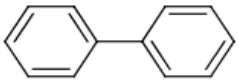
INITIAL TARGETED ASSESSMENT PROFILE

CAS No.	**92-52-4**
Chemical Name	**1,1'-Biphenyl** **(biphenyl)**
Structural Formula	

SUMMARY CONCLUSIONS OF THE TARGETED ASSESSMENT

NOTE: The present assessment is targeted to address the following human health endpoints: carcinogenicity/chronic toxicity and genotoxicity; and the following environment endpoints: stability in air, stability in water, biodegradation in water, bioaccumulation potential, and acute and chronic toxicity to aquatic organisms. It cannot be considered as a full SIDS Initial Assessment. Summary information on exposure is also reported here. Other endpoints for human health and the environment are included in the Canadian screening assessment but have not been presented to OECD member countries, and thus are not included in this profile.

The final screening assessment has been published under the responsibility of the Government of Canada. [http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=70D7175D-1]

Rationale for Targeting the Assessment

The Government of Canada "categorized" or prioritized all 23,000 chemical substances on its Domestic Substances List (DSL) by September 2006, as required by its *Canadian Environmental Protection Act, 1999* (CEPA 1999). Using information from Canadian industry, academic research and other countries, Government of Canada scientists applied a set of rigorous tools to the 23,000 chemical substances on the DSL to identify those that met the following criteria: **persistent** and/or **bioaccumulative** and **inherently toxic** to humans or to non-human organisms and/or having the **greatest potential for exposure**. During this priority-setting exercise, distinct approaches were taken for identifying substances of likely concern for human health and the environment. Through categorization, the Government of Canada has identified approximately 4,000 of the 23,000 chemical substances on the DSL as priorities for further assessment.

A screening assessment was undertaken on 1,1'-Biphenyl (biphenyl) on the basis that this compound was included in Canada's DSL pilot project implemented to develop and apply new approaches for screening assessments. At that time, biphenyl was identified as a substance likely to be prioritized on the basis of greatest potential for human exposure. However, during the categorization of the DSL, although biphenyl did meet the criteria for inherent toxicity to non-human organisms, it was not found to meet the ecological or human health categorization criteria.

Under CEPA 1999, a screening assessment is conducted to determine whether a substance presents or may present a risk to the environment or to human health. 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 the regulatory framework for the Workplace Hazardous

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Materials Information System [WHMIS] for products intended for workplace use.

Physical-chemical properties

Biphenyl is a colourless solid at ambient temperature, and has a melting point of 69 °C, boiling point of 256.1 °C and vapour pressure of 1.19 Pa at 25°C (all measured values). The measured octanol-water partition coefficient (log K_{ow}) is 4.01, and the measured water solubility is 7.48 mg/L at 25 °C. The organic carbon-water partition coefficient (log K_{oc}) was estimated to be 3.71.

Human Health Targeted Endpoints

The majority of the studies described here have been reviewed by the World Health Organization (WHO 2006. Safety evaluation of certain food additives) and the International Programme on Chemical Safety (IPCS 1999. Biphenyl). However, additional or updated data relevant to the screening assessment are designated in square brackets.

Genotoxicity: Investigations of the genotoxicity potential of biphenyl in several *in vivo* and *in vitro* studies have provided mixed results.

- Biphenyl was not mutagenic in a number of *in vitro* bacterial gene mutation assays using multiple strains of *S. typhimurium* and two strains of *E. coli*, but showed mixed results in two strains of *S. cerevisiae*, and positive mutagenicity in mouse L51878Y and Chinese hamster cells with metabolic activation.

- Unscheduled DNA synthesis (UDS) was negative in human lung fibroblasts and rat hepatocytes *in vitro* with and without metabolic activation and *in vitro* DNA damage assays were negative in human fibroblasts with and without metabolic activation and bacterial cells (*E. coli* with and without activation, *B. subtilis* without activation) but were positive in mouse L51878Y cells with metabolic activation.

- Biphenyl induced chromosomal aberrations in human lymphocytes *in vitro* [additional data] and Chinese hamster cells *in vitro*, with metabolic activation, as well as induction of micronuclei and sister chromatid exchange (SCE) in human lymphocytes *in vitro* [additional data].

- In an *in vivo* comet assay, a single oral dose of 2000 mg/kg bw biphenyl caused significant DNA damage in various organs of male mice including stomach, liver, kidney, bladder, lung, brain and bone marrow 24 hours after exposure. In a subsequent comet assay in male mice, a single oral administration of 100 mg/kg bw of biphenyl caused DNA damage in the colon; however, damage to DNA in other tissues including stomach, liver, kidney, bladder, lung, brain, and bone marrow was observed 24 hours after exposure to 1000 or 2000 mg/kg bw of biphenyl [additional data].

- No evidence of chromosomal aberrations was reported in the bone marrow of rats exposed to biphenyl via inhalation to 320 mg/m³ biphenyl or via an unspecified route.

Based on the weight of evidence, 1,1'-biphenyl may have *in vivo* genotoxic potential.

Carcinogenic potential and Chronic Toxicity was determined on the basis of long-term oral studies.

In a carcinogenicity study, male and female SPF F344/DuCrj rats (n = 50/sex/dose) were administered 0, 500, 1500 or 4500 ppm (equivalent to 0, 25, 75, or 225 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 (225 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. A lowest-observed-effect-level (LOEL) of 25 mg/kg bw per day was determined for non-cancer 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.

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Male and female Wistar rats (n = 50/sex/dose) were exposed to biphenyl at dietary concentrations of 0, 630 or 1250 ppm of biphenyl (0, 47, or 94 mg/kg bw per day, respectively) for 104-weeks. There was no evidence of urolithiasis or tumour formation. Dose-dependent effects, i.e., reduced body weight gain, alterations in serum enzymes (aspartate transaminase, alanine transaminase and lactate dehydrogenase) were noted at both doses. The LOAEL was 47 mg/kg bw per day (lowest dose tested).

Male and female Wistar rats (n = 50/sex/dose) were exposed to 0, 0.25 or 0.5% biphenyl in the diet (0, 188, or 375 mg/kg bw per day, respectively) for 75 weeks. 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 observed. The LOAEL was 188 mg/kg bw/day based on these dose-dependent increases and hematuria, which developed as early as 16 weeks of exposure.

In an initiation/promotion study, male Wistar rats (n = 25/dose) were administered 0, 0.125 or 0.5% biphenyl in the diet (0, 94 or 375 mg/kg bw per day, respectively) for 34 weeks. 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). The NOAEL was 94 mg/kg bw per day.

In mice, the liver appears to be a target organ for toxicity of biphenyl. 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). 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 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-cancer effects observed were an increased incidence of basophilic cell foci in the liver of females at 2000 and 6000 ppm (incidences of 1/50, 1/50, 16/50, 14/50, respectively), and in the kidneys, increased incidences of necrotic desquamation of urothelium in the renal pelvis of 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, blood urea nitrogen and calcium were noted at 2000 ppm and above in both sexes. The NOAEL was 97 mg/kg bw per day based on the non-neoplastic effects in the liver and kidney and increases in certain clinical chemistry parameters at the mid- and high doses [updated data].

Carcinogenicity Potential in Humans

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. It is 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. 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. 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.

In mice, biphenyl-induced hepatocarcinogenicity might be explained by peroxisome proliferation [additional data]. Exposure to peroxisome proliferators has been suggested to cause liver tumours via a non-genotoxic mechanism in mice and peroxisome proliferation is not considered as a relevant mode of action of tumour development in humans, but it has also been suggested that there is a lack of data to conclude that peroxisome proliferation is a relevant mode of action [additional data]. 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 [additional data]. These metabolites do not appear to be significant in humans, based on studies in human liver and kidney slices. However, it is also proposed that

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overall data are insufficient to establish a mode of action for the liver tumours in female mice.

1,1'-Biphenyl possesses properties indicating a hazard for human health (mixed results in both *in vitro* and *in vivo* studies for genotoxicity, potential carcinogenicity). The development of bladder tumours in male rats likely occurs subsequent to mechanical injury to urothelium at high doses and has limited relevance in humans. There is uncertainty with respect to the mode of action of biphenyl-induced tumours in the female mouse liver.

Environment

Environmental Fate

According to the results of Level III fugacity modelling (EQC 2003), biphenyl is expected to distribute mainly into air (98.4%) if only released into the atmospheric compartment. If only released into water, the substance is expected to mainly reside in water (88%), to some extent partition to air (2%) and also to be deposited to sediment (~10%). If only released to soil, the substance will entirely reside in this environmental compartment (100%). Based on Level III fugacity modelling, if released equally to air, water and soil, most of the substance will partition to the soil (~70%), followed by water (~25%), air (2%) and sediment (3%).

A measured Henry's Law Constant of 28 Pa•m^3/mole at 25 ^oC also indicates biphenyl volatilizes and may evaporate from the surface of water or moist soil. The modelled log K_{oc}, of 3.71(PCKOCWIN 2008) indicates a strong potential of the substance to accumulate in soil and sediment.

The characteristic travel distance (CTD) has been used as an indicator for long range transport potential. Based on its physical-chemical properties, a CTD for biphenyl has been calculated as 391 km (TaPL3 2000), and 394 km (using the OECD POPs Tool). The substance is considered to have a low potential for long-range transport in air (CTD < 700 km), which is in agreement with its rapid transformation in air from hydroxy radical attack resulting in a calculated half-life of 1.5 days. 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.

In water, biphenyl can be considered both readily and inherently biodegradable, according to experimental results. A test for the ready biodegradability 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. In a study for inherent biodegradability (Sturm test (cfr. ASTM D5209-91)), monitoring of CO_2 evolution indicated that biphenyl is ultimately degraded by 88% after 43 days and around 69% after 28 days. These results are generally consistent with QSAR modelling of the ultimate degradability of the biphenyl structure (BIOWIN 2000, TOPKAT 2004), which suggests that biphenyl is readily biodegraded. However, the model thresholds for ready biodegradation are only just exceeded suggesting that biphenyl is still a fairly stable compound. All models except CATABOL (which suggests a very slow rate of biodegradation) agree on this point.

Estimated half-lives for the primary biodegradation of biphenyl in water range from 1.58 days (die-away test with river water) to 2.8 months (clean seawater). Biodegradation of biphenyl was also examined during 10 days in a natural lake water/sediment system with naturally present microorganisms. 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. A sediment half-life of 333 days is reported in a 394-day mesocosm study with seawater, however this surface layer concentration decrease is attributed to partitioning rather than biodegradation. There is a lack of concentration decrease deeper in the sediment or in less contaminated sediment over the same time period.

In groundwater, calculated primary half-life values range from 3 to 14 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life. In soil, the main removal process for biphenyl appears to be biodegradation, with a calculated primary biodegradation half-life value of 1.5 to 7 days, using scientific judgement and based on the acclimated aqueous aerobic biodegradation half-life.

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

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mineralization half-life of approximately 23 days for water is recommended based on the probability result from the TOPKAT model of 57% after 28 days. Rates of degradation are expected to be approximately the same in aerobic soils and sediments but slower under anaerobic conditions in these media.

At a log k_{ow} of ~4.0 biphenyl is expected to be bioavailable in water resulting in practically all uptake in aquatic biota directly occurring from water. Bioconcentration factors range from approximately 427 (BCFBAF model validation training set) to 1900 for rainbow trout (*Oncorhynchus mykiss*) and 2422 for the eastern oyster *Crassostrea virginaca* (both experimental BCFs). Biphenyl is therefore considered to have a potential to bioaccumulate in organisms (BCF > 500).

Aquatic Toxicity

Experimental data have been identified for biphenyl relating to acute and chronic toxicity of the substance to aquatic species across several taxa. Key endpoints for each are presented below:

Acute

- Algae *Pseudokirchneriella subcapitata*, 72 hour E_rC_{50} = 0.78 mg/L (growth rate, static, OECD Guideline 201); *Scenedesmus vacuolatus*, 24 h E_rC_{50} = 0.231 mg/L (growth rate, measured, static)
- Water flea (*Daphnia magna*), 24 hour LC_{50}= 1.3 mg/L, 48 hour LC_{50} = 0.36 mg/L, NOEC = 0.04 mg/L (measured, flow-through)
- Rainbow trout (*Oncorhynchus mykiss*), 96 hour LC_{50} = 1.5 mg/L (nominal, static)

Chronic

- Water flea (*Daphnia magna*), 21 day NOEC = 0.170 mg/L; 21 day LOEC of 0.32 mg/L, 21 day, MATC = 0.23 mg/L (measured, static)
- Rainbow trout (*Oncorhynchus mykiss*), 87 day NOEC = 0.229 mg/L, 87 day LOEC = 0.331 mg/L (measured, flow-through)

1,1'-Biphenyl possesses properties indicating hazard to the environment (acute and chronic aquatic toxicity below 1 mg/L). The substance is readily biodegradable but there is an indication of a long half-life in sediment. The substance has potential for bioaccumulation.

Exposure Summary Information

In Canada (sponsor country), 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 in Canada for the year 2000, were in the range of 10 000 to 100 000 kg.

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. Other uses identified were: antifreeze/coolant/de-icer, solvent/carrier, preservative, formulation component, functional fluid, i.e. hydraulic dielectric or other additives, catalyst/accelerator/initiator/activator; fragrance/perfume/deodorizer/flavouring agent; and finishing agent. With the exception of the heat transfer agent, these uses are historical in the sponsor country.

Biphenyl is known to be found both in nature and from anthropogenic sources. Biphenyl occurs naturally in coal tar (pitch), crude oil and natural gas. Leftover residue from coal tar distillation was identified in coal tar-based driveway sealants from local retail stores in Canada. Additionally, biphenyl has been detected in coal tar-derived creosotes.

Based on the most recent survey for this substance, no companies in Canada reported manufacturing biphenyl in a quantity greater than or equal to 10 000 kg for the 2000 calendar year. However, it was reported that it was

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imported into Canada in the range of 10 000 to100 000 kg in the same year.

Biphenyl's release into the environment may occur from industrial processing of 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. Fugitive emissions or venting during the handling, transport or storage of biphenyl could also be a source of biphenyl in ambient air.

Under Canada's 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. 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. These emissions and those from small industries across the country are not accounted for by the NPRI.

Industrial uses of biphenyl could result in releases to surface waters. However, most biphenyl in sewage treatment plant influent is removed and does end up in the sewage sludge. Biphenyl could end up in soil from the application of sewage sludge to agricultural land.

The general population exposure to biphenyl in the sponsor country is low from environmental media and food, as supported by monitoring data, and exposure from consumer products is expected to be negligible.

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