1,1-Biphenyl

CAS No. 92-52-4

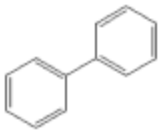

Figure 1: Structure of 1,1-biphenyl

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999) the Minister of Health may gather information, conduct investigations and evaluations, including screening assessments, relevant for the purpose of assessing whether a substance is entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Screening health assessments focus initially on conservative assessment of hazard or effect levels for critical endpoints and upper-bounding estimates of exposure, after consideration of all relevant identified information. Decisions based on the nature of the critical effects and margins between conservative effect levels and estimates of exposure take into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. Additional background information on screening health assessments conducted under this program is available at http://www.hc-sc.gc.ca/ewh-semt/contaminants/existsub/index_e.html.

A State of the Science Report for a screening assessment has been prepared on 1,1-biphenyl (see Figure 1) on the basis that this compound was included in the Domestic Substances List pilot phase for screening as a substance likely to be prioritized on the basis for greatest potential for human exposure.

This draft State of the Science Report for a screening assessment and associated unpublished supporting working documentation were prepared by evaluators within the Existing Substances Division of Health Canada; the content of these documents was reviewed at several meetings of senior Divisional staff. The draft Report was subsequently externally reviewed for adequacy of data coverage and defensibility of the conclusions. The supporting working documentation is available upon request by e-mail from ExSD@hc-sc.gc.ca

Information identified as of July 2003 was considered for inclusion in this Report. The critical information and considerations upon which this Report is based are summarized below. Additional data identified between this date and the end of the external peer review period (March, 2004) were also scoped and determined not to impact upon the conclusions presented here.

Identity, Uses and Sources of Exposure

Biphenyl is a bicyclic aromatic with the chemical structure presented in Figure 1. It occurs naturally in coal tar, crude oil and natural gas (IPCS, 1999) and is also formed during the incomplete combustion of biomass, fossil fuels, rubber, plastic and municipal waste (NLM, 2002).

Results of a Section 71 survey (Environment Canada, 2001) indicate that the pattern of industrial use in Canada is similar to that reported elsewhere. Biphenyl is reported to be used internationally as a dye carrier and heat transfer fluid (Kroschwitz and Howe-Grant, 1991). Based on the results of the Section 71 survey, the total amount of biphenyl manufactured and/or imported into Canada for the year 2000 is greater than 100 000 kg (Environment Canada, 2001). However, the principal industrial source of biphenyl is its formation as a by-product of the hydrodealkylation of toluene to benzene.

Although biphenyl was previously used as a fungicide to control decay in citrus fruits (Nagy and Wardowski, 1981), biphenyl is no longer registered for such use in Canada (Masi, 2002). Biphenyl was also historically used as an intermediate in the production of polychlorinated biphenyls (PCBs) in the 1970s; however, due to the restricted and/or prohibited use of PCBs in many countries, this use is no longer prevalent (IPCS, 1999).

No consumer product uses were reported for biphenyl in the Section 71 survey (Environment Canada, 2001), and no data were identified on exposure to biphenyl through the use of consumer products; therefore, levels of biphenyl in consumer products are not expected to contribute significantly to exposure of the general Canadian population. Biphenyl has been measured in a cream containing coal tar used for treatment of cutaneous diseases, but this specific therapeutic use is not expected to result in widespread exposure of the general population.

Exposure Assessment, Hazard Characterization and Risk Evaluation

Based on intakes of relevant media for six age groups of the general population and concentrations of biphenyl in ambient air (Hoff and Chan, 1987), indoor air (Otson et al., 1994), drinking water (Williams et al., 1982), dust (as a surrogate for soil) (Wilson et al., 2001) and a variety of food items (Braune et al., 1999; U.S. FDA, 2002a, 2003a), the upper-bounding estimate of intake for the most highly exposed age group (i.e., 0.5–4 years) is 1.5 µg/kg-bw per day for the general population (see Table 1). No data on concentrations of biphenyl in formula or breast milk were identified for Canada. However, given the absence of biphenyl in dairy products analysed by the U.S. FDA (2002a, 2003a), exposure of breast-fed infants is not expected to exceed that estimated for the other age groups. The estimates presented in Table 1

indicate that food is the largest source of exposure to biphenyl for most age groups in the general population, but this results in large measure from basing the estimated intakes from this medium on the limits of detection given in the critical studies. This likely results in an overestimate, the magnitude of which cannot be determined, and indoor and ambient air likely contribute proportionally more to exposure than indicated in the upper-bounding estimates. Measured values for air are consistent with what would be expected based on the available information on the environmental releases and chemical and physical properties of biphenyl. Cigarette smoke can also be a source of exposure to biphenyl, although data are currently insufficient to quantify the potential contribution to total intake.

Although there are limitations in the available database on exposure, confidence that actual exposures in Canada will not exceed the estimates presented here is high.

Based on a health assessment published by the International Programme on Chemical Safety (IPCS) in 1999, long-term exposure to biphenyl in the diet resulted in significant increases in the incidence of transitional cell papillomas and carcinomas of the urinary bladder in male rats and in a significant, although not dose-related, increase in the incidence of hepatocellular adenomas and carcinomas in female mice (Japan Bioassay Research Center, 1996; Umeda et al., 2002). In the rats, significant dose-related effects on serum enzyme levels (alkaline phosphatase, aspartate transaminase and alanine transaminase) and blood urea nitrogen levels were observed at 38 mg/kg-bw per day or greater, while hematological effects, calculi and histopathological changes in the bladder and/or kidney were noted at higher doses (Japan Bioassay Research Center, 1996). It has been suggested, as summarized in IPCS (1999), that bladder tumours observed in male rats exposed to some non-genotoxic chemicals may be correlated with regenerative hyperplasia caused by irritation as a result of calculi formed in the urinary bladder (Cohen, 1995). In this regard, IPCS (1999) noted that the mechanism of tumour formation has not been fully elucidated and that several outstanding issues exist that may suggest that such tumours are not solely the result of calculi formation in the urinary bladder; therefore, some concerns exist regarding the potential carcinogenicity of biphenyl to humans. In addition, although available data are not completely consistent, there is some indication in *in vitro* assays that biphenyl has some mutagenic potential (IPCS, 1999) (see Table 2). However, with few exceptions, valid results of quantitative structure–activity relationship and structure–activity relationship modelling, where biphenyl was not included in the training set, were negative.

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 (Deichmann et al., 1947).

Confidence in the database on health effects is moderate to high, owing to an extensive data set, including various short-term, chronic, developmental and *in vitro* genotoxicity assays. However, the mode of action for carcinogenicity remains unclear.

Comparison of the lowest Lowest-Observed-Effect Level (LOEL) for non-neoplastic effects (i.e., alterations of serum enzyme and blood urea nitrogen levels) (38 mg/kg-bw per day)

with the upper-bounding estimate of daily intake (1.5 µg/kg-bw per day) results in a margin of exposure (MOE) of approximately 25 000. However, since estimates of daily intake of biphenyl from food are largely based on detection limits, and as ambient and indoor air may be contributing proportionally more to daily intakes of biphenyl, margins of exposure for inhalation are also considered here. Therefore, an MOE of 5000 was also derived by comparing the lowest Lowest-Observed-Effect Concentration (LOEC) for non-neoplastic effects (mortality and respiratory irritation) (5 mg/m^3) with the upper-bounding estimate of indoor air concentration (1 µg/m^3). Although the margins for non-neoplastic effects are relatively large (5000–25 000), there are considerable uncertainties regarding the mode of induction of bladder and liver tumours in rodents and their relevance to humans

The outcome of this evaluation on 1,1-biphenyl is that it is suspected that these margins may not be adequate to account for the uncertainties in the mode of induction of tumours in experimental animals and intraspecies and interspecies variations in sensitivity. Data addressing these uncertainties would permit a more definitive conclusion.

Table 1: Upper-bounding estimates of daily intake of biphenyl by the general population of Canada

Route of exposure	**Estimated intake (µg/kg-bw per day) of biphenyl by various age groups**						
	0–6 months[1, 2, 3]		**0.5–4 years[4]**	**5–11 years[5]**	**12–19 years[6]**	**20–59 years[7]**	**60+ years[8]**
	formula fed	**not formula fed**					
Ambient air[9]	7.7×10^{-4}		1.7×10^{-3}	1.3×10^{-3}	7.3×10^{-4}	6.3×10^{-4}	5.5×10^{-4}
Indoor air[10]	0.25		0.53	0.41	0.23	0.2	0.17
Drinking water[11]	3.4×10^{-3}	1.3×10^{-3}	1.4×10^{-3}	1.1×10^{-3}	6.4×10^{-4}	6.7×10^{-4}	7.1×10^{-4}
Food and beverages[12]		0.98	0.97	0.74	0.43	0.33	0.28
Soil[13]	3.2×10^{-5}		5.2×10^{-5}	1.7×10^{-5}	4.0×10^{-6}	3.4×10^{-6}	3.3×10^{-6}
Total intake	0.25	1.22	1.5	1.15	0.67	0.53	0.46

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 Williams et al. (1982). No data on concentrations of biphenyl in formula were identified for Canada. Approximately 50% of non-formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW, 1990).

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 The highest concentration of biphenyl measured in outdoor air along the Niagara River in Fort Erie, Niagara Falls and Niagara-on-the-Lake, Ontario, was 0.022 µg/m^3 (Hoff and Chan, 1987). Canadians are assumed to spend 3 hours outdoors each day (EHD, 1998). This concentration is within the range of concentrations reported in another study of outdoor air in Canada (Patton et al., 1991) and many studies in the United States and Norway.

10 The concentration of biphenyl in indoor air, based on a composite of 757 indoor air sample extracts taken from Canadian residential homes, was 1 µg/m^3 (Otson et al., 1994). Canadians are assumed to spend 21 hours indoors each day (EHD, 1998). This concentration is within the range of concentrations reported in studies of indoor air in Canada (Otson and Benoit, 1986), the United States (Wilson et al., 2001) and Finland (Kostiainen, 1995).

11 The highest concentration of biphenyl measured in 24 samples of drinking water from 12 Great Lakes municipalities in Ontario was 0.0319 µg/L (Williams et al., 1982). This was the highest value reported in the available studies carried out in Canada (Benoit et al., 1979a, 1979b; LeBel et al., 1987; City of Toronto Water and Wastewater Services Division, 2002a, 2002b, 2002c, 2002d).

12 Estimates of intake from food are based upon concentrations in foods that are selected to represent the 12 food groups addressed in calculating intake (EHD, 1998):

Dairy products: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Fats: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Fruits and fruit products: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Vegetables: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Cereal products: 48 µg/kg; maximum concentration of five samples of oats, whole grain imported from Canada (U.S. FDA, 2003b)

Meat and poultry: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Fish: 2.64 µg/kg; maximum concentration in 239 samples of freshwater fish from the Northwest Territories (Braune et al., 1999)
Eggs: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Foods, primarily sugar: 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)
Mixed dishes: no data identified
Nuts and seeds: 7 µg/kg, highest concentration of biphenyl in 53 samples of cashews in the U.S. survey (U.S. FDA, 2002b)
Beverages (soft drinks/alcohol/coffee/tea): 5 µg/kg; detection limit in U.S. survey (U.S. FDA, 2002a, 2003a)

[13] Amounts of foods consumed on a daily basis by each age group are described by Health Canada (EHD, 1998). No data for biphenyl in soil in Canada were identified. The highest concentration of biphenyl found in dust samples collected at day care centres in Raleigh-Durham-Chapel Hill, North Carolina, was 8 µg/kg (Wilson et al., 2001). Although higher concentrations were reported in Norway (Vogt et al., 1987; Aamot et al., 1996), the data were not as recent, and U.S. data are considered more appropriate for estimating levels in Canadian soil.

Table 2: Summary of health effects information for biphenyl

Endpoint	**Lowest effect levels[1] /Results**
Acute toxicity	Lowest **oral LD_{50}** > 1900 mg/kg-bw (BUA, 1990) Lowest **inhalation LC_{50}** (rat) > 275 mg/m^3 (Sun Co. Inc., 1977a) [Additional studies: Monsanto Co., 1959; Dow Chemical Co., 1974]
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) [Additional studies: Booth et al., 1956, 1961] Lowest **dermal LOEL** (rabbit) = 500 mg/kg-bw per day: decreased body weight, histopathological effects (28-day study) (Deichmann et al., 1947) Lowest **inhalation NOEC** (mice) = 160 mg/m^3 (no LOEL identified) (14-day study) (Sun Co. Inc., 1977b)
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) [Additional studies: Takita, 1983; Kurata et al., 1986; Shibata et al., 1989a, 1989b] Lowest **inhalation LOEC** (mice) = 5 mg/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)
Chronic toxicity/ carcinogenicity	Lowest **oral (diet) non-neoplastic LOEL** (rat) = 38 mg/kg-bw per day: increased serum enzyme and blood urea nitrogen levels (2-year study) (Japan Bioassay Research Center, 1996; Umeda et al., 2002) [Additional studies: Newell, 1953; Takita, 1983; Shiraiwa et al., 1989] **Dietary carcinogenicity bioassay in male and female rats**: 0, 500, 1500 or 4500 mg/kg (0, 38, 113 or 338 mg/kg-bw per day; IPCS [1999] conversion) for 2 years; 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 (Japan Bioassay Research Center, 1996; Umeda et al., 2002) **Dietary carcinogenicity bioassay in male and female mice**: 0, 667, 2000 or 6000 mg/kg (0, 100, 300 or 900 mg/kg-bw per day; Health Canada [1994] conversion) for 104 weeks; female mice had significant increases in the incidence of hepatocellular adenomas at 300 and 900 mg/kg-bw per day and in hepatocellular carcinomas at 300 mg/kg-bw per day (Japan Bioassay Research Center, 1996)
Developmental toxicity	Lowest **oral (gavage) LOEL** (rat) = 500 mg/kg-bw per day: fetal toxicity, including non-significant 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) [Additional studies: Stanford Research Institute, undated; Ambrose et al., 1960]
Reproductive toxicity	Lowest **oral (diet) LOEL** = 750 mg/kg-bw per day: decreased fertility, litter size and growth rate (Stanford Research Institute, undated)

Endpoint	Lowest effect levels[1] /Results
Genotoxicity and related endpoints: *in vivo*	**Chromosomal aberrations** Negative: Rat, bone marrow (Kawachi et al., 1980) (no further information available) Negative: Rat, bone marrow (Dow Chemical Co., 1976) (inhalation, 64 or 320 mg/m^3, 30 days) **Comet assay** Positive: Mice, stomach, liver, kidney, bladder, lung, brain, bone marrow (Sasaki et al., 1997) (oral, 200 mg/kg-bw)

Endpoint	Lowest effect levels[1] /Results
Genotoxicity and related endpoints: *in vitro*	**Chromosomal aberrations** Positive: Chinese hamster cells, with activation (Sofuni et al., 1985) Negative: Chinese hamster cells, without activation (Abe and Sasaki, 1977; Ishidate and Odashima, 1977; Kawachi et al., 1980; Sofuni et al., 1985) **DNA damage** Positive: L5178Y cells (alkaline unwinding assay), with activation (Garberg et al., 1988) Negative: L5178Y cells (alkaline unwinding assay), without activation (Garberg et al., 1988) Human fibroblasts ("nick translation assay"), without activation (Snyder and Matheson, 1985) *Bacillus subtilis* (rec assay), without activation (Kawachi et al., 1980) *Escherichia coli* P637, with and without activation (Brams et al., 1987) **Gene conversion** Negative: *Saccharomyces cerevisiae* D3, with and without activation (Waters et al., 1982; Zimmermann et al., 1984) **Mutagenicity** Positive: L5178Y T/K+/- mouse lymphoma assay, with activation (Wangenheim and Bolcsfoldi, 1988) *S. cerevisiae* D7, with and without activation (Pagano et al., 1983) Chinese hamster cells (V79), with activation (Glatt et al., 1992) Negative: *Salmonella typhimurium* TA92, TA94, TA97, TA97a, TA98, TA100, TA102, TA1532, TA1535, TA1537, TA1538, TA2636, with and 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) *E. coli*, with and without activation (Cline and McMahon, 1977; Probst et al., 1981; Waters et al., 1982) *S. cerevisiae* D3, with and without activation (Waters et al., 1982; Zimmermann et al., 1984) Chinese hamster cells, without activation (Glatt et al., 1992) L5178Y T/K+/- mouse lymphoma assay, without activation (Wangenheim and Bolcsfoldi, 1988) **Sister chromatid exchange** Negative: Chinese hamster cells, without activation (Abe and Sasaki, 1977; Kawachi et al., 1980) **Unscheduled DNA synthesis** Negative: Rat, hepatocytes, with activation (Williams, 1978; Brouns et al., 1979; Probst et al., 1981) Human lung fibroblasts, with and without activation (Waters et al., 1982)

[1] LC_{50} = median lethal concentration; LD_{50} = median lethal dose; LOEC = Lowest-Observed-Effect Concentration; LOEL = Lowest-Observed-Effect Level; NOEC = No-Observed-Effect Concentration; NOEL = No-Observed-Effect Level.

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