaging for citrus fruits; however, this application was not identified as a current practice in Canada (2009 email from Food Directorate, Health Canada, to Risk Assessment Bureau,

Health Canada; unreferenced). In 1988, 32% of the tested citrus samples in UK contained residues of biphenyl; however, over the period from 1988 to 1997, frequency and percent occurrence decreased steadily and in 1997, no residues were detected in test samples (MAFF 1998). In Penang, Malaysia, biphenyl was found in imported apples and imported oranges at concentration ranges of 0.16 to 0.71 µg/g and 0.35 to 1.65 µg/g, respectively (Saad et al. 2004). In a total diet study in the United States from 1991–1993 through to 2003–2004, approximately 280 foods were sampled and analyzed. Traces of biphenyl were detected in a few food items including bread, cereals, lettuce, cabbage, English muffin, baby food biscuit, baby food cookies, baby food oatmeal and zwieback toast (summarized in Appendix E). Generally, only one out of the 44 analyzed samples of each food type contained detectable traces of biphenyl except for baby food oatmeal, in which biphenyl was detected in one out of the four analyzed samples (USFDA 2006).

Screening-level (or upper bound) dietary intake estimates for biphenyl were generated using maximum levels reported in the literature and are outlined in Appendix F. Dietary intake was lowest in the 20-59 and the 60+ age groups with an intake estimate of 0.003 µg/kg-bw per day and highest in 0-0.5 years age group at 0.013 µg/kg-bw per day. English Muffis were the primary contributors to dietary intake estimates. However, it is noted that the reported concentrations of biphenyl in foods were obtained mainly from non-Canadian databases which may not necessarily represent primary sources of these foods for the Canadian population. Furthermore, use of maximum concentrations may overestimate potential dietary exposure to biphenyl, particularly since concentrations vary widely among published data sets and maximum values were extended to all foods within a food group.

10.2 Products

Coal tar-based driveway sealants may be a source of consumer exposure to biphenyl. Coal tar-based pavement sealants are mainly applied outdoors by consumers using rollers, however, taking into account the physical and chemical properties of biphenyl and as it is likely present at a very low concentration, the use of pavement sealants would not significantly elevate the biphenyl concentration in outdoor air.

10.3 Confidence in Exposure Database

Confidence in the exposure database for environmental media is considered to be low to moderate. The two Canadian indoor and outdoor surveys were considered semi-quantitative and no Canadian data pertaining to concentrations

in food and soil are available. However, confidence is moderate to high that exposure from use of consumer products is negligible as available information indicate that biphenyl is not used directly in products.

10.4 Health Effects Assessment

A summary of the available information on the health effects of biphenyl is presented in Appendix G.

The critical effects of biphenyl exposure have been reported as development of tumours of the urinary bladder in F344 rat and liver tumours in BDF_1 mice, following long-term dietary exposure. In a carcinogenicity study (Japan Bioassay Research Center, 1996) male and female F344 rats were administered 0, 500, 1500 or 4500 ppm (0, 38, 113 or 338 mg/kg bw per day, respectively) of biphenyl in diet for two years. A significant increase was reported in the incidence of papilloma or carcinoma of the bladder only in male rats in the high dose (338 mg/kg bw per day) group. Although calculi development and transitional cell hyperplasia (focal, nodular or papillary) were noted in the bladder of both sexes at the high dose, the incidences were much greater in males than in females. There was also a significant increase in hyperplasia and mineralization in renal pelvis in male and female rats in the high dose group. The International Programme on Chemical Safety (IPCS) reported a lowest-observed-effect-level (LOEL) of 38 mg/kg bw per day for non-neoplastic effects, including increase in serum enzymes (alkaline phosphatase, aspartate transaminase and alanine transaminase) and elevated blood urea nitrogen (BUN) levels in low-dose male and mid-dose female rats, which elevated with an increase in dose. Changes in haematological parameters (reduced haemoglobin and haematocrit) were also noted in mid and high-dose females and high-dose males (Japan Bioassay Research Center 1996; cited in IPCS 1999). Similar data were reported in Umeda et al (2002); however, according to a World Health Organization assessment of food additives (2006)[2] the dose administered by Umeda et al (2002), i.e., 0, 500, 1500 or 4500 ppm of biphenyl was

[2] According to the WHO (2006) and Health Canada (1994) dietary conversion factors, the doses of 0, 500, 1500 or 4500 ppm (Japan Bioassay Research Center, 1996) of biphenyl were estimated as 0, 25, 75 or 225 mg/kg bw per day in the rat study. Umeda et al. (2002) did not present actual daily intakes of biphenyl over the 2-year administration period. . In the present assessment, the WHO or Health Canada's conversion factors have been used for dose calculation. However, in order to adopt a conservative approach the conversion of the lowest dose tested as 25 mg/kg bw per day (which caused alterations in the serum enzyme levels in rats (IPCS 1999) was considered to be a LOEL for the purposes of calculating a margin of exposure, although this dose was reported in WHO (2006) as a NOEL.

converted and reported as 0, 25, 75, or 225 mg/kg bw per day. This conversion is in accordance with Health Canada's (1994) dose conversion guidance, and thus the LOEL = 25 mg/kg bw per day for this study.

Exposure of male and female Wistar rats for two years to dietary concentrations of 0, 630 or 1250 ppm of biphenyl (0, 47, or 94 mg/kg bw per day, respectively) did not produce stones in the urinary bladder or kidneys and no tumour formation was reported. However, similar to the results in F344 rats, dose-dependent alterations were observed in serum enzymes (aspartate transaminase, alanine transaminase and lactate dehydrogenase) in Wistar rats at both doses. The IPCS (1999) reported a lowest-observed-adverse-effect-level (LOAEL) of 47 mg/kg bw per day, based on the alterations in serum enzymes and reduced body weight gain (Takita, 1983; cited in IPCS 1999).

No evidence of carcinogenicity was reported in male and female Wistar rats following exposure to higher concentrations of 0, 2500 or 5000 ppm (0, 188, or 375 mg/kg bw per day, respectively) of biphenyl for 75 weeks. However, a dose-dependent increase was seen in the incidence of stones in the kidney in both sexes, while stones were observed in the bladder in males and females only at the highest dose (Shiraiwa et al. 1989). The IPCS suggested a NOAEL to be less than 188 mg/kg bw per day as rats developed hematuria at 188 mg/kg or greater after as early as 16 weeks of exposure (IPCS 1999). Additionally, in a 34-week study, male Wistar rats were administered 0, 0.125 or 0.5% biphenyl in the diet for 34 weeks (converted to doses of 0, 94 or 375 mg/kg bw per day by IPCS (1999). Doses of up to 5000 ppm of biphenyl did not enhance tumour formation in male Wistar rats pre-treated (in diet) with an initiator, *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN), for 2 weeks. Despite some urolithiasis (stones in the kidney, bladder and/or urinary tract) in the highest dose group in both sexes, biphenyl appeared to exhibit inhibitory effects on the initiation of carcinogenicity by EHEN. The authors suggested that biphenyl may have the ability to stimulate urolithiasis, but it did not promote EHEN induced carcinogenesis in the kidney (Shiraiwa et al. 1989). A NOAEL was suggested as 94 mg/kg bw per day from this study (IPCS 1999). In addition, strain-related differences in urine composition may play a role as male Wistar rats were found less susceptible to urolithiasis as compared to male Sprague-Dawley, when they were subjected to 15-week oral gavage studies with or without sodium chloride (Tannehill-Gregg et al 2009).

In mice, the liver appears to be a target organ for toxicity of biphenyl. In a carcinogenicity study in male and female BDF_1 mice exposed to 0, 667, 2000, or 6000 ppm (equal to to 0, 97, 291, or 1050 mg/kg-bw per day in males and 0, 134, 414 or 1420 mg/kg-bw per day in females, respectively). [IPCS (1999) converted these concentrations to doses of 0, 100, 300 and 900 mg/kg bw per day.] of

biphenyl for two years. The authors reported a significant dose-related increase in the incidence of hepatocellular adenoma and combined incidence of hepatocellular adenomas and carcinomas in female mice at 414 and 1420 mg/kg bw per day. As well, non-neoplastic effects were observed in the liver in females at 414 mg/kg bw per day and above (increased incidence of basophilic cell foci) and in the kidney in females at 414 mg/kg bw per day and above (mineralization in the inner stripe of the outer medulla) and in both sexes at 1050 mg/kg bw per day (necrotic desquamation of urothelium in the renal pelvis) (Umeda et al. 2005; Japan Bioassay Research Center 1996, cited in IPCS 1999). The NOAEL = 97 mg/kg bw/day (IPCS suggested a NOAEL of 100 mg/kg bw per day) based on the non-neoplastic effects in the liver and kidney at the mid- and high doses, as well as increases in serum enzymes (alkaline phosphatase, aspartate transaminase and alanine transaminase) and an increase in blood urea nitrogen levels and calcium in male and female mice (Umeda et al. 2005).

Investigations of the genotoxicity potential of biphenyl in several *in vivo* and *in vitro* studies have provided mixed results (see Appendix G for details). Biphenyl was not mutagenic in a number of *in vitro* bacterial gene mutation assays; however, positive results were noted in mutation frequency and mitotic recombination in cultured mammalian cells in the presence of exogenous metabolic activation and mixed results were reported in *Saccharomyces cerevisiae*. Biphenyl also induced chromosomal aberrations in human and hamster cells *in vitro*, in the presence of metabolic activation. Similarly, positive results were obtained for other endpoints (DNA damage and sister chromatid exchange) in mammalian cells *in vitro* only in the presence of activation.

The *in vivo* genotoxicity data also provided mixed; however, limited information. A single oral dose of 2000 mg/kg bw of biphenyl caused significant DNA damage in various organs of male CD_1 mice including stomach, liver, kidney, bladder, lung, brain and bone marrow after 24 hour of exposure (Sasaki et al. 1997). In a subsequent study, a single oral administration of 100 mg/kg bw of biphenyl caused DNA damage in colon; however, damage to DNA in other tissues including stomach, liver, kidney, bladder, lung, brain, and bone marrow was observed following 24 hours of exposure to 1000 or 2000 mg/kg bw of biphenyl (Sasaki et al. 2002). In contrast, no evidence of chromosomal aberrations was reported in the bone marrow of rats exposed to biphenyl via inhalation.

Available information indicates that long-term high-dose exposure to biphenyl causes the induction of bladder tumours in male rats by a non-genotoxic mechanism or mechanical irritation secondary to formation of bladder calculi. Similarly, biphenyl-induced hepatocarcinogenicity in female mice has been attributed to induction of peroxisome proliferation, which also reflects a non-

genotoxic mechanism and may not be a relevant mode of action for humans at the current level of exposure (see risk characterization).

As summarized in IPCS (1999), bladder tumours observed in male rats exposed to some chemicals may be associated with regenerative hyperplasia caused by mechanical irritation as a result of calculi formed in the urinary bladder (Cohen, 1995). Although long-term dietary exposure to biphenyl (4500 ppm, equivalent to 225 mg/kg bw per day) has induced calculi formation in the kidney or urinary bladder of both sexes of rats, the incidence was much higher in males than in females (Umeda et al. 2002). As well, stones were induced in male rats exposed to 5000 ppm biphenyl in the diet after only 34 weeks (Shiraiwa et al. 1989). No tumours were observed in either study in rats at doses below which calculi were formed. The formation of urinary calculi following high dose exposure to biphenyl in male rats has been associated with the alkaline environment of urine (pH 7.5-8.5), higher concentration of potassium salt, and a subsequent formation of urinary calculi with certain structural characteristics (Ohnishi et al. 2000; 2001). This association is supported by the observation of elevated urinary pH in male rats administered the high dose in the Umeda et al. (2002) study. Likewise, the observation of biphenyl induced tumours in male rats only is consistent with the higher incidence of calculi formation than in female rats or in mice of either sex (Ohnishi et al. 2000; 2001; Umeda et al. 2005). A potential threshold of exposure for induction of bladder tumours in male rats by biphenyl is suggested by these data, as bladder tumours were observed only in male rats following long term administration of doses sufficiently high to cause significant calculi formation and subsequent regenerative hyperplasia. The biphenyl metabolites, sulphate conjugates of 4-hydroxybiphenyl (4-HBP) and 4,4’-dihydroxybiphenyl (4,4’-DHBP), are considered to be mainly involved in the formation of urinary calculi in male rats (Ohnishi et al. 1998).

It is very probable that the induction of tumours is secondary to the formation of bladder calculi, which in male rats results from the precipitation of the potassium salt of 4-hydroxybiphenyl-O-sulfate. Analysis of the urinary calculi formed in the long-term rat study revealed that the calculi consisted principally of potassium 4-hydroxybiphenyl O-sulfate (4-HBPOSK) in males and of 4-hydroxybiphenyl (4-HBP) and KHSO4 in females. The shape and colour of the calculi were also different between sexes, as were the structure and distribution of component elements. Ohnishi et al. (2000) attributed the differences in the principal constituents and the structural formation of the calculi to the increased hydrolysis of 4-HBPOSK to 4-HBP and KHSO4 in the female rat as compared with the male rat. They also noted that this was consistent with the observed lower pH of the female urine compared with the male urine, as the lower the pH, the greater the extent of hydrolysis (Ohnishi et al., 2000). These calculi then induce sustained mechanical damage, which in turn evokes haematuria and a regenerative

response in the bladder epithelium. This is supported by the findings that bladder tumours occurred in close association with calculus formation and haematuria, and also supported by the observed sex differences in structure and composition of calculi and in occurrence of haematuria, which was absent in females. The postulated mechanism appears to be dose dependent, given the steep dose–response relationships found for the neoplastic and associated preneoplastic lesions (WHO 2006).

In the only long term study in mice, dietary exposure to biphenyl also produced a dose-dependent increase in the preneoplastic (increase in basophilic cell foci) or neoplastic lesions (hepatocellular adenoma or carcinoma) in females, but not males, exposed to 2000 or 6000 ppm (414 or 1420 mg/kg bw per day). Non-neoplastic effects in the liver included an increased incidence of basophilic cell foci in females at 414 and 1420 mg/kg bw per day. Non-neoplastic effects observed in the kidneys included necrotic desquamation of urothelium in the renal pelvis was noted in males and females (significant at 6000 ppm only), as well as mineralization in the inner stripe of the outer medulla in females (significant at 2000 ppm and above). Alterations in the blood biochemistry also indicated liver damage in females (Umeda et al. 2005). It has been suggested that a metabolite of biphenyl, 2,5-DHBP, may cause induction of peroxisomes, which may lead to the development of liver tumours, as subchronic (13-week) dietary exposure to 16000 ppm biphenyl induced formation of peroxisomes in hepatocytes in female, but not in male mice (Umeda et al., 2004). Although long-term high-dose exposure to chemicals known to be peroxisome proliferators has been reported to cause liver tumours in rodents, peroxisomes were not induced in this study at the lower concentrations (i.e., 500, 2000, 4000, 8000 or 10000 ppm), which were still greater than the dietary concentrations which induced liver tumours in female mice. However, no information was reported regarding the induction of peroxisome proliferation in this study (Umeda et al 2005). Therefore, although the induction of liver tumours by some chemicals has been attributed to peroxisome proliferation in mice (Bentley et al. 1993), and of limited relevance to humans (Moody et al. 1991; Klaunig et al. 2003), this mode of action may not be responsible for biphenyl induced hepatocarcinogenicity.

Sustained cytotoxicity and subsequent regenerative cell proliferation has also been hypothesized as another mode of action by which certain substances may cause development of liver tumours in mice or rat (reviewed in Meek et al 2003). However, there is no evidence that biphenyl or its metabolites may act through such mechanism in female mice.

A US EPA draft assessment on biphenyl was published in 2011. This assessment stated that data are insufficient to establish a mode of action for the liver tumours in female mice and thus assumed that they were relevant to

humans. Reasons cited included lack of information, including lack of data to conclude that peroxisome proliferation via peroxisome proliferator-activated receptor alpha is a relevant mode of action. However, the US EPA acknowledged that this is an area of controversy, citing for example, the high dose threshold potential for the appearance of liver tumours. The human data presented by the US EPA mainly reflected occupational exposure, which is representative of long-term and probably high-dose exposure, and all of the human data were suggestive of liver toxicity rather than liver tumours (e.g., hepatitis, chronic inflammation of liver cells, reversible changes in serum enzyme levels) (US EPA 2011).

It has been suggested that species- and sex-specific differences in the hepatocarcinogenicity of biphenyl may be due to differences in the relative importance of metabolic pathways in different species. Biphenyl was reported to be hydrolyzed in the liver followed by glucuronide or sulphate conjugation and excretion through the urine in rodents (Williams, 1967, cited in Umeda et al. 2005; Ohnishi et al. 2000). The metabolism of biphenyl is rapid and extensive in mammals. In the male rat, most of the orally administered dose (100 mg/kg bw) of biphenyl was excreted in urine within 24 hours and the mean total excretion was 84.8% after 96 hours (Meyer et al 1976). The major urinary metabolite of biphenyl (dietary exposure) has been reported as 4-hydroxybiphenyl (4-HBP) in most mammals including humans and rodents; other metabolites may include, 4,4'-dihydroxybiphenyl (4,4'-DHBP), 3,4'-dihydroxybiphenyl (3,4'-DHBP) and 2-hydroxybiphenyl (2-HBP). The overall qualitative profile of biphenyl metabolism is similar in rat, mice, pig and human; however, quantitative differences may exist. Although 4-HBP is considered as the principal metabolite of biphenyl in most animals, mice excrete more 2-HBP than rats and 2-HBP was not detected in human liver (West et al. 1956; Meyer and Scheline 1976; Meyer et al. 1976; USEPA 1984; Powis et al. 1987). 2-HBP may be further metabolized to 2,5-DHBP and 2-PBQ (which was genotoxic in rats) (Morimoto et al. 1987). It has been suggested that the hepatocarcinogenicity in mice but not in rats may be attributed to the greater propensity of mice than rats to metabolize biphenyl to 2-HBP (USEPA 1984; Umeda et al. 2005). Therefore, although limited, data suggest that humans are less likely to metabolize biphenyl to putatively active metabolites.

As discussed in Umeda et al. (2005), the sex-specific difference in the hepatocarcinogenicity of biphenyl may be due to differences in peroxisomal fatty acid *ß*-oxidation activity between male and female mice. The electron-microscopic finding of the biphenyl-induced peroxisome proliferation in female mice but not male mice in the 13-week oral study of Umeda et al. (2004) was consistent with the result of Sunouchi *et al.* (1999) that oral administration of

biphenyl to female mice increased the peroxisomal fatty acid ß-oxidation activity, while the ß-oxidation activity was not increased in the male mice.
In addition, it has been proposed that a threshold for tumour development may exist, as tumours have only been observed following a high-dose exposure to biphenyl or its metabolites and after the saturation of detoxification pathways (Meyer and Scheline 1976; also discussed in Umeda et al. 2002).

With respect to non-cancer effects considered critical, an increase in the incidence of non-neoplastic lesions in kidney, including hyperplasia and calculi formation in male and female rats and mineralization of inner strip of outer medulla in female mice was reported after chronic dietary exposure to biphenyl. Based on the data obtained from these studies, LOELs of 2000 ppm (414 mg/kg bw per day) and of 1500 ppm (75 mg/kg bw per day) were estimated for histopathological changes in the kidney of mice and rats, respectively (Japan Bioassay Research Center, 1996, cited in IPCS, 1999; Umeda et al. 2002; 2005; WHO 2006). However, alterations in biochemical parameters were reported in all groups of rats exposed for 2 years (Japan Bioassay Research Center, 1996, cited in IPCS 1999); therefore, this dose (i.e., 25 mg/kg bw per day) is considered a conservative LOEL for biphenyl induced non-neoplastic effects. Although reproductive and developmental effects have been observed in rats exposed to biphenyl, those effects were observed at doses greater than associated with renal or biochemical effects, based on a limited dataset.

In a series of early subchronic inhalation assays, non-neoplastic effects were observed in rats, including increased mortality and irritation of the mucous membranes, and in mice, including increased mortality and bronchopulmonary changes, at concentrations of 5–300 mg/m^3 (equivalent to internalized doses of 8.3-496 mg/kg bw per day) (Deichmann et al. 1947).

Confidence in the database on health effects is moderate as studies are available for most health endpoints, although limited in some cases.

10.5 Characterization of Risk to Human Health

The available data on the potential health effects of biphenyl indicate that the urinary tract and liver are targets in rodents. Long-term exposure to high doses of biphenyl induced bladder tumours in rats and hepatocellular adenoma or carcinoma in mice. Although there is some indication the biphenyl is genotoxic in some systems, available information indicates that the mode of action for induction of these tumours is not dependent on direct interaction with genetic material.

The development of bladder tumour in rat has been proposed as the result of formation of urinary calculi (associated with elevated pH) which causes mechanical damage in the bladder and subsequent regenerative hyperplasia of the bladder epithelium (Umeda et al. 2002). The formation of calculi is considered to represent a process of threshold carcinogenesis for some chemicals, including biphenyl, as high doses of these chemicals are required to produce calculi (Cohen 2002).

The development of bladder tumours following a mechanical injury by urinary calculi is a well-documented process caused by high-dose exposure to some chemicals in rodents (Moody et al. 1991; Bently et al. 1993, Cohen 2002; also discussed in Umeda et al. 2004). Bladder stones may form in humans; however, because of several anatomical or physiological differences (the bladder is vertical in humans versus horizontal in rodents, and humans will more easily lose calculi formed) and likely much lower exposures to such chemicals, the risk of bladder tumour development is considered very unlikely in humans (DeSesso 1995; Cohen 2004).

In mice, biphenyl-induced liver tumours have has been attributed to peroxisome proliferation; however, the induction of peroxisome proliferation was seen only in female mice treated with a high-dose (16000 ppm or 2000 mg/kg bw per day) of biphenyl for 13 week (Umeda et al. 2004), as was hepatocarcinogenicity in female mice exposed to 260 or 780 mg/kg bw per day for two years (Umeda et al. 2005). In chronic rodent assays, liver is considered as the most common target organ and mouse is the most sensitive species (Holsapple et al. 2006). Exposure to peroxisome proliferators has been suggested to cause liver tumour via non-genotoxic mechanism in mice (Bentley et al. 1993) and peroxisome proliferation is not considered as a relevant mode of action of tumour development in humans (Moody et al. 1991; Klaunig et al. 2003). In addition, it is unlikely that, in real-life scenario, humans may be exposed to the biphenyl dose which caused peroxisome proliferation or liver tumours in mice.

Although the induction of liver in tumours in mice by some chemicals has been attributed to a mode of action involving peroxisome proliferation (Bentley et al. 1993), it has also been proposed that biphenyl-induced carcinogenicity of liver in mice may be associated with possible DNA damage by formation of reactive biphenyl metabolites, i.e., 2-HBP, 2,5-DHBP or 2-PBQ (Umeda et al. 2005). Fortunately these metabolites do not appear to be significant in humans, based on studies in human liver and kidney slices (Powis et al. 1987). A US EPA (2011) draft assessment on biphenyl stated that data are insufficient to establish a mode of action for the liver tumours in female mice and thus assumed that they were relevant to humans. However, the US EPA acknowledged that this is an area of controversy, citing for example, the high dose threshold potential for the

appearance of liver tumours. In contrast to the US EPA assessment, this assessment focuses on possible risks to the general population. Although there is some evidence to speculate that the mode of action of biphenyl-induced tumours in the female mouse liver may be relevant to humans, the available data suggest that it is not likely to occur in humans at current levels of exposure to the general population

In light of the likely threshold mode of action of the bladder tumours in rats, the possible threshold of liver tumours in mice, but more importantly, the limited relevance of the liver tumours possibly induced by metabolites in mice to humans, the characterization of risk to humans associated with biphenyl in Canada is based on a comparison of levels associated with non-neoplastic effect to estimated levels of exposure, taking into consideration limitations in the available database.

Comparison of the lowest inhalation and oral LOELs (8.3 and 25 mg/kg bw per day respectively) for non-neoplastic effects (i.e., inflammatory changes in the lungs of mice or alterations in serum enzyme levels in rat) with the upper-bounding estimate of daily intake (0.95 µg/kg-bw per day for Canadian children) results in margins of exposure of 8700- or 26000-fold). These margins are considered adequate to address uncertainties related to health effects and exposure for cancer and non-cancer effects.

Based on the information available, it is concluded that biphenyl does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as it is 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.

10.6 Uncertainties in Evaluation of Risk to Human Health

There is uncertainty in the air concentrations of biphenyl in Canadian environment due to lack of concurrent measurements of standard samples. The maximum concentration in ambient air and indoor air samples from retrospective analysis of 74 homes in Ottawa, Ontario conducted during the winter of 2002-2003 was used to calculate the upper bounding estimate of exposure. There is uncertainty in the soil concentration of biphenyl in Canadian environment due to lack of monitoring data. The maximum concentration in dust samples from a child day care centre in Durham, Carolina was used as a surrogate. Reported concentration of biphenyl in foods were obtained from non-Canadian database. The potential dietary exposure may be overestimated because the maximum concentration of biphenyl found in a particular food item was extended to other foods within the cereal food group. There are also uncertainties regarding the

interspecies or intraspecies variation and possible mode(s) of action of the development of the tumours in experimental animals.

Uncertainties also exist due to lack of inhalation effects data in experimental animals and limited or no information regarding the toxicity potential of biphenyl in humans.

11 Conclusion

Based on the information presented in this screening assessment, there is low risk of harm to organisms or the broader integrity of the environment from this substance. It is therefore concluded that biphenyl does not meet the criteria under paragraph 64(*a*) or 64(*b*) of CEPA 1999 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.

Based on the available information on its potential to cause harm to human health, it is concluded that biphenyl biphenyl does not meet the criteria under paragraph 64(*c*) of CEPA 1999 as it is 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 concluded that biphenyl does not meet any of the criteria set out in section 64 of CEPA 1999.

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Appendix A: Model Overview of EQC (2003) and Model Input Parameters for Calculating the Level III Fugacity of Biphenyl

Model Overview

The EQC model uses chemical-physical properties to quantify a chemical's behaviour in an evaluative environment. Levels I and II assume thermodynamic equilibrium is achieved; Level II includes advective and reaction processes. Level III is a non-equilibrium, steady state assessment.

This model is useful for establishing the general features of a new or existing chemical's behaviour, ie. the media into which the chemical will tend to partition, the primary loss mechanisms, and its tendency for intermedia transport, and comparing chemicals. The result of various emission scenarios can be explored.

Level III

This calculation is of the steady state distribution of a chemical, in an environment not at equilibrium. The chemical is continuously discharged at a constant rate into the chosen environmental media, and achieves a steady-state condition at which input and output rates are equal. This involves calculating the rates of degradation and advection, from half-lives or rate constants, and advective flow rates and considering the emission. Intermedia transport processes (e.g. wet deposition, evaporation, or sedimentation) are included. The media receivingthe emissions are very important and have a controlling influence on the overall fate of the chemical.

Table Series A1: Model Inputs

Table A1-1: Chemical Parameters Table

Chemical Type	2
Molecular Mass	154 g/mol
Data Temperature	25°C

Table A1-2: Partition Coefficients Table

Partition Coefficients	Dimensionless	(L/kg)
Air-Water(Kaw)	0.01	–
Soil-Water	576	240
Sediment-Water	1152	480
Suspended Sediment-Water	2250	1500
Fish-Water(Kfw)	2835	2835

Aerosol-Water	100	–
Aerosol-Air	10000	–

Table A1-3: Half-Lives Table

Half-Lives	Hours	Days
Air	19	0.79
Water	408	17
Soil	408	17
Sediment	1632	68

Appendix B. SCREEN3: Model Overview and Inputs for Calculating Biphenyl Concentration in Air

SCREEN3 (US EPA 1995) uses a Gaussian plume model which the European Commission (2003) recommends for calculating local exposure concentrations from point sources. For area sources, SCREEN3 uses a numerical integration algorithm, the area source is assumed to be a rectangular shape, and the model can be used to estimate concentrations within that area. The model incorporates source-related factors and meteorological factors to estimate chemical concentrations from continuous sources. It assumes that the chemical does not undergo any chemical reactions, and that no other removal processes, such as wet or dry deposition, act on the plume during its transport from the source. Because the releases of interest are fugitive, this model will give very conservative exposure values. Based on the assumptions used in the European Commission (2003), Table 1 presents the inputs for the SCREEN3 model and the rationale for the selection of these inputs.

Table B1: SCREEN3 Air Model Inputs

Inputs	Selected Value	Rationale	Reference
Emission rate (g/s)	0.15	Based on NPRI database, one company in Kingston, Ontario reported releasing a total of 1.6 tonnes of biphenyl to the air throughout 2008 (equal amounts each quarter), with an estimated daily release of 6.4 kg/day or 0.15 g/s assuming that the facility is operating and releasing biphenyl 12 hours/day, 250 days/year	Environment Canada, 2013b
Stack height (m)	10	Representing the height of buildings in which production, processing or use takes place	European Commission, 2003
Stack diameter	0.5	Assumed to be conservative; greater	Based on modeling a

(m)		stack diameter resulted in decreased concentration and distance traveled	stack with 0.5 m and 1.0 m diameter
Exit velocity (m/s)	1	Average wind speed in the ambient environment	Environment Canada, 2010a
Stack gas temperature and ambient temperature (Kelvin)	293	Default for SCREEN3, assumes there is no extra plume rise caused by excess heat of vapours compared to the outdoor temperature	European Commission, 2003
Receptor height above ground (m)	0.1	Assumed to represent height of small terrestrial organisms	Assumption
Urban/Rural Option	Urban	Ontario facility is situated in an urban setting	Environment Canada, 2009a
Building downwash option	Selected	Both options were modeled, with higher concentrations at greater distances with building downwash option selected – building dimensions were assumed to be 10 m x 100 m	Based on modeling both options, the more conservative result was used in the assessment
Simple terrain with terrain below stack	Selected	Assumed more consistent deposition would occur with simple terrain below stack, also representative of expected site conditions at Ontario facility	Based on general topography surrounding facility in Ontario
Full meteorological conditions	Selected	SCREEN3 recommends using this default for all potential meteorological conditions. This includes all stability classes and wind speeds likely to contribute to the maximum concentrations	USEPA, 1995
Minimum and maximum distances (m)	1 and 100	100 metres was selected to represent the average distance between the emission source and the border of an industrial site	European Commission, 2003

Appendix C: Empirical Data for Aquatic and Terrestrial Toxicity

Table Series C1: Empirical data for aquatic toxicity

Table C1-1: Algae

Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Agmenellum quadruplicatum (blue-green algae) and *Chlorella autotrophica* (green algae)	Not stated	EC_{100} (inhibition)	10 mg biphenyl/plate	Pulich et al. 1974
Scenedesmus vacuolatus	Acute (24h)	ErC_{50} (growth rate)	1.5 umol/L	Walter et al.
Pseudokirchneriella subcapitata	Chronic (72 h)	NOEC	0.62 umol/L	CHRIP c2008
Pseudokirchneriella subcapitata	Chronic (72 h)	ErC_{50} (growth rate)	0.78	CHRIP c2008
Pseudokirchneriella subcapitata	Chronic (72 h)	E_bC_{50}	0.28	CHRIP c2008
Pseudokirchneriella subcapitata	Chronic (72 h)	NOE_rC (growth rate)	0.007	CHRIP c2008
Pseudokirchneriella subcapitata	Chronic (72 h)	NOE_bC	0.0072	CHRIP c2008
Pseudokirchneriella subcapitata	Chronic (72 h)	NOEC	0.62 umol/L	CHRIP c2008

Table C1-2: Invertebrates

Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Artemia salina (Brine shrimp) (larvae)	Acute (24 h)	24 h LC_{50}	4.01 mg/L	Abernethy et al. 1986
Colpidium campylum (Protozoa)	Acute (43 h)	LOAEL	5.6 mg/L	Dive et al. 1980
Daphnia magna Straus <24 h old	Acute (24 and 48 h)	24 h LC_{50} 48 h LC_{50} NOEC LC_{100}	1.3 mg/L 0.36 mg/L * 0.04 mg/L >0.96 mg/L	Gersich et al. 1989
Daphnia magna	Chronic	NOEC (LC100, survival)	0.17 mg/L	Gersich et al.

Straus <24 h old	(21 days)	LOEC (LC20, survival) MATC (calculated (static)(survival, mean brood size, mean number of young, and mean dry weight)	0.32 mg/L 0.23 mg/L	1989
Daphnia magna (<24 hr old)	Acute (24 and 48 h)	24 h LC_{50} 48 h LC_{50} NOEC	27 mg/L 4.7 mg/L <2.2 mg/L	LeBlanc 1980
Daphnia magna	Acute (48 h)	LC_{50}	2.1 mg/L	Dill et al. 1982
Daphnia magna (<24 hr old)	Acute (24 and 48 h)	24 h EC_{50} (immobilization) 48 h EC_{50} (immobilization) LOAEL (3.3% immobilization) EC_{100} (immobilization)	>4 mg/L 0.73 mg/L 0.25 mg/L 2.0 mg/L and 4.0 mg/L	Adams 1982
Daphnia magna (<24 hr old)	Acute (24 and 48 h)	24 h EC_{50} (immobilization) 48 h EC_{50} (immobilization) NOAEL	>5 mg/L 3.65 mg/L 1.8 mg/L	Heidolph and Gledhill 1983
Daphnia magna (4-6 day old females)	Acute (48 h)	48 h LC_{50}	3.1 mg/L	Bobra et al. 1983
Daphnia	Not stated	NOEC	0.275 mg/L	USEPA 1994
Mytilus edulis (Blue mussel)	Acute (40 min)	EC_{50} (effect on food intake)	0.3 mg/L water concentration	Donkin et al. 1989
Paracentrotus lividus and *Sphearechinus granularis* (sea urchin zygotes, embryos, sperm cells and eggs)	Acute (48 h)	Induced developmental abnormalities; pathologic, mesenchyme-billed blastulae, exogastrulae, and prehatching blockage; mitotic activity was affected, mitotic abnormalities induced	1.54	Pagano, et al. 1983

* Value chosen as CTV

Table C1-3: Fish

Test Organism	Test Type	Endpoint	Value (mg/L)	Reference
Brachydanio rerio (Zebra fish)	Acute (96 h)	96 h LC_0 96 h LC_{100}	38 mg/L 39 mg/L	BUA 1990; European Commission 2000
Cyprinodon variegates (Sheepshead minnow)	Acute (96 h)	LC_{50}	4.6 mg/L	Dill et al. 1982
Lepomis macrochirus	Acute (96 h)	LC_{50}	4.7 mg/L	Dill et al. 1982

(Bluegill sunfish)				
Oncorhynchus mykiss (Rainbow trout) (60 days old)	Acute (96 h)	LC_{50}	1.5 mg/L	Dill et al. 1982
Oncorhynchus mykiss (Rainbow trout)	Not stated	NOEC	0.23 mg/L	USEPA 1994
Oncorhynchus mykiss (Rainbow trout)	Chronic (87 d)	NOEC	0.229	ECHA c2007-2013h A
Oncorhynchus mykiss (Rainbow trout)	Chronic (87 d)	LOEC	0.332	ECHA c2007-2013h ECHA
Pimephales promelas (Fathead minnow)	Acute (96 h)	NOAEL 96 h LC_{50} 96 h EC_{50} (concentration required to cause a definite end effect – not further explained)	1.8 mg/L 5.3 mg/L 2.5 mg/L	Batchelder 1977
Pimephales promelas (Fathead minnow)	Acute (96 h)	NOAEL LOAEL LC_{10} LC_{50} LC_{90} EC_{10} (loss of equilibrium) EC_{50} (loss of equilibrium) EC_{90} = (loss of equilibrium)	0.9 mg/L 1.2 mg/L 2.5 mg/L 3.0 mg/L 3.5 mg/L 1.1 mg/L 1.3 mg/L 1.5 mg/L	Brossier 1975
Pimephales promelas (Fathead minnow)	Acute (96 h)	LC_{50}	6 mg/L	Dill et al. 1982

Table Series C2: Empirical data for terrestrial toxicity

Information on mammalian toxicity from ingestion and inhalation exposure is provided in Appendix G.

Table C2-1: Avian toxicity

Test Organism	Test Type	Endpoint	Value	Reference
Agelaius phoeniceus (Red-winged black-bird)	Not stated	Oral LD_{50}	96 mg/kg	Schafer et al. 1983

Table C2-2: Plant toxicity

Test Organism	Test Type	Endpoint	Value	Reference
Sorghum bicolor (sorghum)	21 days	EC_{50}	>1000 mg/kg dry soil	Windeatt et al. 1991

Glycine max (soybean)	21 days	EC_{50}	>1000 mg/kg dry soil	Windeatt et al. 1991
Helianthus annuus (sunflower)	21 days	EC_{50}	>1000 mg/kg dry soil	Windeatt et al. 1991
Lactuca sativa (lettuce) seeds	16 days	EC_{50} (biomass)	2.1 mg/L	Hulzebos et al. 1993
Lactuca sativa	7 days and 14 days	7 day EC_{50} 14 day EC_{50}	54 mg/kg soil ***** 68 mg/kg soil	Hulzebos et al. 1993
Pinus taeda L. (Loblolly pine) 1 and 2 year old seedlings	90 days (first experiment) 100 days (second experiment)	Biphenyl applied to the soil of Pinus taeda L. seedlings had no phytotoxic effect; however, seedlings treated with 1, 10 or 100 ppm of biphenyl in their potting soil produced less total dry weight and less shoot and root dry weight as compared to controls; Seedlings grown in biphenyl contaminated soil were found to be more susceptible to airborne phytotoxincs such as acetic acid, acetic anhydride, and aniline and water stress	–	Gorman 1979

* Value chosen as CTV

Appendix D: Calculations for Estimating the Concentration of Biphenyl in Biosolids

To estimate the approximate concentration of biphenyl in biosolids, the following equation is used:

$$C_{biosolids} = L_{infl} \times (P_{sludge} + W_{sludge}) \times 10^6 \div SP$$

Symbols:

$C_{biosolids}$ = concentration in biosolids (mg/kg dry weight)
L_{infl} = STP influent load of substance from industrial plant (kg/d)

P_{sludge}	=	percentage sorption to primary sludge
W_{sludge}	=	percentage sorption to wasted secondary sludge
10^6	=	conversion factor from kg to mg
SP	=	sludge production (kg/day)

The total amount of biphenyl in wastewater influent has been determined previously as 1.47 kg/day (Linfl). The values for Psludge (0.377) and Wsludge (0.052) were estimated using the STP modelling program (Environment Canada 2013c). To calculate the sludge production, the quantity generated per person is calculated using the population (315,000) served by the Mississauga Clarkson STP which is assumed to receive the wastewater discharge from the Mississauga facility. In Ontario, primary and secondary sludge are generated at a combined quantity of 195 g/day-person (Droste 1997). Therefore the daily sludge production from the Mississauga Clarkson STP is:

SP = 195 g/day-person x 315,000 persons = 61,425,000 g/day dry weight

= 61,425 kg/day dry weight

Therefore the estimated concentration of biphenyl in biosolids is:

$C_{biosolids}$ = (1.47 kg/day x (0.377 + 0.052) x 106 mg/kg) ÷ 61,425 kg/day

= 10.27 mg/kg dry weight

This $C_{biosolids}$ is used as a PEC for biosolids land application to determine the risk in soil.

Appendix E: Concentration of Biphenyl in Various Food Items

Table E1: Concentration of biphenyl in various food items (US FDA 2006)

Food item	Maximum (µg/kg)	Minimum (µg/kg) [1]	Number of analyses	Number of results ≥ LOQ	Number of traces[2]
Bread white, enriched	2	2	44	0	1
Bread, whole wheat	2	2	44	0	1
Shredded wheat cereal	1	1	44	0	1
Raisin bran cereal	2	2	44	0	1

Lettuce, iceberg raw	2	2	44	0	1
Cabbage, fresh boiled	1	1	44	1	0
English muffin, plain toasted	5	5	44	0	1
Baby food, teething biscuit	3	3	44	0	1
Baby food, cereal, oatmeal	2	2	4	1	0
BF, arrowroot cookies	2	2	44	0	1
BF, zwieback toast	2	2	44	0	1

Abbreviation: LOQ, limit of quantification.

[1] Assuming 1 µg/kg (lowest concentration of biphenyl quantified in any of the food items) to represent the detection limit.

[2] Traces: number of results that were greater than or equal to the limit of detection but less than the LOQ.

Appendix F: Upper-bounding Estimates of Daily Intake of Biphenyl by the General Population in Canada

Table F1: Estimated intake (ug/kg bw per day) of Biphenyl in Canadians

Route of Exposure	Breast Milk Fed 0 - 0.5 yr[a]	Formula Fed 0 - 0.5 yr[b]	Not Formula Fed 0 - 0.5 yr[c]	0.5 - 4 yr[d]	5 - 11 yr[e]	12 - 19 yr[f]	20 - 59 yr[g]	60+ yr[h]
Ambient Air[i]	0.007	0.007	0.007	0.015	0.012	0.007	0.006	0.005
Indoor Air[j]	0.420	0.420	0.420	0.890	0.700	0.400	0.340	0.300
Drinking Water[k]	0.000	0.064	0.024	0.027	0.021	0.012	0.013	0.013
Food and Beverages[l]	0.000	0.000	0.013	0.011	0.006	0.004	0.003	0.003
Soil[m]	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Total Intake	**0.42**	**0.49**	**0.46**	**0.95**	**0.74**	**0.42**	**0.36**	**0.32**

[1] No data were identified on concentrations of biphenyl in breast milk.

[2] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed), and to ingest 30 mg of soil per day (EHD, 1998).

[3] For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of biphenyl in water used to reconstitute formula was based on modelling. No data on concentrations of biphenyl in formula were identified for Canada. For non-formula fed infants approximately

50% are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990 in EHD, 1998).

[4] 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 and to ingest 100 mg of soil per day (EHD, 1998).

[5] 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 and to ingest 65 mg of soil per day (EHD, 1998).

[6] 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 and to ingest 30 mg of soil per day (EHD, 1998).

[7] 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 and to ingest 30 mg of soil per day (EHD, 1998).

[8] 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 and to ingest 30 mg of soil per day (EHD, 1998).

[9] Maximum **c**oncentration of biphenyl (0.2 µg/m^3) identified in ambient air samples from retrospective analysis of 74 homes in Ottawa, Ont. (Zhu et al. 2005) was used to calculate the upper bounding estimate of exposure. It is assumed that Canadians spend 3 hours/day outdoors (Health Canada 1998).

[10] Maximum **c**oncentration of biphenyl (1.7 µg/m^3) identified in indoor air samples from retrospective analysis of 74 homes in Ottawa, Ont. (Zhu et al. 2005) was used to calculate the upper bounding estimate of exposure. It is assumed that Canadians spend 21 hours/day indoors (Health Canada 1998).

[11] Detection limit of 0.6 µg/L found in drinking water from distribution plants in city of Toronto, Ont. between Jan. and Dec. 2008 was used as all samples contained less than detection limit.

[12] No Canadian-specific data on concentrations of biphenyl in food items have been identified. Estimates of intake from food are based upon concentrations in foods identified in a total diet study conducted in the United States from 1991–1993 through to 2003–2004 and are shown in Appendix 4 (US FDA 2006). Biphenyl was identified in bread, cereals, lettuce, cabbage, English muffin and baby food biscuit, baby food cookies and oatmeal, but generally detected in only 1 out of the 44 analysed samples except for baby food oatmeal, it was detected in one out of four analyzed samples. Actual concentration detected in each food item was used in the intake estimate. Amounts of foods consumed for each item on a daily basis by each age group are described by Health Canada (Health Canada 1998).

[13] Since no data were identified on concentration of biphenyl in soil, upper bounding intake estimate was not quantified

Appendix G: Health Effects Information for Biphenyl

Table G1: Summary of Health Effects for Biphenyl

Endpoint	Lowest effect levels1 /Results
Acute toxicity	Lowest oral LD50 (rat and mice) > 1900 mg/kg-bw (BUA, 1990; cited in IPCS 1999) Lowest inhalation LC50 (rat) > 275 mg/m^3 (Sun Co. Inc., 1977a; cited in IPCS 1999) [Additional studies: Monsanto Co., 1959; Dow Chemical Co., 1974; cited in IPCS 1999]
Short-term repeated dose toxicity	Lowest oral (diet) LOEL (rat) = 50 mg/kg-bw per day: increased relative kidney weights, polycystic renal changes, increased urine volume and specific gravity (21-day study) (Sondergaard and Blom, 1979; cited in IPCS 1999) [Additional studies: Booth et al. 1956, 1961; cited in IPCS 1999] Lowest dermal LOEL (rabbit) = 500 mg/kg-bw per day: decreased body

	weight, histopathological effects (28-day study) (Deichmann et al. 1947; cited in IPCS 1999) Lowest inhalation NOEC (male or female mice) = 160 mg/m^3 (no LOEL identified) (14-day study). No evidence of histopathological changes in lung, trachea, liver, kidney or spleen when mice were exposed to 25 or 55 ppm (160 or 350 mg/m^3) of biphenyl (Sun Co. Inc., 1977b; cited in IPCS 1999)
Subchronic toxicity	Lowest oral (diet) LOEL (rat) = 75 mg/kg-bw per day: polyuria, cloudiness of the urine, tubular dilation of the kidney (24-week study) (Booth et al. 1961; cited in IPCS 1999) Male or female mice: 0, 500, 2000, 4000, 8000, 10000 or 16000 ppm biphenyl in diet for 13 weeks. Centrilobular hepatocytes of female mice in 16000 ppm group were larger than control. Using transmission electron microscopy, the cytoplasm of these enlarged hepatocytes was filled with eosinophilic granules identified as peroxisomes. No such granules observed in male mice (Umeda et al. 2004). [Additional studies: Takita, 1983; Kurata et al. 1986; Shibata et al. 1989a, 1989b] Lowest inhalation LOEC (mice) = 5mg/m^3 (increased mortality and irritation of the respiratory tract) (4-week study) (based on limited study [Deichmann et al. 1947] involving no controls, small number of animals and exposure at one concentration only) [a]
Chronic toxicity/carcinogenicity	Lowest oral (diet) non-neoplastic LOEL (rat) = 500 ppm (considered equivalent to 25 mg/kg bw per day) (Japan Bioassay Research Center, 1996, cited in IPCS 1999) **Rat** **Dietary carcinogenicity bioassay in male and female F344 rats**: Male and female F344 rats (n = 50/sex/dose) received 0, 500, 1500, or 4500 ppm of biphenyl in diet for 2 years. IPCS (1999) converted these concentrations to doses of 0, 38, 113 or 338 mg/kg bw per day. There were significant increases in the incidence of transitional cell papillomas and carcinomas of the urinary bladder in male rats at 338 mg/kg-bw per day (31/50 versus 0/50 in controls and lower dose groups). Non-neoplastic lesions in the bladder included significant increases of calculi formation and hyperplasia of transitional epithelium of high dose males. Urinary pH was significantly higher in high-dose males. A much lower (non-significant) incidence of transitional cell hyperplasia and calculi was also observed in high dose females. Hematuria was noted in both sexes at the high dose, with the incidence much higher in males than females; urinary pH was also increased in high dose males. Calculus formation, hyperplasia and mineralization of the renal pelvis were also observed in exposed rats of both sexes.

	Serum enzyme and blood urea nitrogen levels were increased at 38 mg/kg bw per day and above. (LOEL = 38 mg/kg bw per day (IPCS 1999) (Japan Bioassay Research Center, 1996; cited in IPCS 1999) or LOEL = 25 mg/kg bw per day, based on Health Canada conversion) Umeda et al (2002) reported similar data in a separate publication. Note that a WHO assessment (WHO, 2006) converted the doses as 0, 25, 75 or 225 mg/kg bw per day for 2 years; this conversion is consistent with conversion factors presented in Health Canada (1994). **Dietary exposure study in male and female Wistar rats:** Male and female Wistar rats (n = 50/sex/dose) were exposed to biphenyl for 104-weeks. There was no evidence of urolithiasis or tumour formation following biphenyl exposure (0, 47, or 94 mg/kg bw per day; dose conversion by IPCS 1999). Dose-dependent effects, i.e., reduced body wt gain, alterations in serum enzymes (aspartate transaminase (decreased), alanine transaminase (increased and decreased) and lactate dehydrogenase (increased and decreased) were noted at both doses (Takita 1983; cited in IPCS 1999). LOAEL = 47 mg/kg bw per day (cited in IPCS 1999). **Tumour initiation/promotion study in Wistar rat:** Experiment 1: Dietary exposure of 50 male and female Wistar rats per group to 0, 0.25 and 0.5% biphenyl in the diet for 75 weeks (converted to doses of 0, 188, or 375 mg/kg bw per day by IPCS (1999)). There were dose-dependent increases in the presence of stones in the kidney, ureter and bladder in both sexes, but no evidence of carcinogenicity was seen (Shiraiwa et al. 1989; dose conversion by IPCS 1999). The LOAEL = 188 mg/kg bw per day based on these dose-dependent increases and hematuria. NOAEL = < 188 mg/kg bw per day; suggested by the IPCS based on hematuria, which occurred as early as 16 weeks of exposure to biphenyl (IPCS 1999). Experiment 2: 25 male Wistar rats per group were administered 0, 0.125 or 0.5% biphenyl in the diet for 34 weeks (converted to doses of 0, 94 or 375 mg/kg bw per day by IPCS (1999)). Some rats in each dose group also received 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) for 2 weeks before exposure to biphenyl in diet. An increase was reported in the incidence of stones in the kidney, ureter and bladder in rats in the high dose group. No rats exposed to biphenyl alone developed tumours, and exposure to biphenyl did not enhance tumour development initiated by EHEN (incidences of 52, 54.5 and 28% at 0, 0.125 and 0.5% biphenyl, respectively) (Shiraiwa et al. 1989). NOAEL = 94 mg/kg bw per day for 34 weeks (cited in IPCS 1999). **Mouse** **Dietary carcinogenicity bioassay in male and female mice**: Male and female BDF_1 mice (n = 50/sex/dose) were administered 0, 667, 2000 or 6000 ppm biphenyl in the diet for 104 weeks (equal to 0, 97, 291, or 1050 mg/kg-bw per day in males and 0, 134, 414. or 1420

	mg/kg-bw per day in females, respectively]). [IPCS (1999) converted these concentrations to doses of 0, 100, 300 and 900 mg/kg bw per day.] Female mice had significant increases in the incidence of hepatocellular adenomas at 2000 and 6000 ppm (incidences of 2/50, 3/50, 12/50 and 10/49, respectively) and in the combined incidence of hepatocellular adenoma and carcinoma (16/50, 14/50) and hepatocellular carcinomas at 2000 ppm (incidences of 1/50, 5/50, 7/50 and 5/49, respectively). There were no increases in tumour incidences in male mice. Non-neoplastic effects in the liver included an increased incidence of basophilic cell foci in females at 2000 and 6000 ppm. Non-neoplastic effects in the liver included an increased incidence of basophilic cell foci in females at 414 and 1420 mg/kg bw per day. Non-neoplastic effects observed in the kidneys included necrotic desquamation of urothelium in the renal pelvis was noted in males and females (significant at 6000 ppm only), as well as mineralization in the inner stripe of the outer medulla in females (significant at 2000 ppm and above). Significant increases in serum enzymes (alkaline phosphatase, aspartate transaminase and alanine transaminase), blood urea nitrogen level increased in mid- and high-dose males and high-dose females and calcium levels increased in mid- and high-dose females . Body weights were significantly decreased at 6000 ppm in both sexes throughout the study. NOAEL = 97 mg/kg-bw per day. (Umeda et al. 2005; Japan Bioassay Research Center 1996, cited in IPCS 1999). [Additional studies: Newell, 1953 (a chronic 2-year ingestion study involving rats, with an LOAEL of 47.2 mg/kg body weight/day for female rats)] [No inhalation studies were identified]
Developmental toxicity	Lowest oral (gavage) LOEL (rat) = 500 mg/kg-bw per day. Rats were administered 0, 125, 250, 500 or 1000 mg/kg biphenyl on GD 6-15. Fetal toxicity, including nonsignificant increases in fetuses with missing or non-ossified sternebrae; maternal toxicity at 1000 mg/kg-bw per day (gestation days 6–15) (Khera et al. 1979; cited in IPCS 1999). [Additional studies: Stanford Research Institute, undated; Ambrose et al. 1960]
Reproductive toxicity	Lowest oral (diet) LOEL (rat) = 750 mg/kg-bw per day In a three-generation dietary exposure study rats were administered 100, 1000 or 10 000 mg/kg (7.5, 75 or 750 mg/kg bw per day) of biphenyl. Decreased fertility, litter size and growth rate were noted in rats in 750 mg/kg bw dose group. No further information available (Stanford Research Institute, undated; cited in IPCS 1999)
Genotoxicity and related endpoints: *In*	No evidence of chromosomal aberrations in rat, bone marrow (Kawachi

vivo	et al. 1980) (no further information available). No chromosomal aberrations seen in rat, bone marrow after inhalation exposure to 64 or 320 mg/m^3 of biphenyl for 30 days (Dow Chemical Co., 1976; cited in IPCS 1999). Positive. Mice (male): lowest single oral dose of biphenyl (100 mg/kg) induced DNA damage in colon. DNA damage in stomach, liver, kidney, bladder, lung, brain and bone marrow reported 24 hr following ≥ 1000 mg/kg bw exposure (Sasaki et al. 2002). Positive. Mice (male): DNA damage in stomach, liver, kidney, bladder, lung, brain, bone marrow, 24 hr after single oral exposure to 2000 mg/kg of biphenyl (Sasaki et al. 1997).
Genotoxicity and related endpoints: *I*n *vitro*	Positive. Evidence of chromosomal aberration in human lymphocytes. When compared with the control, a dose-dependent increase was seen in the induction of structural chromosomal aberration following 24 hr of 50 or 70 µg/ml of exposure to biphenyl, but not after 48 hr of exposure. A dose-dependent increase was seen in mean sister chromatid exchange 24 hr after 50 or 70 µg/ml or 48 hr after 30, 50 or 70 µg/ml dose. Induction of micronuclei was seen 24 hr after exposure to 30, 50 or 70 µg/ml of biphenyl or after 48 hr following treatment with 50 or 70 µg/ml dose (Rencuzogullari et al. 2008). Positive. Chromosomal aberration in Chinese hamster cells, with activation. Negative evidence of chromosomal aberration and sister chromatid exchange in cells without activation (Abe and Sasaki, 1977; Ishidate and Odashima, 1977; Kawachi et al. 1980; Sofuni et al. 1985; cited in IPCS 1999). Positive. Evidence of DNA damage in L5178Y cells (alkaline unwinding assay), with activation. Negative in cells without activation (Garberg et al. 1988; cited in IPCS 1999). No DNA damage in Human fibroblasts (“nick translation assay”), without activation (Snyder and Matheson, 1985) No DNA damage in *Bacillus subtilis* (rec assay), without activation (Kawachi et al. 1980). No DNA damage in *Escherichia coli* P637, with and without activation (Brams et al. 1987; cited in IPCS 1999). No evidence of gene conversion in *Saccharomyces cerevisiae* D3, with and without activation (Waters et al. 1982; Zimmermann et al. 1984; cited in IPCS 1999).

	Positive. Mutagenicity in L5178Y T/K+/- mouse lymphoma assay, with activation (Wangenheim and Bolcsfoldi, 1988) Positive. Mutagenicity in *S. cerevisiae* D7, with and without activation (Pagano et al. 1983; cited in IPCS 1999) Positive. Mutagenicity in Chinese hamster cells (V79), with activation (Glatt et al. 1992). Negative for mutagenicity in *Salmonella typhimurium* TA92, TA94, TA97, TA97a, TA98, TA100, TA102, TA1532, TA1535, TA1537, TA1538, TA2636, with or without activation (Cline and McMahon, 1977; Purchase et al. 1978; Kawachi et al. 1980; NTP, 1980; Bronzetti et al. 1981; Probst et al. 1981; Waters et al. 1982; Haworth et al. 1983; Pagano et al. 1983, 1988; Ishidate et al. 1984; Fujita et al. 1985; Brams et al. 1987; Bos et al. 1988; Glatt et al. 1992; cited in IPCS 1999). Negative for mutagenicity in *E. coli* WP2 and WP2 uvrA-, with and without activation (Cline and McMahon, 1977; Probst et al. 1981; Waters et al. 1982; cited in IPCS 1999). Negative for mutagenicity in *S. cerevisiae* D3, with and without activation (Waters et al. 1982; Zimmermann et al. 1984; cited in IPCS 1999). Negative for mutagenicity in Chinese hamster cells, without activation (Glatt et al. 1992). Negative for mutagenicity in L5178Y T/K+/- mouse lymphoma assay, without activation (Wangenheim and Bolcsfoldi, 1988) Negative evidence of unscheduled DNA synthesis in Rat, hepatocytes, with activation (Williams, 1978; Brouns et al. 1979; Probst et al. 1981; cited in IPCS 1999). Negative evidence of unscheduled DNA synthesis in Human lung fibroblasts, with and without activation (Waters et al. 1982; cited in IPCS 1999).

Acronyms: LC50 = median lethal concentration; LD50 = median lethal dose; LOEC = Lowest-Observed-Effect Concentration; LOEL = Lowest-Observed-Effect Level; NOEC = No-Observed-Effect Concentration; NOEL = No-Observed-Effect Level.

[a] This value was chosen in the ecological assessment as the CTV for inhalation by terrestrial organisms