Screening Assessment for the Challenge

Phenol, 4,4' -(1-methylethylidene)bis-
(Bisphenol A)

Chemical Abstracts Service Registry Number
80-05-7

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of phenol, 4,4' -(1-methylethylidene)bis- or bisphenol A, Chemical Abstracts Service Registry Number 80-05-7. This substance was identified as a result of the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge, since it was considered to pose the greatest potential for exposure to individuals in Canada and had been classified by the European Commission on the basis of reproductive toxicity. Bisphenol A also met the ecological categorization criterion for inherent toxicity to aquatic organisms, but it did not meet the ecological categorization criteria for persistence or bioaccumulation potential.

Bisphenol A is a high volume chemical, with global production at 4 billion kg in 2006. In the United States, production quantities increased from 521 million kg in 1990 to 736 million kg in 1995. Estimated production in the U.S. in 2007 was 1 billion kg. Canadian market values may be lower than those for the U.S; however, approximately 12 million kg of bisphenol A were reported as manufactured, imported or in commerce in Canada during the calendar year 1986. In 2006, no bisphenol A was manufactured in Canada at quantities equal to or greater than a reporting threshold of 100 kg. However, bisphenol A was used in Canada in the range of 100 000 to 1 000 000 kg and approximately half a million kg was imported into Canada either alone, in a product, in a mixture or in a manufactured item.

The available data indicate that bisphenol A does not persist significantly under aerobic conditions. However, the substance has been found not to degrade or to degrade only slowly under conditions of low or no oxygen. Bisphenol A has been detected in Canadian and U.S. surface waters, sediment, groundwater and soil, as well as in municipal and industrial waste treatment products. Studies from North America, Europe and Japan document detectable levels in several species of aquatic biota. The data demonstrate that bisphenol A is present in a wide range of environmental media.

Most data indicate relatively low bioaccumulation potential and a capacity for metabolism in various species. Most measured bioaccumulation and bioconcentration factors range only up to about 150 L/kg, with one study reporting a bioaccumulation factor of 650 L/kg in lower trophic levels. These studies confirm that bisphenol A is bioavailable and can accumulate in tissues to some degree. Bisphenol A is acutely toxic to aquatic organisms and has been shown to adversely affect growth and development in both aquatic and terrestrial species. There is evidence that low-level exposure to bisphenol A, particularly at sensitive life cycle stages, may lead to permanent alterations in hormonal, developmental or reproductive capacity. In laboratory testing, these effects have occurred within the range of concentrations measured in Canada, indicating that there is potential for adverse effects in populations, particularly close to point sources.

On the basis of expected continued or increasing exposure of biota, and information indicating the potential for long-term adverse effects to organisms within the range of

concentrations currently measured in the environment, it is considered appropriate to apply a precautionary approach when characterizing risk. As such, it is concluded that bisphenol A is 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.

Human exposure to bisphenol A in Canada can result from dietary intake (e.g., migration from food packaging, migration from repeat-use polycarbonate containers), from environmental media (i.e., ambient air, indoor air, drinking water, soil and dust), from use of consumer products and other sources. Dietary intake is the primary source of exposure. Exposure estimates for the general population of Canada range from 0.08 μg/kg body weight/day to 4.30 μg/kg-bw per day. Specific exposure estimates for the most highly exposed subpopulation (i.e., infants) range from an average of 0.50 μg/kg body weight/day (maximum 4.30 μg/kg-bw per day) for infants aged 0 to 1 month to an average of 0.27 μg/kg body weight/day (maximum 1.75 μg/kg body weight/day) for infants aged 12 to 18 months. A critical effect for characterization of risk to human health is reproductive and developmental toxicity. The neurodevelopmental and behavioural dataset for rodents, though highly uncertain, is suggestive of potential effects at doses the same order of magnitude to 1-2 orders of magnitude higher than exposures. Given that toxicokinetics and metabolism data from experimental animal and limited human studies indicate potential sensitivity to the maternal-fetal unit and infant, and that animal studies suggest a trend towards heightened susceptibility during stages of development in rodents, it is considered appropriate to apply a precautionary approach when characterizing risk. As such, it is concluded that bisphenol A be considered as a substance that may be 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.

In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, bisphenol A meets one or more of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999.*

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Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance, phenol, 4,4' -(1-methylethylidene)bis- or bisphenol A was identified as a high priority for assessment of human health risk because it was considered to present greatest potential for human exposure (GPE) and had been classified by other agencies on the basis of reproductive toxicity. The Challenge for bisphenol A was published in the *Canada Gazette* on May 12, 2007. A substance profile was released at the same time (Canada 2007). The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although bisphenol A was determined to be a high priority for assessment with respect to human health, and it also met the ecological categorization criterion for inherent toxicity to aquatic organisms, it did not meet the categorization criteria for potential for persistence or bioaccumulation. Therefore this assessment focuses principally on information relevant to the evaluation of risk to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to September 2008 for human health effects and exposure sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

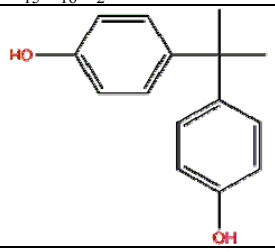
Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). 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 and incorporates input from other programs within these departments. The draft of this screening assessment was subject to a 60-day public comment period. Additionally, this assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from Toxicology Excellence for Risk Assessment (TERA), Dr. Sergio Pellis of University of Lethbridge, Alberta, and Dr. Alfonso Abizaid of Carleton University, Ottawa. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as bisphenol A.

Table 1. Substance identity

Chemical Abstracts Service Registry Number (CAS RN)	**80-05-7**
Name on Domestic Substances List (DSL)	***Phenol, 4,4' -(1-methylethylidene)bis-***
Inventory names[1]	*Phenol, 4,4'-(1-methylethylidene)bis- (TSCA, PICCS, ASIA-PAC)* *4,4'-isopropylidenediphenol (EINECS, PICCS)* *2,2-Bis(4'-hydroxyphenyl) propane (ENCS)* *Phenol, 4,4'-(1-methylethylidene)bis- (AICS, PICCS)* *4,4'-(1-Methylethylidene)bisphenol (ECL)* *4,4'-Bisphenol A (ECL)* *Phenol, 4,4'-(1-methylethylidene)bis- (SWISS)* *Bisphenol A (SWISS, PICCS)* *p,p'-isopropylidene diphenol (PICCS)* *Diphenol methylethylidene (PICCS)* *bis[phenol], 4,4'-(1-methylethylidene)- (PICCS)* *Bisphenol-a (PICCS)* *Bisphenol, 4,4'-(1-methylethylidene)- (PICCS)* *4,4-isopropylidene diphenyl (PICCS)* *4,4'-dihydroxyphenyl-2,2-propane (PICCS)* *2,2-di(4-hydroxyphenyl)propane (PICCS)* *2,2-di(4-hydroxyphenyl) propane (PICCS)* *2,2-bis-(4-hydroxy-phenyl)-propane (PICCS)*
Other names	*Bisphenol A, Diphenylolpropane, BPA*
Chemical group	Discrete organics
Chemical subgroup	Phenols
Chemical formula	$C_{15}H_{16}O_2$
Chemical structure	
Simplified Molecular Input Line Entry System (SMILES)	Oc(ccc(c1)C(c(ccc(O)c2)c2)(C)C)c1
Molecular mass	228.29 g/mol

[1] National Chemical Inventories (NCI). 2006: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); SWISS (Inventory of Newly Notified Substances and Giflist 1 – List of Toxic Substances) and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of bisphenol A that are relevant to its environmental fate.

Table 2. Physical and chemical properties for bisphenol A

Property	Type	Value	Temperature (°C)	Reference
Melting point (ºC)	Experimental	150-157		Howard 1989; Dow Europe 1993
	Modelled	132		MPBPWIN 2000
Boiling point (ºC)	Experimental	220-398		Howard 1989; Dow Europe 1993
	Modelled	364		MPBPWIN 2000
Density (kg/m^3)	Experimental	1195	25	Sax and Lewis 1996
Vapour pressure (Pa)	Experimental	5.3×10^{-6}	25	Bayer AG 1988
	Modelled	3.0×10^{-5} (2.27×10^{-7} mm Hg)	25	MPBPWIN 2000
Henry's Law constant ($Pa \cdot m^3/mol$)	Experimental	1.0×10^{-6} (1.0×10^{-11} $atm \cdot m^3/mol$)		Hine and Mookerjee 1975
	Modelled	9.3×10^{-7} (9.16×10^{-12} $atm \cdot m^3/mol$) Water solubility 120 mg/L: 4.0×10^{-5} (3.95×10^{-10} $atm \cdot m^3/mol$) Water solubility 257 mg/L: 4.7×10^{-6} (4.7×10^{-11} $atm \cdot m^3/mol$)	25	HENRYWIN 2000 (Bond estimation) HENRYWIN 2000 (VP/Water solubility estimation)
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Experimental	3.32		Howard 1989; Hansch et al. 1995
	Modelled	3.64		KOWWIN 2000
Log K_{oc} (Organic carbon-water partition coefficient – L/kg) (dimensionless)	Experimental	2.53-2.85 (pH 4.5-5.9)		Loffredo and Senesi 2006
	Calculated	2.85		ECB 2003
	Modelled	4.88		PCKOCWIN 2000

Property	Type	Value	Temperature (°C)	Reference
Log K_{oa} (Organic carbon-air partition coefficient) (dimensionless)	Modelled	12.7		KOAWIN 2000
Water solubility (mg/L)	Experimental	253-257	22-24	Lee and Peart 2000b
		301	room temperature	Bayer AG 1988
		120	25	Dorn et al. 1987
	Modelled	173	25	WSKOWWIN 2000
Other solubilities (g/L)	Experimental (alcohol)	soluble		Lewis 2000
pK_a (Acid dissociation constant) (dimensionless)	Experimental	9.59 – 11.30		Staples et al. 1998
	Modelled	9.73-10.48		ACD 2005

Bisphenol A is characterized as having low vapour pressure, moderate water solubility and a moderate organic carbon-water partition coefficient (log K_{oc}). EPIWIN (2000) indicates that, based on the chemical structure of the substance, the K_{oc} of bisphenol A may be sensitive to and vary significantly with pH. The high pK_a range of 9.59 to 11.30 (see Table 2) indicates that bisphenol A is a very weak acid. While ionization of the substance may occur at high pH, there is unlikely to be appreciable ionization at environmental pH levels of 7 and lower (Cousins et al. 2002). Cousins et al. (2002) predict that chemicals such as bisphenol A, which have measurable vapour pressures, aqueous solubilities and octanol-water partition coefficients (K_{ow}), will likely partition to some extent in all available environmental phases.

Sources

There is no reference in the published literature to the natural occurrence of bisphenol A in the environment.

Global production of bisphenol A was 4 billion kg in 2006. In the United States (U.S.), production quantities increased from 521 million kg in 1990 to 736 million kg in 1995. Estimated production in the U.S. in 2007 was 1 billion kg (SRI Consulting, 2007).

Based on a survey conducted under section 71 of CEPA 1999, no bisphenol A was manufactured in Canada in 2006 at quantities greater than or equal to 100 kg. However, 26 companies reported using bisphenol A in Canada in the range of 100 000 1 000 000 kg or importing approximately half a million kg into Canada either alone, in a product, in a mixture or in a manufactured item (Environment Canada 2007a). The extent to which the reported values represent quantities of bisphenol A present in finished and semi-finished

goods entering Canada from other parts of the world is unknown as these uses would be unlikely to meet the reporting criteria for the survey.

Uses

Bisphenol A is primarily used as a monomer in the production of polycarbonates and as a precursor or a starting material for monomers of certain epoxy resins (EFSA 2006). In 2003, consumption patterns of bisphenol A in the U.S. indicated that approximately 72% of bisphenol A was used to manufacture polycarbonates, 21% was used in epoxy resins and 6% was used in other applications (NTP 2007).

The type of mixture, product or manufactured item reported for 2006 in response to a survey of Canadian industry under section 71 of CEPA 1999 included resins, curing agents, epoxy curing agents, hardeners, plastic resin formulations, monomer, paperboard packaging, metal cans, phenolic resins, industrial coatings, plasticizers, adhesives, two part epoxy adhesives, chain oil, brake fluid, heat transfer fluid and lubricant formulations. Information voluntarily submitted in 2007 in response to the Challenge Questionnaire and other information submitted by industry additionally include use in epoxy polymer flooring, as a laminating adhesive, in custom colour powder coating and as a curing agent for resurfacing concrete.

The literature indicates that polycarbonate is used in the manufacture of compact discs, food and beverage contact containers (e.g., baby bottles, repeat use water bottles, pitchers, water carboys, tableware and storage containers), water pipes, medical devices, and in glazing applications and film. Polycarbonate blends find application in the electric and electronics industry (e.g., alarm devices, mobile phone housings, computer parts, household electric equipment, lamp fittings, power plugs) and the automotive industry (e.g., car headlight and rear light reflectors and coverings, bumpers, radiator and ventilation grills, safety glazing, inside lights, motorcycle windshields and protective helmets) (NTP 2007; EFSA 2006). Medical devices which contain polycarbonate (e.g., hemodialyzers, hemofilters, blood oxygenators and respiratory devices) have been approved or licensed for use in Canada under the *Medical Devices Regulations* of the *Food and Drugs Act* (Health Canada, Medical Devices Bureau, Health Products and Food Branch, pers. comm., 2008 Feb 5, unreferenced).

Epoxy resins made with bisphenol A are commonly used in protective coatings, structural composites, electrical laminates, electrical applications and adhesives (NTP 2007). Epoxy-phenolic resins are used as liners in metal cans for foods and beverages and as coatings on metal lids for glass jars and bottles, as well as surface coatings on residential drinking water storage tanks (EFSA 2006). Cans used for food and beverages, including ready-to-use, concentrate and powdered infant formula, that were evaluated by Health Canada are lined with epoxy resin (Health Canada, Chemical Health Hazard Assessment Division, Health Products and Food Branch, pers. comm., 2008 Feb 26, unreferenced).

Epoxy resins are used in automotive electro-coating and in automotive and industrial primer and topcoat applications. Epoxy resins are also used industrially in powder coatings used on reinforcing bars for concrete, oil pipelines, wire racks and shelving, as automotive primers and as general industry primers and topcoats. Aerospace coatings (e.g., decals or logos on the sides or tails of planes) also contain bisphenol A (Environment Canada 2007b).

Dental products containing bisphenol A-based polymers (e.g., resin-based composite restorative materials and sealants) have been approved or licensed for use in Canada under the Medical Devices Regulations of the *Food and Drugs Act* (Health Canada, Medical Devices Bureau, Health Products and Food Branch, pers. comm., 2008 Feb 5, unreferenced).

Bisphenol A is also used in the production of phenolplast, phenolic and unsaturated polyester resins, thermal paper, polyvinylchloride (PVC), alkoxylated bisphenol A and polyols/polyurethane (NTP 2007). Additionally, it may be used in the manufacture of brake fluids, tires, modified polyamide, and tetrabromobisphenol A (ECB 2003). Other products of bisphenol A include protective window glazing, building materials, optical lenses and development of dyes (NTP 2007).

The U.S. National Library of Medicine Household Products Database reports that bisphenol A-based polymers are used in coatings, adhesives and putties available to the general public for use in automobiles, home maintenance and repair, and hobbies (NTP 2007). Response to a survey conducted under section 71 of CEPA 1999 indicated that these products were also reported to be available for use in Canada. Bisphenol A-based polymers may also be used in the production of cosmetics, such as lipsticks, face and eye makeup and nail lacquers (Health Canada, Cosmetics Division, pers. comm., 2008 March 18, unreferenced).

Releases to the Environment

There are no known natural sources of bisphenol A and potential releases to the environment are restricted to those associated with anthropogenic activities.

Releases of bisphenol A may occur during production, processing, use or disposal of the substance or products containing it. Results from a section 71 *Notice with respect to certain Batch 2 Challenge substances* conducted for 2006 (Environment Canada 2007a) indicated that bisphenol A was not manufactured in Canada in that year in an amount equal to or greater than 100 kg, although it was imported into the country for use in processing. As production of bisphenol A is not known to be occurring in Canada, potential releases from this source will not be considered further in this assessment.

Based on its moderate water solubility and low vapour pressure, wastewaters and washing residue generated during production and processing of application materials such as polycarbonates and epoxy resins are the most likely industrial sources of release

of bisphenol A into the Canadian environment. Unintentional release of fugitive dust from closed systems during handling and transportation of the substance may also occur. Bisphenol A has low vapour pressure at typical environmental temperatures; however, elevated temperatures occurring during some processing operations may increase the vapour pressure, resulting in formation and possible emission of gaseous bisphenol A from manufacturing facilities.

Bisphenol A released to wastewater would likely be transported to a treatment facility. Once at the plant, the moderate organic carbon-water partition coefficient (log K_{oc} 2.53) suggests that a fraction of the release will be sequestered by sludge. However, the moderate water solubility of 120 to 300 mg/L indicates that a portion will likely remain in the water phase and will therefore be present in final effluents discharged to receiving waters. Lee et al. (2004) measured concentrations of 1.0×10^{-5} to 1.73×10^{-2} mg/L in effluents and 0.07 to 10.6 mg/kg dry weight in raw sludge samples collected in 1999 and 2000 from four Toronto wastewater treatment plants. The results provide evidence that bisphenol A partitions into both the solid and liquid phases within treatment plants. A more detailed review of concentrations measured in waste treatment products is provided in Table 9a. Bisphenol A present in sewage sludge could be released into the soil compartment through application of sludge biosolids to agricultural and pasture lands. Lee and Peart (2000a) examined the efficiency of bisphenol A removal by the sewage treatment plant process. Overall reduction rates of < 1% to 99% were determined from influent/effluent sample pairs collected from 36 Canadian sewage treatment plants, with a median reduction value of 68%. Plants exhibiting greater than 50% reduction rates were those employing secondary waste treatment.

The National Pollutant Release Inventory (NPRI) has tracked the release of bisphenol A from industrial facilities in Canada since the 1990s. Table 3 provides a summary of NPRI on-site release and total disposal data over the period 2001 to 2005. Where information was provided, on-site releases were exclusively to the air compartment. In recent years, total annual releases have varied between about 44 and 8770 kg, with no clear temporal trend apparent. Most recent reporting (2005) indicates total on-site releases of 120 kg, a decrease from that seen in previous years (NPRI 2007). It should be noted that only facilities meeting established criteria are required to report to the NPRI, and therefore NPRI data are likely to underestimate total Canadian releases of bisphenol A. For example, all of the following reporting criteria must have been met before NPRI reporting of bisphenol A was required for the 2005 calendar year: (1) employees at the facility worked a total of 20 000 hours or more or the facility was used for an activity to which the 20 000-hour employee threshold does not apply; and (2) the facility manufactured, processed or otherwise used 10 tonnes (10 000 kg) or more of the substance in one year; and (3) the substance was manufactured, processed or otherwise used at a concentration greater than or equal to 1% by weight, with the exception of NPRI substances considered to be by-products. Facilities not meeting all of these criteria were not required to submit information relating to the release and/or disposal of bisphenol A at their facility. While the number of such facilities is not known, any such releases would not be reported and would therefore be over and above those reported through the NPRI.

Bisphenol A also appears on the United States Environmental Protection Agency Toxics Release Inventory (TRI), a database of chemicals managed through disposal and other releases, recycling, energy recovery and waste treatment. In 2005, a total of approximately 675 000 kg (1.5×10^6 pounds) of bisphenol A were reported to the TRI as disposed or released, with land disposal predominating (about 550 000 kg) and releases occurring to air (about 90 000 kg) and surface waters (about 4 500 kg; USEPA 2007).

Table 3: NPRI release and disposal data (kg) for bisphenol A from 2001 to 2005

Year	Releases to air	Releases to water	Releases to land	Releases to unspecified compartment	Total releases	Total disposals
2001	2904	-	-	-	2904	4919
2002	-	-	-	44	44	5543
2003	8765	-	-	5	8770	13 953
2004	4523	-	-	2	4525	8512
2005	120	-	-	-	120	1154

Release over the service life of end products may occur through volatilization or leaching. The majority of bisphenol A appears to be effectively retained within the polymer matrix of materials such as polycarbonates and therefore losses through leaching from the product surface are expected to be limited (ECB 2003). As well, the low vapour pressure suggests bisphenol A will have little tendency to volatilize from products at normal environmental temperatures. Some losses could occur at elevated temperatures, for example, during heating of end products. Losses may also take place through weathering and breakdown of end products, particularly those with outdoor applications.

Bisphenol A may enter the environment through physical and chemical degradation of end products during disposal and recycling operations. Releases would be primarily to soil, and to a lesser extent, to water and air. Moderate water solubility suggests there is potential for leaching from disposal sites under some circumstances (e.g., during rainfall events) and concentrations up to 1.41×10^{-3} mg/L have been reported in groundwater samples collected in the vicinity of municipal landfills (Rudel et al. 1998; see section on Ecological Exposure Assessment). Higher concentrations would be expected should the leachates have an elevated pH.

Environmental Fate

Based on its physical and chemical properties (Table 2) and compartments to which it is released, the results of Level III fugacity modelling (Table 4) suggest that bisphenol A is expected to partition predominantly to soil or water, depending on the compartment of release.

As a moderately hydrophobic substance with some water solubility, bisphenol A can be expected to partition to organic phases such as sediments and soils; however, an appreciable fraction will also likely be present in the dissolved phase (Cousins et al.

2002). This suggests that the medium of release may be particularly important in predicting the partitioning behaviour and fate of bisphenol A in the environment.

Level III fugacity modelling (Table 4) predicts that when bisphenol A is released exclusively into water, the majority (96.9%) will remain within the water column with only a small fraction (3.1%) moving into sediment. When released to air or soil, or when equal proportions are released to all three media, most bisphenol A (78.7% to 99.3%) will partition to the soil compartment, with smaller amounts expected to be present in water and sediment. Bisphenol A is not predicted to remain within air, even when released exclusively into that compartment.

Table 4: Results of the Level III fugacity modelling (EQC 2003)[1]

	Fraction of substance partitioning to each medium (%)			
Substance Released to:	**Air**	**Water**	**Soil**	**Sediment**
- Air (100%)	0.0	5.3	94.5	0.2
- Water (100%)	0.0	96.9	0.0	3.1
- Soil (100%)	0.0	0.7	99.3	0.0
- Air, water, soil (33% each)	0.0	20.7	78.7	0.6

[1] Input values used in the model were: Type 2 substance; molar mass 228 g/mol; data temperature 25°C; reaction half-life (h) 3.1 in air, 81.6 in water, 326 in soil and sediment; partition coefficients 4.5×10^{-10} (dimensionless) for air-water, 9.7 L/kg for soil-water, 19.4 L/kg for sediment-water, 97 L/kg for suspended particles-water, 5.5 L/kg for fish-water, 100 (dimensionless) for aerosol-water

Eisenreich et al. (1981) predicted that bisphenol A released into the atmosphere would exist almost entirely in the particulate phase and would be subject to removal through dry deposition or photolysis. The small fraction present as vapour would react with photochemically generated hydroxyl radicals (half-life approximately 0.13 day; AOPWIN 2000) or undergo photolysis. Photodegradation products formed include phenol, 4-isopropylphenol, and a semiquinone derivative of bisphenol A (PhysProp 2006).

Biodegradation is expected to be the dominant loss process for bisphenol A in most aquatic and terrestrial environments. Biodegradation half-lives of less than four days were measured in natural waters following an adaptation period (acclimation) from one to four days (Dorn et al. 1987). A slower rate of biodegradation is expected to occur in non-acclimated waters; other processes such as sorption to suspended solids and sediments and photolysis may also take place. Recent research (e.g., Chin et al. 2004; Peng et al. 2006; Zhan et al. 2006) documents both direct and indirect photochemical transformation of bisphenol A in aquatic media. Chin et al. (2004) reported that the rate of direct photolysis was significantly slower than that of indirect photolysis, which includes the presence of dissolved organic matter (DOM), and hypothesized that indirect photodegradation may proceed via multiple pathways involving DOM-derived phototransient substances. Bisphenol A is not expected to undergo hydrolysis due to a lack of hydrolyzable functional groups (Lyman et al. 1982). The low Henry's Law constant suggests that volatilization is unlikely to be a significant removal process.

The moderate water solubility of bisphenol A implies that the substance will exhibit low to moderate mobility when released to soil (Dorn et al. 1987). However, Loffredo and

Senesi (2006) examined the adsorption kinetics and adsorption/desorption isotherms of bisphenol A onto four soil samples collected from the surface (0-30 cm) and deep (30-90 cm) horizons of two acidic sandy soils. The researchers concluded that soil adsorption of bisphenol A is generally reversible, with desorption occurring quickly and completely. Thus, the substance is expected to move down the soil profile and could possibly contaminate groundwater in acidic sandy soils (Loffredo and Senesi 2006). The movement of bisphenol A through the soil matrix and/or into groundwater will be influenced by the physical and chemical properties of the receiving soil and of water travelling through it, and in particular the pH of these media, as well as the nature and properties of organic material present in the soil and water. Quantities of bisphenol A available for transport will be determined by factors such as the loading rate of the substance into the receiving medium and degradation processes. Potential contamination of groundwater from soil-based bisphenol A contamination is thus site-specific and difficult to predict across the Canadian landscape. Rudel et al. (1998) reported concentrations of up to 1.41×10^{-3} mg/L in groundwater samples collected in the vicinity of municipal landfills and wastewater treatment plants. Bisphenol A was present in monitoring wells located downgradient of secondary wastewater treatment plant infiltration beds to which no wastewater had been discharged for six months, suggesting no or only slow degradation of the substance in subsurface waters.

Persistence and Bioaccumulation Potential

Environmental Persistence

Data relevant to the evaluation of potential environmental persistence of bisphenol A are summarized in Tables 5a and 5b.

Table 5a. Empirical data for persistence

Medium	Fate process	Degradation value	Degradation endpoint, units	Reference
Water	Biodegradation (aerobic)	74.7-81.4	28-day biodegradation, %	West et al. 2001
Water	Biodegradation (aerobic)	0	14-d biochemical oxygen demand, %	NITE 1977
Water	Biodegradation (aerobic)	0.5-3.4 (lag phase of 2-8 days required)	Half-life, days	Klečka et al. 2001
Water	Biodegradation (aerobic)	2-3	Half-life, days	Kang and Kondo 2002
	Biodegradation (anaerobic)	< 10	10-day biodegradation, %	

Medium	Fate process	Degradation value	Degradation endpoint, units	Reference
Sediment	Biodegradation (anaerobic)	0	90-day (3-month) biodegradation, %	Ronen and Abeliovich 2000
Sediment	Biodegradation (anaerobic)	0	120-day biodegradation, %	Voordeckers et al. 2002
Water, Sediment	Biodegradation (anaerobic)	0	70-day biodegradation, %	Ying and Kookana 2003
Water, Sediment	Biodegradation (aerobic)	1.212 1.38	50% dissipation time, days 90% dissipation time, days	Sarmah and Northcott 2008
	Biodegradation (anaerobic)	2.75 4.901	50% dissipation time, days 90% dissipation time, days	
Soil	Biodegradation (aerobic)	3	Dissipation half-life, days	Fent et al. 2003
Soil	Biodegradation (aerobic)	7	Half-life, days	Ying and Kookana 2005
	Biodegradation (anaerobic)	0	70-day biodegradation, %	
Aquifer water, sediment	Biodegradation (anaerobic)	0	70-day biodegradation, %	Ying et al. 2003
Ground-water, Aquifer Material	Biodegradation (aerobic)	0.57 2.26	50% dissipation time, days 90% dissipation time, days	Sarmah and Northcott 2008
	Biodegradation (anaerobic)	2.315 306.0	50% dissipation time, days 90% dissipation time, days	

Aerobic biodegradation is likely to be the dominant loss process for bisphenol A in most aquatic and terrestrial environments (Staples et al. 1998). Bisphenol A has demonstrated rapid biodegradation in standard aerobic 28-day ready biodegradability testing using

OECD Test Guideline No. 301F (West et al. 2001), but is indicated to be non-biodegradable using another aerobic OECD method, Test Guideline 301C (NITE 1977). Klečka et al. (2001) reported biodegradation half-lives of less than 3.5 days in river surface water samples, including those to which 0.05% surface sediment mixtures (top 1-2 cm) were added. A lag phase of from two to eight days was required prior to the onset of degradation.

A number of studies report resistance to biodegradation under conditions of low oxygen, suggesting there may be circumstances under which bisphenol A remains stable in the environment. Kang and Kondo (2002) measured rapid biodegradation in spiked river water samples incubated under aerobic conditions, but a less than 10% decrease in samples incubated anaerobically for an equivalent time period of 10 days. The researchers postulated that anaerobic bacteria may have little or no capability of degrading bisphenol A, although chemical degradation of the substance (for example, by lipoperoxide and sodium chloride) could still occur. Ying and Kookana (2005) documented rapid degradation of bisphenol A in soil within 7 days, but no degradation of the substance under anaerobic conditions in the soil. Bisphenol A was reported to persist in an anaerobic slurry of river bed sediment, with no degradation evident after 3 months of incubation (Ronen and Abeliovich 2000). The substance also remained stable in anoxic estuarine sediments, with no degradation observed after 120 days (Voordeckers et al. 2002). Concentrations of bisphenol A remained unchanged in 70-day anaerobic biodegradation studies conducted using spiked samples of seawater and marine sediment (Ying and Kookana 2003), four different soil types (Ying and Kookana 2005), and water and sediment collected from an aquifer (Ying et al. 2003). Little or no degradation was reported for periods of up to 4 months, suggesting that half-lives of bisphenol A in anoxic and anaerobic media could well exceed one year.

Sarmah and Northcott (2008) examined degradation of bisphenol A in river water-sediment and groundwater-aquifer test systems. A biphasic degradation pattern was observed under both aerobic and anaerobic testing conditions, with rapid initial degradation of greater than 90% occurring in the first four days and trace amounts still remaining at the end of the 70-day study period. The formation of degradation products was monitored for the duration of the study; however, no potential metabolites were detected. Measured data were fitted using a first-order double exponential decay model, with results being presented as dissipation times (i.e., losses from the test system) rather than degradation half-lives. Reported 50% dissipation times (DT50s) were 0.57 to 1.212 days for aerobic conditions and 1.38 to 2.315 days for anaerobic conditions. Times for 90% dissipation were 2.26 to 2.75 days and 4.901 to 306 days for aerobic and anaerobic conditions, respectively. The researchers noted the incongruency of their results with those of previous studies which found little or no biodegradation of bisphenol A under anaerobic conditions, and suggested that lower test concentrations used in the study and variations in experimental protocols may have contributed to the observed differences. In addition, losses of up to 40% of the initial amount applied occurred in the sterile (control) treatments; this was considered significantly high and attributed to the possible occurrence of abiotic degradation processes or irreversible sorption of bisphenol A to test vessels.

The modelled data generally support the empirical evidence, with BIOWIN (2000) predicting a half-life for ultimate aerobic biodegradation of 37.5 days but no or very slow anaerobic biodegradation (Table 5b). The results from Table 5b show that the majority of the probability models suggest this substance does not biodegrade fast. However, only the MITI non-linear model produced a result less than 0.3, the cut-off suggested by Aronson et al. (2006) in identifying substances as having a half-life >60 days (based on the MITI probability models). CPOPs (2008), which uses the CATABOL model, predicts that bisphenol A will fail ready biodegradation testing based on OECD method 301C, supporting the experimental results reported by NITE (1977).

Table 5b. Modelled data for persistence

Medium	Fate process	Degradation value	Degradation endpoint, units	Reference
Air	Atm. oxidation	0.133	Half-life, days	AOPWIN 2000
Air	Ozone reaction	No estimate. Reaction with nitrate radicals may be important.	Half-life, days	AOPWIN 2000
Water	Biodegradation	37.5	Half-life, days	BIOWIN 2000, Ultimate survey
Water	Biodegradation	0.6866	Probability	BIOWIN 2000, Linear
Water	Biodegradation	0.4653	Probability	BIOWIN 2000, Non-linear
Water	Biodegradation	0.2956	Probability	BIOWIN 2000, MITI linear
Water	Biodegradation	0.1559	Probability	BIOWIN 2000, MITI non-linear
Water	Biodegradation	-0.2593	Probability	BIOWIN 2000, Anaerobic linear
Water	Biodegradation	11.7[1]	BOD, % (301C)	CPOPs 2008; Mekenyan et al. 2005
Soil	Biodegradation	37.5	Half-life, days	Based on the modelled half-life in water[2]
Sediment	Biodegradation	150	Half-life, days	Based on the modelled half-life in water[2]

[1] In all domains of applicability (global parameter, structural and metabolic)
[2] Values were derived from the modelled half-life in water using the extrapolation factors of Boethling et al. (1995): $t_{1/2\ soil} : t_{1/2\ water} : t_{1/2\ sediment} = 1 : 1 : 4$

The predicted half-life for atmospheric degradation of bisphenol A due to reaction with the hydroxyl radical is 0.133 day (Table 5b), indicating the substance will likely be rapidly oxidized in air. AOPWIN (2000) predicts reaction with atmospheric nitrate radicals may also occur.

There is conflicting evidence on the aerobic biodegradation potential of bisphenol A. Laboratory tests show positive and negative results of ready biodegradation potential. However, there is insufficient detail for the only laboratory aerobic biodegradation test showing a negative ready biodegradation test (NITE 1977) to determine whether the lack of biodegradation was the result of a lag phase. This test received lower weighting overall. There is greater concordance with the remaining laboratory and field evidence showing a fairly rapid loss of bisphenol A under aerobic conditions. Field tests are expected to be more indicative of the biodegradation potential of bisphenol A under natural conditions than the laboratory studies or QSARs based on laboratory data. Therefore, field data received greater weight. Results for the majority of aerobic

biodegradation models also suggest a fairly short half-life, but some models (e.g., CPOPS and MITI non-linear model) suggest greater persistence of bisphenol A. Both these models, however, are trained on the NITE ready biodegradation data which, as already suggested, may not adequately account for a potential lag phase of bisphenol A. Therefore, these predictions are subject to test error which will not be captured by bisphenol A's structural characteristics alone and thus receive a lower weight. When combined laboratory, field and model evidence are considered, there is greater reliable evidence to suggest that bisphenol A does not meet persistence criterion for air (half-life in air $\geq$ 2 days), water and soil (half-life in soil and water $\geq$ 182 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). There are many studies showing that bisphenol A does not degrade or degrades only slowly under conditions of low or no oxygen and the measured presence in sediment, a medium to which there is no direct release, is further evidence of this slow degradation. Therefore, bisphenol A meets criteria for persistence in sediments (half-life in sediments $\geq$ 365 days) under these conditions.

Potential for Bioaccumulation

The empirical and modelled log K_{ow} values of 3.32 and 3.64, respectively, suggest that bisphenol A may have some potential to accumulate in organisms. However, the substance demonstrates low bioaccumulation potential based on laboratory-derived bioconcentration factor (BCF) values obtained in testing with fish and other aquatic species (Table 6a). Measured BCF values range from 3.5 to 68 in fish, but are higher in freshwater clams (107 to 144; Heinonen et al. 2002) and frogs (131 to 147; Kopenen et al. 2007). Takahashi et al. (2003) calculated bioaccumulation factors (BAF; i.e., incorporating consideration of uptake through food) of from 18 to 650 for periphyton (presence of detritus not reported, uncertain whether steady-state concentrations achieved) and from 8 to170 for benthos (procedures for sampling/collection, species not specified), and postulated that food may be an important uptake route for organisms in the aquatic environment.

Table 6a. Empirical data for bioaccumulation

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Periphyton Benthos	BAF	18-650 8-170	Takahashi et al. 2003
Fish	BCF	5.1-67.7	NITE 1977
Fish	BCF	3.5-5.5	Lindholst et al. 2001
Fish	BCF	38±21	Lee et al. 2004
Clam	BCF	107-144	Heinonen et al. 2002
Frog	BCF	131-147	Koponen et al. 2007

Heinonen et al. (2002) reported very slow depuration of bisphenol A in freshwater clams, *Pisidium amnicum*, exposed at temperatures ranging from 2°C to 12°C, with statistically insignificant depuration occurring at the lowest test temperature of 2°C. This suggests that in addition to environmental exposure concentrations, body clearance rates and metabolism are important in determining final tissue levels of the substance. Metabolism

of bisphenol A has been reported in fish (Lindholst et al. 2001), with the formation of glucuronides identified as the primary metabolic pathway. Kang et al (2006c) conducted a review of existing literature and also found that various organisms, including plants, fish, birds and mammals have capacity to metabolize bisphenol A.

A range of QSAR modelled bioaccumulation and bioconcentration values are available, with BAF or BCF values of from 5.8 (Baseline BCF Model) to 955 (OASIS Forecast; Table 6b). Most modelled values support a conclusion of low bioaccumulation potential.

Table 6b. Modelled data for bioaccumulation

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Fish	BAF	107-170	GOBAS BAF three trophic level model (Arnot and Gobas 2003)
Fish	BCF	104-170	GOBAS BCF three trophic level model (Arnot and Gobas 2003)
Fish	BCF	955	OASIS Forecast 2005
Fish	BCF	5.8	Baseline BCF model (all mitigating factors) (Dimitrov et al. 2005)
Fish	BCF	71.8	BCFWIN 2000

Both the empirical and modeled BCF and BAF data are in good agreement and indicate that bisphenol A does not meet the bioaccumulation criterion (BCF, BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). This conclusion is consistent with the physical-chemical properties of the substance and evidence for metabolism in biota.

Potential to Cause Ecological Harm

Ecological Effects Assessment

A - In the Aquatic Compartment

There is modelled and experimental evidence that bisphenol A causes harm to aquatic organisms at relatively low concentrations (Tables 7a, 7b and 7c)

Table 7a. Empirical data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Algae freshwater marine	Chronic (96 hours)	EC_{50}[1]	 2.7, 3.1[2] 1.0, 1.8[3]	Alexander et al. 1988
Daphnid	Acute (48 hours)	EC_{50} LC_{50}[4] LC_{50}	10 7.75 12.8	Alexander et al. 1988 Brennan et al. 2006 Hirano et al. 2004

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
	Chronic (7 days)	IC_{25}[5] NOEC[6] LOEC[7]	3.92 0.94 1.88	Tatarazako et al. 2002
	Chronic (21 days)	NOEC Threshold concentration[8]	≥ 1.0 1.3	Brennan et al. 2006 Mu et al. 2005
Fish freshwater	Acute (96 hours) Chronic (14 days) Chronic (28 days) Chronic (164 days) Chronic (103 days) marine	LC_{50} NOEC LOEC NOEC LOEC NOEC LOEC NOEC LOEC LC_{50}	4.6 3.2 10.15 3.64 11.0 0.001-0.16 0.16-0.64 < 0.00175 0.00175 9.4	Alexander et al. 1988 Bayer AG 1999a Bayer AG 1999b Sohoni et al. 2001 Lahnsteiner et al. 2005 Alexander et al. 1988
Mysid	Acute (96 hours)	LC_{50} LC_{50}	1.1 1.03	Alexander et al. 1988 Hirano et al. 2004
Amphipod	Acute (14 days)	NOEC LOEC	0.1 1.0	Johnson et al. 2005

[1] Median effective concentration
[2] Endpoint value based on cell count (2.7 mg/L) or total cell volume (3.1 mg/L)
[3] Endpoint value based on cell count (1.0 mg/L) or chlorophyll a content (1.8 mg/L)
[4] Median lethal concentration
[5] Inhibiting concentration for a specified percent effect. A point estimate of the concentration of a test substance that causes 25% reduction in a quantitative biological measurement such as growth rate.
[6] No observed effect concentration; highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls. In this case, the study identified that the highest concentration tested did not result in statistically significant results. Since the NOEC could be higher, the NOEC is described as being greater than or equal to the highest test concentration.
[7] Low observed effect concentration; lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
[8] Minimum concentration in a toxicity test that just causes an observable effect

Alexander et al. (1988) conducted a series of standard freshwater and saltwater toxicity tests on bisphenol A. Lowest endpoint values were a 96-hour EC_{50} of 1.0 mg/L for the marine diatom, *Skeletonema costatum*, based on cell counts, and a 96-hour LC_{50} of 1.1 mg/L for the mysid shrimp, *Mysidopsis bahia.* The mysid 96-hour LC_{50} value agrees well with that of 1.03 mg/L reported by Hirano et al. (2004).

Brennan et al. (2006) examined the potential for acute and chronic effects in two generations of water flea, *Daphnia magna*. The measured acute value was in the range of that reported by Alexander et al. (1988; see Table 7a). However, in chronic testing, higher mortality was observed in second generation daphnids compared with first generation animals exposed to the same test concentrations. The researchers postulated that elevated mortalities in the second generation may indicate weakening of the offspring relative to the first (parental) generation, leading to greater susceptibility to lethal effects in the second generation. This trend could indicate action at the cellular level of organisms, possibly DNA damage.

The same study also examined potential reproductive effects. No significant impacts were observed in the fecundity of first and second generation daphnids exposed to concentrations up to 1.0 mg/L. Mu et al. (2005). However, reported reduced reproductive

success for *Daphnia magna* at a threshold concentration of 1.30 mg/L and proposed that the substance could elicit chronic effects through interference with ecdysis (moulting).

Seven-day NOEC and LOEC values of 0.94 and 1.88 mg/L, respectively, were reported for reproduction in the daphnid species, *Ceriodaphnia dubia* (Tatarazako et al. 2002); the IC_{25} for the study was 3.92 mg/L. These values are similar to results obtained using *Daphnia magna* and provide further evidence of possible chronic toxicity.

Johnson et al. (2005) investigated potential impacts to the freshwater amphipod, *Gammarus pulex*. No statistically significant effects were evident on female moulting and juvenile production following a 14-day exposure period, although adult survival was reduced at the highest test concentration of 1.0 mg/L.

Potential effects following long-term exposure (164 days) were studied in the fathead minnow, *Pimephales promelas* (Sohoni et al. 2001). The growth of adult male fish and hatchability of offspring were significantly inhibited at a lowest concentration of 0.64 mg/L, while more subtle reproductive effects (i.e., induction of vitellogenin synthesis, alterations to sex cells) occurred at 0.016 mg/L. The researchers concluded that bisphenol A acts as a weak estrogen mimic to fish exposed via the water.

Lahnsteiner et al. (2005) exposed male and female brown trout, *Salmo trutta f. fario*, during the late pre-spawning and spawning period, and investigated effects on maturation, quantity and quality of semen and eggs. Bisphenol A was added into the flow-through test system by means of an injection pump, with final reported test concentrations of 0.00175, 0.00240 and 0.005 mg/L calculated based on water flow and test chemical injection rates. Similar numbers of males (6-8) provided semen in the control group and at the two lowest concentrations, while only one male from the high test group gave semen. Semen quality was lower at estimated concentrations of 0.00175 and 0.00240 mg/L compared with the controls (reduced sperm density, motility rate, and swimming velocity), both at the beginning and in the middle of spawning. Production of high quality semen was restricted to the end of the spawning season and delayed for approximately 4 weeks in comparison to the control. The percentage of ovulated females was similar in the control group and two lowest exposure groups; however, females at the highest exposure group did not ovulate over the 103-day investigation period. Ovulation was delayed by approximately 2 weeks in the 0.00175 mg/L exposure group and by approximately 3 weeks in the 0.00240 mg/L group. Therefore, the tested bisphenol A concentrations affected the percentage of ovulated females and the time point of ovulation. No effects were observed on the quality of eggs (egg mass, percentile mass increase during hardening, egg fertility).

Acute aquatic toxicity estimates derived from QSAR models are in the range of 3 to 9 mg/L (Table 7b), slightly above results obtained experimentally. However, the predicted values are sufficiently close to those of laboratory studies to support a decision of potential acute aquatic toxicity at low concentrations. The weight of experimental and modelled evidence indicate that bisphenol A can be considered highly hazardous to the

aquatic environment (i.e., (L(E)C_{50} values at or approaching 1 mg/L and/or chronic NOEC equal to or less than 0.1 mg/L**)**.

Table 7b. Modelled data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 hours)	LC_{50}[1]	3.3	ECOSAR 2004
Fish	Acute (96 hours)	LC_{50}	4.3	TOPKAT 2004
Fish	Acute (96 hours)	LC_{50}	4.9	ASTER 1999
Fish	Acute (96 hours)	LC_{50}	≤6.3[3] (± 1.2)[4]	CPOPS 2005
Fish	Acute (96 hours)	LC_{50}	8.5	AIES 2003-2005
Fish	Chronic (30 days)	MATC[5]	0.5	ECOSAR 2004
Daphnid	Acute (48 hours)	LC_{50}	2.6	ECOSAR 2004
Daphnid	Acute (48 hours)	EC_{50}[2]	5.1(± 2.6)[4]	CPOPS 2005
Daphnid	Acute (48 hours)	EC_{50}[2]	5.2	TOPKAT 2004
Daphnid	Chronic (21 days)	MATC[5]	0.4	ECOSAR 2004
Green Algae	Acute (96 hours)	EC_{50}	4.0	ECOSAR 2004
Green Algae	Chronic (96 hours)	MATC[5]	1.0	ECOSAR 2004

[1] Median lethal concentration
[2] Median effective concentration
[3] CPOPS has identified bisphenol A as having an unspecified reactive model of toxicity in the fish 96hr LC50 QSAR. The ≤ denotes that the median lethal concentration is expected to be lower than the reported default value which is based on a baseline narcotic mode of action
[4] ± 95% confidence interval
[5] Maximum Allowable Toxicant Concentration, generally presented as the range between the No Observed Effect Concentration and Lowest Observed Effect Concentration or as the geometric mean of the two measures

Evidence of disruption to reproductive and developmental processes following exposure to bisphenol A at concentrations below those causing acute effects has been reported in fish, aquatic invertebrates, amphibians and reptiles. A selection of reported endpoint values relevant to potential hormonal disruption is presented in Table 7c. While there is a widespread variation in reported values, many fall in the range of 0.001 to 1 mg/L. In addition, differing sensitivities are evident between groups of organisms, with endpoint values for fish generally higher than those for aquatic invertebrates. Considered together, the data provide strong evidence that bisphenol A is capable of eliciting adverse effects: (1) following prolonged exposure at levels below those usually seen to elicit effects in standard toxicity tests (i.e., tests based on recognized methods which evaluate endpoints such as survival, reproduction and growth); (2) following brief low-dose exposure, particularly at sensitive developmental stages, with effects apparent later in the life cycle; (3) on filial generations following parental exposure; and (4) using more than one mode of action.

Table 7c. Selected endpoint values relating to potential hormonal effects

Test organism	Duration of test (days)	Endpoint observed	Lowest effect value (mg/L)	Reference
Fish:				
Carp	4	Vitellogenin induction	22.8	Letcher et al. 2005
Goldfish	8	Altered plasma calcium homeostasis	0.228	Suzuki et al. 2003
Rainbow trout	12	Vitellogenin induction	0.070	Lindholst et al. 2000
Carp	14	Altered sex steroid levels	0.001[1]	Mandich et al. 2007
Turbot	21	Altered steroid hormone balance	0.059[2]	Labadie and Budzinski 2006
Guppy	21	Reduced total sperm count	0.274[1]	Haubruge et al. 2000
Fathead minnow	21	Reduced egg number at spawning	0.500	Brian et al. 2007
Medaka	21	Vitellogenin induction	0.500	Tabata et al. 2004
Medaka	21	Altered gonad development	1.720	Kang et al. 2002
Medaka	60	Altered growth, sex ratio	1.820	Yokota et al. 2000
Zebrafish	Fertilization to adult (65-75 days)	Vitellogenin induction, altered gonad histology	0.375	Segner et al. 2003
Brown trout	103	Reduced sperm quality and motility; delayed ovulation, reduced percent ovulation	0.00175[1]	Lahnsteiner et al. 2005
Medaka	110	Altered gonad development	0.006[1]	Metcalfe et al. 2001
Invertebrates:				
Copepod	21	Delayed development	0.00001[1]	Marcial et al. 2003
Mussel	21	Induction of vitellogenin-like proteins and spawning in both sexes	0.050[2]	Aarab et al. 2006
Mussel	21	Resorption of male and female gonads	0.050[2]	Ortiz-Zarragoitia and Cajaraville 2006
Mudsnail	56	Increased embryo production	0.001 (mg/kg)	Duft et al. 2003
Mudsnail	63	Increased embryo production	0.005	Jobling et al. 2004
Ramshorn snail	180	Increased egg and clutch production	0.0000483	Oehlmann et al. 2006
Chironomid	2 life cycles	Delayed emergence (2nd generation) mouthpart deformities	0.078 0.010	Segner et al. 2003

Test organism	Duration of test (days)	Endpoint observed	Lowest effect value (mg/L)	Reference
Amphibians:				
Frog	< 1	Competitive binding to estrogen receptor	0.107[3]	Suzuki et al. 2004
Frog	9	Suppressed metamorphosis	0.228[1]	Goto et al. 2006
Frog	75	Altered gonad development	0.228	Jagnytsch et al. 2006
Frog	84	Feminized sex ratio	0.0228	Kloas et al. 1999
Frog	90	No observable effect on larval growth, development or sexual differentiation	Highest: 0.500	Pickford et al. 2003
Frog	120	Feminized sex ratio at 0.0228 mg/L, no observable effect at 0.00228 and 0.228	0.0228	Levy et al. 2004
Reptiles:				
Caiman	10	Reversed gonadal sex and altered gonad structure	1.400[1] (mg/kg egg)	Stoker et al. 2003

[1] Significant effects occurred at the lowest test concentration
[2] One test concentration
[3] Test concentration was reported as 4.7×10^{-7} M

B - In Other Environmental Compartments

Only limited toxicity data are available for non-mammalian terrestrial species; these are summarized in Table 8.

Table 8. Empirical data for terrestrial toxicity

Test organism	Type of test	Endpoint	Value	Reference
Earthworm	Acute (14 days) Chronic (56 days)	NOEC[1] LOEC[2] NOEC	32 mg/kg dw 100 mg/kg dw ≥ 100 mg/kg dw[3]	Johnson et al. 2005
Springtail	Chronic (28 days)	NOEC	500 mg/kg dw	ECT 2007a
Enchytraeid worm	Chronic (28 days)	NOEC	> 100 mg/kg dw	ECT 2007b
Terrestrial plant (cabbage, corn, oat, soybean, tomato, wheat)	Chronic (21 days)	Emergence, Growth	Effects at 150 and 1000 mg/kg soil	Dow Chemical Canada Inc. 2007
Terrestrial plant (cabbage, corn, oat, soybean, tomato, wheat)	Chronic (21 days)	Lowest: NOEC EC_{25}[4] EC_{50}[5]	 20 mg/kg dw 19 mg/kg dw 67 mg/kg dw	Springborn Smithers 2007
Terrestrial plant (bean, tomato, lettuce, wheat)	Chronic (21 days)	Growth, morphology	10 mg/L	Ferrara et al. 2006
Chicken	Chronic (23 weeks)	NOAEL[6] LOAEL[7]	1 mg/kg-bw per day 100 mg/kg-bw per day	Furuya *et al.* 2006

[1] No observed effect concentration; highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.
[2] Low observed effect concentration; lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
[3] Study identified that the highest concentration tested did not result in statistically significant results. Since the NOEC could be higher, the NOEC is described as being greater than or equal to the highest test concentration.
[4] The concentration which causes an effect on 25% of the test organisms.
[5] Median effective concentration.

[6] No observed adverse effect level; highest dose in a toxicity test not causing a statistically significant effect in comparison to the controls.
[7] Lowest observed adverse effect level; lowest dose in a toxicity test that caused a statistically significant effect in comparison to the controls.

No statistically significant effects on reproduction were evident in earthworm, *Eisenia sp.*, exposed for 56 days to concentrations of up to 100 mg/kg dw of soil; however, statistically significant and concentration-dependent mortality occurred at concentrations of 100 mg/kg dw of soil and above (up to 10 000 mg/kg dw; Johnson et al. 2005).

A "limit test" using concentrations of 150 and 1000 mg/kg soil was performed using six species of terrestrial plants (cabbage, corn, oat, soybean, tomato and wheat) (Dow Chemical Canada Inc. 2007). Effects were evident at both concentrations tested. No information on statistical endpoints was provided in the summary report submitted to Environment Canada.

Ferrara et al. (2006) reported phytotoxicity and morphological anomalies in four plant species (broad bean, tomato, lettuce and durum wheat) grown hydroponically for 21 days at doses of 10 and 50 mg/L bisphenol A.

ECB (2008) reported results from three unpublished studies conducted using springtail (*Folsomia candida*; ECT 2007a), enchytraeid worm (*Enchytraeus crypticus*; ECT 2007b), and six terrestrial plant species (Springborn Smithers 2007). In springtail testing, no significant effects on survival occurred up to a highest exposure level of 1000 mg/kg dw; however, reproduction was significantly reduced at this concentration and the NOEC for this endpoint was therefore 500 mg/kg dw (EBC 2008). No significant effects on survival and reproduction were reported in enchytraeid worms up to a maximum exposure concentration of 100 mg/kg dw. Emergence in six species of terrestrial plants was significantly inhibited at a lowest exposure level of 320 mg/kg dw (cabbage, tomato), while the lowest effect level for growth was 50 mg/kg dw (tomato; ECB 2008).

Furuya et al. (2006) reported on the development of male chicken phenotypes (comb, wattle and testes) in White Leghorn, *Gallus domesticus*, chicks administered oral doses of 0.002 to 200 mg/kg-bw bisphenol A in corn oil/alcohol carrier every two days from 2 to 25 weeks of age. Dose-dependent growth inhibition of all three endpoints occurred even at the minimum dosage, although recovery was evident at all but the highest dosage. This suggests development was delayed at lower doses and permanently altered at the highest dose of 200 mg/kg-bw per 2 days (i.e., 100 mg/kg-bw per day).

While there is little information on potential effects in wildlife species, a number of studies examine toxicity in rodents (see Health Effects Assessment section). Chronic oral exposure to low levels of contaminants, for example through ingestion in food, is more likely to be the scenario of concern for wildlife and there are some studies that, though limited when subject to a weight of evidence analysis, are suggestive of potential effects at doses well below the NOAELs of 5 and 50 mg/kg-bw per day established for bisphenol A in rodent species. There is also evidence that the pregnant female/fetus and developing offspring may be a sensitive subpopulation (see Health Effects Assessment section). A

more detailed consideration of potential impacts in mammalian species is provided in the Health Effect Assessment section of this document.

Ecological Exposure Assessment

Table 9a provides a summary of Canadian and North American water and sediment concentrations, as well as levels reported in water and wastewater treatment products.

Table 9a. Concentrations of bisphenol A in the ambient environment and waste treatment products

Medium	Location; year	Concentration (mg/L or mg/kg dw[1])	Number of samples	Reference
Surface sediment	Lake Erie, Canada; 2004	$< 1.5\times10^{-4} – 6.1\times10^{-3}$	55	Chu et al. 2005
MWWTP[2] effluent Surface water (river) Drinking water	Calgary, Canada; 2002–2004	1.25×10^{-4}, 1.95×10^{-4} $6.4\times10^{-7} – 1.88\times10^{-5}$ 4.5×10^{-7}, 7.6×10^{-7}	2 3 2	Chen et al. 2006
Pulp & paper mill: 1° effluent[3, 4] 2° effluent[5] Sludge	Across Canada; 1998	 $2.6\times10^{-5} – 0.139$ $< 5.0\times10^{-6} – 4.06\times10^{-4}$ $< 0.020–3.330$	 15 15 15	Lee and Peart 2000a
MWWTP effluent Surface water (rivers), upstream and downstream of MWWTPs	Alberta, Canada; 2002 - 2003	$<1.29\times10^{-6} – 1.95\times10^{-4}$ $1.8\times10^{-6} – 1.53\times10^{-3}$	8 5	Sosiak and Hebbin (2005)
Industrial wastewaters discharged to MWWTP: • Chemical & chemical products • Commercial laundries • Textile products & clothing industries • Fabricated metal products industries • Paper & allied products industries • Miscellaneous industries • Plastic products	Toronto, Canada; 1999–2000	 $8.0\times10^{-5} – 0.09127$ (median 1.5×10^{-3}) $7.5\times10^{-4} – 0.04345$ (median 6.56×10^{-3}) $1.0\times10^{-4} – 4.8\times10^{-4}$ (median 2.1×10^{-4}) $< 1.0\times10^{-5} – 6.51\times10^{-3}$ (median 7.0×10^{-4}) $< 1.0\times10^{-5} – 0.14923$ (median 8.72×10^{-3}) $2.0\times10^{-4} – 1.70\times10^{-3}$ (median 6.7×10^{-4}) $5.0\times10^{-5} – 2.12\times10^{-3}$ (median 6.3×10^{-4})	 37 17 10 11 8 5 9	Lee et al. 2002
Bleached Kraft Pulp Mill Effluent	Western Canada; 2002–2005	$1.1\times10^{-5} – 4.0\times10^{-5}$ (mean 2.1×10^{-5})	6	Fernandez et al. 2007b
MWWTP sludge: Raw sludge Digested sludge	Across Canada; 1994–2001	 0.100 – 39.8 0.100 – 11.1	 13 22	Lee and Peart 2002
MWWTP: Influent & effluent Sludge	Across Canada; 1998–1999	 $3.1\times10^{-5} – 0.0499$[6] 0.104 – 36.7	 47 51	Lee and Peart 2000b
MWWTP:	Across Canada; 1999–			Lee and Peart 2000a

Medium	Location; year	Concentration (mg/L or mg/kg dw[1])	Number of samples	Reference
Influent Effluent Sludge	2000	8.0×10^{-5} – 4.98×10^{-3} 1.0×10^{-5} – 1.08×10^{-3} 0.033 – 36.7	36 34 50	
MWWTP: Influent Effluent Raw sludge Digested sludge	Toronto, Canada; 1999–2000	 1.6×10^{-4} – 0.0281 1.0×10^{-5} – 0.0173 0.070– 10.6 0.120– 12.5	 15 15 16 18	Lee et al. 2004
MWWTP : Primary effluent Final effluent	British Columbia, Canada; 2002 – 2003	 1.0×10^{-5} – $4.5\times10^{-5,7}$ 1.0×10^{-5} – 3.5×10^{-5}	 8 8	Fernandez et al. 2007a
MWWTP: Influent Effluent	Western Canada; 2002 – 2005	 < 2.1×10^{-6} – 5.9×10^{-4} < 2.1×10^{-6} – 3.53×10^{-4}	 11 29	Fernandez et al. 2007b
MWWTP effluent	Vancouver, Canada; 2003	5.8×10^{-5} – 1.054×10^{-3}	16	Campbell et al. 2006; Fernandez, pers. comm. 2007
MWWTP: Influent Effluent	Vancouver, Canada; 2003	 4.19×10^{-5} – 7.18×10^{-5} 2.9×10^{-6} – 7.64×10^{-5}	 5 5	Nelson et al. 2007
MWWTP: Influent Effluent	Ontario, Canada; 2004	 2.1×10^{-4} – 2.4×10^{-3} 2.0×10^{-5} – 4.5×10^{-4}	 8 8	Lee et al. 2005
MWWTP sludge	Ontario, Canada; 2004	3.78×10^{-3} – 0.07438	4	Chu et al. 2005
Surface water: Stream	United States; 1996–1997	 < 0.001– 0.008	72	Staples et al. 2000
Surface water: Stream	United States; 1999–2000	1.4×10^{-4} (median) 0.012 (maximum)	85	Kolpin et al. 2002
Surface water: Stream	Iowa, United States; 2001	 < 8.8×10^{-5} – 7.4×10^{-4}	76	Kolpin et al. 2004
Surface water: River Lake Canal Bayou	Louisiana, United States; 2003	 6.0×10^{-6} – 1.13×10^{-4} < 1.0×10^{-7} – 5.7×10^{-5} < 1.0×10^{-7} – 1.58×10^{-4} < 1.0×10^{-7} – 4.4×10^{-5}	 8 7 14 5	Boyd et al. 2004
Surface water : River	Missouri, United States; 2003–2004	1.8×10^{-5}, 2.4×10^{-5} (median)[8] 7.2×10^{-5}, 1.98×10^{-4} (maximum)	31	Solís et al. 2007
Surface water : River	Louisiana, United States; 2004	0 – 1.472×10^{-4}	6	Zhang et al. 2007
Surface sediment	Massachusetts, United States; 2003–2004	< 4.0×10^{-6} – 0.005	15	Stuart et al. 2005
Groundwater	Massachusetts, United States; 1996–1997	< 3.0×10^{-6} – 1.41×10^{-3}	9	Rudel et al. 1998
MWWTP: Biosolids	United States; 2003–2004	 0.100 – 4.6	45	Kinney et al. 2006

[1] Sediment or sludge concentrations are reported on a dry weight basis
[2] Municipal wastewater treatment plant
[3] Primary effluent
[4] Influent to secondary treatment
[5] Secondary effluent
[6] Values are reported as a combined range of both influent and effluent concentrations

[7] Values estimated from graph
[8] Median and maximum values are for different sample sets collected from two rivers in the same region

The highest reported values for surface water and sediment were 0.012 mg/L and 0.0061 mg/kg dw, respectively. Most surface water concentrations were much lower than the maximum reported value, however, with levels more in the range of 0.0001 to 0.001 mg/L. In their study on sediment concentrations in Lake Erie, Chu et al. (2005a) reported that highest concentrations of bisphenol A (up to 0.0061 mg/kg dw) were measured in the western basin of the lake, likely reflecting the substantial loading and input from numerous wastewater treatment plants in the region into Lake Erie and the Detroit River, which empties into it.

Rudel et al. (1998) reported a maximum concentration of 0.00141 mg/L in groundwater samples collected in the vicinity of municipal landfills, while up to 2.9×10^{-5} mg/L was detected in monitoring wells located downgradient of secondary wastewater treatment plant infiltration beds to which no wastewater had been discharged for six months.

High levels have been measured in some industrial wastewaters, most notably those associated with paper and allied products (maximum 0.14923 mg/L; median 0.00872 mg/L), chemicals and chemical products (maximum 0.09127 mg/L; median 0.00150 mg/L) and commercial laundries (maximum 0.04345 mg/L; median 0.00656 mg/L) (Lee et al. 2002).

Bisphenol A has also been detected in influent, effluent and sludge collected from municipal wastewater treatment plants across Canada. In general, effluent levels are lower than those found in influents from the same plant, indicating some removal from wastewater streams during processing. Lee and Peart (2000a) estimated a median reduction rate of 68% (range < 1-99%) based on concentration differences measured in 36 influent/effluent sample pairs collected from Canadian municipal wastewater treatment plants over the period 1999-2000. The values incorporate consideration of losses through degradation and from partitioning to sludge. The presence of high concentrations in some sludge samples (up to around 40 mg/kg dw) confirms that bisphenol A partitions into this medium, even while some portion remains within the water phase. This supports the prediction made by Cousins et al. (2002; see Environmental Fate section) that based solely on properties of moderate hydrophobicity and water solubility, bisphenol A will partition into organic phases such as sediments and soils while an appreciable fraction remains in the dissolved phase.

High levels of up to 4.6 mg/kg dw were measured in biosolid products produced by municipal wastewater treatment plants in seven different U.S. states (Kinney et al. 2006). The maximum concentration was found in a wet cake product intended for use in agriculture.

Bisphenol A has been measured in surface waters, sediments, and wastewater treatment products in many European countries. These data are well summarized in ECB (2003).

Limited information on measured levels in soil was found in the published literature, and this was more relevant to the assessment of human health (see Environmental Media section of Human Health Exposure Assessment).

Only limited North American data were found for levels in biota; however, some European and Japanese data are available (see Table 9b).

Table 9b. Concentrations of bisphenol A in biota

Organism	Location; year	Concentration (mg/kg)	Number of samples	Reference
Zooplankton	Massachusetts, United States; 2003–2004	$< 4.0\times10^{-6} – 0.013$[1]	12	Stuart et al. 2005
Clam	Massachusetts, United States; 2003–2004	0.0154, 0.0283[1]	4	Stuart et al. 2005
Fish	The Netherlands; 1999	$< 1.8\times10^{-4} – 0.0026$[2]	6	Vethaak et al. 2005
Fish: Freshwater Marine	Norway; 2003	 0.001 – 0.0141[2] < 0.0017 – 0.06197[2]	 18 6	Fjeld et al. 2004
Fish: Liver Muscle	The Netherlands; 1999	 0.002 – 0.075[1] 0.001 – 0.011[1]	 4[3] 6[4]	Belfroid et al. 2002
Mussel	The Netherlands; 1999	0.010[1]	1	Belfroid et al. 2002
Snail	Japan; 2002–2003	< 0.002–0.011[1]	12	Kang and Kondo 2006a

[1] Concentrations are reported on a dry weight basis
[2] Concentrations are reported on a wet weight basis
[3] Pooled samples muscle tissue from 50 fish
[4] Pooled samples liver tissue sample from10 fish

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine available scientific information and develop conclusions based on a weight-of-evidence approach and using a precautionary approach, as required under section 76.1 of CEPA 1999. Lines of evidence with respect to bisphenol A relate to persistence, bioaccumulation potential, toxicity, environmental occurrence, and trends in production and use.

The available data indicate that bisphenol A does not persist under aerobic conditions. However, the substance has been found not to degrade or to degrade only slowly under conditions of low or no oxygen. This stability, combined with significant anthropogenic production and use, could lead to the formation of areas of accumulation or “sinks” in the environment, with the potential to act as future sources of exposure for organisms.

The available data generally point to low bioaccumulation potential and a capacity for metabolism in various species. Most measured bioaccumulation and bioconcentration factors range upwards to approximately 147 L/kg; however, a lower trophic level study suggests a potential bioaccumulation factor of up to 650. These studies confirm that bisphenol A is bioavailable and can accumulate in tissues to some degree.

Bisphenol A has been detected in surface waters, sediment, and groundwater over wide areas in Canada and the United States. It has also been measured in municipal and industrial wastewaters, sludge and biosolids. The published literature contains no reference to North American air concentrations; however, releases reported to the NPRI (see Table 3) were exclusively to the air compartment and therefore at least some presence in air can be expected from steady emission to the atmosphere. In addition, some limited data are available for concentrations in North American soils (see Exposure Assessment for Human Health). While few data exist for levels in North American biota, concentrations of up to 0.075 mg/kg dw are documented in fish and invertebrates from Europe and Japan. The data indicate that bisphenol A is present in a wide range of environmental media.

Bisphenol A has shown high toxicity to aquatic organisms, with acute toxicity values falling below 13 mg/L and chronic values below 2 mg/L. The empirical and modelled data demonstrate that bisphenol A can be considered highly hazardous to the aquatic environment.

A quantitative evaluation of exposure and ecological effects was conducted for bisphenol A as part of the weight of evidence evaluation of its potential to cause harm. Predicted Environmental Concentrations (PECs) were determined based on an analysis of exposure pathways, and these exposure pathways were used to identify sensitive receptor organisms. For bisphenol A, PECs were derived using Canadian environmental monitoring data, or if monitoring data were not available, the PECs were based on simple calculation procedures that took into account some degree of local environmental conditions, but largely relied on generic environmental parameters. A Predicted No-Effects Concentration (PNEC) was determined for each exposure pathway, by dividing a Critical Toxicity Value (CTV) by an application factor. CTVs typically represented the lowest ecotoxicity value (e.g., an EC_{10}, LOEC, etc.) from an acceptable data set. A risk quotient analysis, integrating estimated potential exposures with potential adverse effects, was performed and the resulting risk quotient (PEC/PNEC) was used to estimate the potential for ecological risk.

An effluent concentration of 0.0173 mg/L was reported for a municipal wastewater treatment plant in the Toronto area (Lee et al. 2004). This value is selected for derivation of the Predicted Exposure Concentration (PEC) for pelagic organisms as it represents the highest reliable Canadian effluent concentration from a municipal treatment plant providing both primary and secondary wastewater treatment and is therefore deemed both realistic and conservative. Applying a dilution factor of 10 (to account for exposures in the immediate mixing zone) yields a PEC value of 0.00173 mg/L. Lahnsteiner et al. (2005) reported significantly reduced semen quality and delayed ovulation in the brown trout, *Salmo trutta f. fario*, at a Lowest Observed Effect Concentration (LOEC) concentration of 0.00175 mg/L and this value is selected as the CTV. To derive a Predicted No-Effects Concentration (PNEC), the CTV is divided by an application factor of 10 in order to account for variability in interspecies and intraspecies sensitivity and extrapolation from laboratory to field conditions. The resulting PNEC for the pelagic compartment is 0.000175 mg/L and the risk quotient (PEC/PNEC) is 0.00173/0.000175 =

9.9. The results indicate that bisphenol A concentrations in water have the potential to cause adverse effects on populations of pelagic organisms in Canada.

For the sediment compartment, Johnson et al. (2005) reported a LOEC of 1.0 mg/L for reduced adult survival in the freshwater amphipod, *Gammarus pulex*, and this value is selected as the CTV. While this testing used water only as the exposure medium, the results reflect adverse effects on an epibenthic organism and are therefore considered appropriate for use in estimating potential risk to sediment species. A higher assessment factor of 100 is selected due to the paucity of data for this environmental compartment, and the resulting PNEC is 0.01 mg/L.

While measured concentrations are available for sediment (e.g., Chu et al. 2005), the PEC value of 0.00173 mg/L derived for the pelagic compartment will also be used in the calculation of a risk quotient for the sediment compartment. This approach allows direct comparison with the PNEC value, which was determined in water-only testing, and is reasonable given that a significant exposure route for sediment species will be by means of interstitial water or water in the boundary layer directly above the sediment surface. The risk quotient for benthic species is then 0.00173 / 0.01 = 0.173. The risk quotient analysis results suggest there is currently a low risk of direct adverse effects to sediment organisms in Canada.

The limited soil concentration data were deemed more relevant for the assessment of exposure to humans (see Exposure Assessment, Human Health); however, several studies provide Canadian data on measured levels of bisphenol A in sewage sludge. Application of sewage sludge to agricultural lands represents a direct pathway for bisphenol A into soil. A maximum concentration of 36.7 mg/kg dw was reported for digested sewage sludge collected from a municipal wastewater treatment plant in southern Ontario (Lee and Peart 2000a,b), and this value is selected for derivation of the PEC. The PEC is estimated for tilled agricultural soil and pastureland based on an approach described in Bonnell Environmental Consulting (2001). This approach uses the same basic approach as outlined in the EU's Technical Guidance Document (European Communities 1994) but modified for Canadian conditions. The following assumptions were used: dry sludge is applied annually to soil at the rate of 0.5 kg/m^2; soil has a bulk density of 1700 kg/m^3; sludge is mixed in soil to a depth of 0.2 m (depth of tillage) in agricultural soil and 0.1 m in pastureland (Bonnell Environmental Consulting 2001 and European Communities 1994); no loss of the target substance due to erosion; no input from atmospheric deposition; and no background bisphenol A accumulations in the soil. It is also assumed that bisphenol A persists in the soil for a period of at least 56 days, the exposure period of the study used for the derivation of the PNEC value (see below).

The PEC is then: $PEC_{agricultural\ soil}$ = (36.7 x 0.5) / (0.2 x 1700)
= 0.054 mg/kg dw

$PEC_{pastureland}$ = (36.7 x 0.5) / (0.1 x 1700)
= 0.11 mg/kg dw

A 56-d LOEC of 100 mg/kg dw was reported for significant mortality in the earthworm, *Eisenia* sp. (Johnson et al. 2005), and this value is selected as the CTV. A lower toxicity value of 10 mg/L was reported for significantly reduced growth in several terrestrial plant species (Ferrara et al. 2006), however, this value is not suitable for comparison with the PEC as the plant study was reported in terms of water concentrations only. An application factor of 100 is applied to the CTV in order to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity. The application factor is larger than that used for pelagic organisms as fewer data are available for soil species and therefore the uncertainty in extrapolating between species is greater. The resulting PNEC value is 1.0 mg/kg dw. No information is available on the organic carbon (OC) content of the sludge samples or the soil used in the earthworm study, therefore both will be assumed to have a standard OC content of 2%. The risk quotient, PEC/PNEC, for soil organisms is therefore 0.054/1.0 = 0.054 for tilled agricultural soil and 0.11/1.0 = 0.11 for pastureland. The risk quotient analysis results suggest there is currently a low risk of direct adverse effects to soil species in the Canadian environment.

A PEC for mammalian wildlife was estimated based on a calculation of the total daily intake of the target substance by mink and otter. An energetics model based on the general exposure model for wildlife from the U.S. Environmental Protection Agency's (EPA) Exposure Factors Handbook (USEPA 1993) was used:

$$TDI = \left[FMR\left(\frac{C_i \cdot P_i}{GE_i \cdot AE_i} \right) \right] \cdot Pt$$

where,

TDI = total daily intake (mg/kg-bw per day)
FMR = normalized free metabolic rate of wildlife receptor of interest (236 kcal/kg-bw per day for mink and 183 kcal/kg-bw per day for river otter)
C_i = concentration of contaminant in the ith prey species (mg/kg-bw) (see below)
P_i = proportion of the ith prey species in the diet (unitless) (default = 35% for mink; 100% for otter)
GE_i = gross energy of the ith prey species (default = 1240 kcal/kg-bw prey)
AE_i = assimilation efficiency of the ith prey species by the wildlife receptor (default = 0.91)
P_t = proportion of the time the receptor spends in the contaminated area (50% for mink and 50% for otter)

The model incorporated the metabolic rate of the wildlife receptors of interest (mink and otter), the proportion of food uptake by the receptors and the amount of time the animals spend in the contaminated area, which is based on the typical habitat range of the wildlife receptors.

As there are no Canadian data for bisphenol A concentrations in fish, concentrations of the target substance in fish (Ci) were estimated based on the highest PEC_{water} and a BAF. The BAF was estimated using the GOBAS BAF three trophic level model (Arnot and Gobas 2003; see Bioaccumulation section). The BAF represents a benthic/pelagic food chain and estimates the accumulation from all sources in a mid-trophic-level fish that would typically be eaten by a mammalian piscivore.

$C_i = PEC_{water} \cdot BAF$

where:

C_i = concentration in a prey fish (mg/kg-bw)
PEC_{water} = PEC of 0.00173 mg/L calculated above for the pelagic compartment
BAF = bioaccumulation factor of 148 L/kg estimated for mid-trophic level fish based Arnot and Gobas (2003)
$C_i = 0.00173 \cdot 148 = 0.256$ mg/kg-bw

The model estimated PECs of 0.009 mg/kg-bw per day and 0.021 mg/kg-bw per day for mink and otter, respectively.

As identified in Characterization of Risk to Human Health, Health Effects Section, the dataset of neurodevelopmental and behavioural studies, though limited when subject to a weight of evidence analysis, is suggestive of potential effects at doses in the range of 0.01 to 0.1 mg/kg-bw per day and higher (study details are provided in Appendix D). The range of 0.01 – 0.1 mg/kg-bw per day is selected as an estimate for CTVs in mammalian wildlife. The CTVs for predictive sentinel wildlife species (in this case, mink and otter) can then be calculated from the range of CTVs of the mammalian test species, using the formula (Sample et al. 1996):

$$CTV_{wildlife} = CTV_{ts} \cdot (bw_{ts}/bw_w)^{1/4}$$

where:

$CTV_{wildlife}$ = critical toxicity value for wildlife
CTV_{ts} = critical toxicity value for test species
bw_{ts} = mean body weight of test species (0.35 kg)
bw_w = mean body weight of predictive sentinel species (0.807 kg for mink, 6.01 kg for otter; Canadian Wildlife Service, Ontario Region, pers. comm., 2004, unreferenced).

Therefore, the $CTV_{wildlife}$ ranges are then 11 to 112 mg/kg-bw per day for mink and 42 to 420 mg/kg-bw per day for otter. Applying an application factor of 10 to account for extrapolation from laboratory to field conditions yields PNEC values of 0.0008 to 0.008 mg/kg-bw per day and 0.0005 to 0.005 mg/kg-bw per day for mink and otter, respectively. The resulting risk quotients (PEC / PNEC) are 1.25 to 12.50 for mink and 4.2 to 42.0 for otter. It is concluded that bisphenol concentrations in biota have the potential to cause adverse effects in populations of wildlife in Canada.

A similar methodology was used to derive a risk quotient relevant to avian wildlife species. The total daily intake (TDI) was calculated for a sentinel avian wildlife species, the lesser scaup (*Aythya affinis*). The lesser scaup was selected as a suitable avian sentinel species as it is abundant through much of North America and consumes clams as part of its normal diet of aquatic invertebrates and vegetation (USEPA 1993). As clams are present in the diet of lesser scaup, the tissue concentration of 0.0283 mg/kg dw reported in clam collected off the Massachusetts coast (Stuart et al. 2005) is selected for use in the development of a PEC for avian wildlife. This concentration is converted to 0.00535 mg/kg wet weight (ww) using a dry weight to wet weight ratio of 5.29 for clams (Vinogradov 1953). The total daily intake (TDI) for lesser scaup is then:

$$TDI = \left[FMR\left(\frac{C_i \cdot P_i}{GE_i \cdot AE_i} \right) \right] \cdot Pt$$

where,

TDI = total daily intake (mg/kg-bw per day)
FMR = normalized free metabolic rate of wildlife receptor of interest (216 kcal/kg-bw per day for adult female scaup; USEPA 1993)
C_i = concentration of contaminant in the ith prey species (mg/kg-bw) (0.00535 mg/kg ww)
P_i = proportion of the ith prey species in the diet (unitless) (19.2% for adults; Dirschl 1969)
GE_i = gross energy of the ith prey species (default = 800 kcal/kg-bw prey)
AE_i = assimilation efficiency of the ith prey species by the wildlife receptor (default = 0.77)
P_t = proportion of the time the receptor spends in the contaminated area (assume 50%)

The model estimated a PEC value of 0.00018 mg/kg-bw per day for adult lesser scaup.

A LOAEL of 100 mg/kg-bw per day, based on permanently altered development in male White Leghorn chicks, *Gallus domesticus*, was reported by Furuya *et al.* (2006), and this value will be used as the CTV for the derivation of a PNEC for avian wildlife. The CTV for lesser scaup can then be calculated using the same formula as for mammalian wildlife (Sample et al. 1996). Sample et al. (1996) recommend using a scaling factor of 1 for interspecies extrapolation among birds; however, as the reported mean body weight for the lesser scaup considers the adult bird, while the toxicity value for Leghorn was derived using juveniles, an extrapolation which considers body weight was deemed appropriate in order to incorporate consideration of weight differences relating to life stage.

The CTV for avian wildlife is then:

$$CTV_{wildlife} = CTV_{ts} \cdot (bw_{ts}/bw_{w})$$

where:

$CTV_{wildlife}$ = critical toxicity value for wildlife
CTV_{ts} = critical toxicity value for test species (100 mg/kg-bw per day)
bw_{ts} = mean body weight of test species (1.3 kg; estimated from Leeson and Caston 1991)
bw_{w} = mean body weight of predictive sentinel species (0.77 kg; Nelson and Martin 1953)

The CTV for avian wildlife is therefore 169 mg/kg-bw per day. Applying an application factor of 100 to account for extrapolation from laboratory to field conditions and interspecies and intraspecies variations in sensitivity yields a PNEC value of 1.69 mg/kg-bw per day and the risk quotient is then 0.00018/1.69 = 0.0001. The results suggest there is currently a low risk of direct adverse effects to avian wildlife species in Canada.

Considered together, the various lines of evidence indicate that the potential impacts of bisphenol A in the Canadian environment are of sufficient magnitude to warrant use of a precautionary approach in response to uncertainties in the evaluation of risk.

There is evidence that bisphenol A is capable of altering hormonal, development or reproductive function: following prolonged exposure at levels below those usually seen to elicit effects in standard toxicity tests (i.e., tests based on recognized methods which evaluate endpoints such as survival, reproduction and growth); following brief low-level exposure, particularly when this occurs at sensitive developmental stages, with effects apparent later in the life cycle; in filial generations following parental exposure; and using more than one mode of action. Studies conducted using fish, aquatic invertebrates and amphibians demonstrate impacts in the range of 0.001 to 1 mg/L, levels that have been measured in Canadian and U.S. wastewaters, receiving waters and sediments. For this reason, potential exists for adverse effects in populations of aquatic organisms, particularly those residing in close proximity to treatment plant outfalls or other point sources. While the ability of bisphenol A to cause adverse low-dose effects appears clear, there is uncertainty respecting the extent to which organisms in the Canadian environment are exposed to levels sufficient to elicit the types of impacts observed in laboratory studies. Further information is needed to more clearly delineate the relationship between exposure levels measured in the Canadian environment and the potential for adverse effects in organisms.

Bisphenol A is one of the highest volume chemicals produced worldwide and global demand for the substance is predicted to continue increasing at a rate of 6 % to 10% annually. The total quantity of bisphenol A reported as imported or in use in Canada during the calendar year 2006 was approximately 0.5 million kg. Actual quantities available for release to the Canadian environment could be much higher, however, as these values likely do not fully capture amounts entering Canada in finished and semi-

finished products. This is particularly so, given the wide application of the substance and number of bisphenol A derivative products.

In summary, the lines of evidence relating to persistence, bioaccumulation, toxicity, environmental occurrence and trends in production and use raise concerns regarding the presence of bisphenol A in the environment. The substance is predicted to degrade fairly rapidly under aerobic conditions (half-life in the order of days), suggesting that bisphenol A released into receiving waters should remain only a short time in this medium. However, it has been widely detected in surface waters. Possible explanations for this may be that because inputs to the environment are sufficiently large and continuous, measurable concentrations are always present and/or that the substance is not degrading as rapidly as laboratory testing would indicate. Measurable levels in sewage sludge and effluent are also suggestive of some level of stability of this substance. Further, bisphenol A is present in media to which there is no direct release, such as sediment and groundwater. This implies that the substance remains sufficiently long enough in the environment to move from its point of release into other environmental media. There is evidence that bisphenol A is stable in some environmental compartments, most notably under conditions of low oxygen, such as those found beneath the surface layers of sediment and soil and in marshes and bogs. Levels in the environment are expected to increase given that bisphenol A is a high production chemical and global demand for the substance is increasing. Bisphenol A has been detected in aquatic species, confirming that the substance can be taken up by organisms and stored in tissues. The potential for food web impacts is still undetermined, although bioaccumulation factors of 650 have been measured in lower trophic level species, suggesting that possible exposure of predator species could occur through consumption of prey. Bisphenol A is acutely toxic to aquatic organisms and adversely affects reproduction in earthworms, growth in terrestrial plants, and development in birds. Results from an analysis of risk quotients, which compare the potential for exposure with possible effects in organisms, indicate that bisphenol A concentrations in the Canadian environment have the potential to cause adverse effects in populations of pelagic organisms and mammalian wildlife but are unlikely to cause adverse effects in benthic and soil organisms and bird species in Canada. In addition to acute toxicity, bisphenol A can impact the normal development of individual organisms and influence the development of their offspring. In laboratory testing, these effects have occurred at concentrations below those shown to cause acute effects, and these effect concentrations have been measured in the Canadian environment. Considered together, the various lines of evidence indicate that the potential impacts of bisphenol A in the Canadian environment are of sufficient magnitude to warrant use of a precautionary approach in response to uncertainties in the evaluation of risk.

Uncertainties in Evaluation of Ecological Risk

There is uncertainty regarding sources of release and release quantities of bisphenol A into the Canadian environment. An industry survey was used to collect information on Canadian manufacture, import and use of bisphenol A for the calendar year 2006. However, it is not clear whether potential releases from partially-finished and finished

goods being imported into Canada and from products currently in use in Canada have been adequately captured. This information is needed to more accurately estimate potential exposure concentrations for organisms in the Canadian environment. The presence of a recent database of measured environmental concentrations for some locations in Canada and the United States assisted with characterizing exposure potential in this assessment. However, quantitative exposure estimates were possible only for pelagic organisms. Increasing the size of this database by including a wider range of Canadian locations, more information on possible time trends, and more data on sediment, soil and surface water concentrations, as well as possible presence in leachates and groundwater, would increase the level of certainty in exposure estimation and allow estimation of potential exposure for benthic and terrestrial species.

There is uncertainty about the measured presence and accumulation potential of bisphenol A in biota. The available information indicates that bisphenol A does not meet bioaccumulation criteria as specified in the *Persistence and Bioaccumulation Regulations* of CEPA 1999. However, bioaccumulation factors of up to 650 have been determined for lower trophic level aquatic species, and this suggests there may be circumstances or conditions under which bisphenol A may accumulate within organisms. Lower trophic aquatic organisms form an important bridge between primary producers (i.e., phytoplankton) and higher trophic species such as fish. Therefore, while high tissue levels could indicate the presence of a site-specific condition, such as very high local concentrations, it is also possible that bioaccumulation is occurring with the subsequent potential for food chain transfer and secondary poisoning of predator species. An increased database of measured concentrations in Canadian biota, including trophic magnification studies, would provide greater clarity on the potential for accumulation within individual organisms and along food webs.

There is uncertainty regarding the potential for adverse effects in Canadian biota resulting from single-dose or prolonged (i.e., lifetime and multigenerational) low-level exposure to bisphenol A, particularly during sensitive life cycle stages. This uncertainty reflects a need for greater clarification of minimum effects levels in pelagic, sediment, soil and wildlife species, and of exposure concentrations in the Canadian environment. Based on the weight of available data, the assessment indicates that there is a potential for adverse impacts in aquatic organisms, particularly those residing in the vicinity of treatment plant outfalls or other point sources. However, information is needed in order to more clearly delineate the relationship between exposure levels in the Canadian environment and possible effects in organisms.

Potential to Cause Harm to Human Health

Exposure Assessment

Dietary Intake

With respect to dietary intake, two sources of potential exposure are (i) migration into food and beverages from packaging materials that directly contact food, specifically food and beverage containers with internal epoxy resin coatings and (ii) migration from polycarbonate repeat use containers such as baby bottles and drinking bottles.

(i) Migration from Food Packaging

Epoxy resins are used as an interior protective lining for food and beverage cans and for metal closures for some jars and bottles. As a result of these food contact uses, very small quantities of the monomer bisphenol A can migrate into the food and beverage contents of the containers.

Exposure to bisphenol A from food packaging uses has been characterized based on bisphenol A concentrations reported in a survey of canned foods on the U.S. market in 2007 (EWG 2007). EWG (2007) tested foods and beverages from 97 cans purchased in grocery stores in three states. Twenty-eight different types of foods were analyzed for bisphenol A, including canned fruits, vegetables, pasta, beans, infant formula, meal replacement and canned milk. Results are presented in Table 10. Reported concentrations were considered to be representative of additional data available to Health Canada and of data reported in the literature (EFSA 2006).

Table 10. Average bisphenol A concentrations for various canned food types

Canned foods	Number of cans tested	Average bisphenol A (ppb)[1]	Bisphenol A concentration range (ppb)
All foods	97	7.9	Nd[2]-385
Pasta	6	63.5	Nd-247
Soup	19	57.6	Nd-385
Beans (baked)	6	9.7	Nd-38
Tuna	6	9.6	Nd-108
Vegetable	17	7.8	Nd-330
Meal replacement	5	4.2	Nd-66
Evaporated milk	3	3.5	Nd-9
Infant formula	6	2.4	Nd-17
Fruit	17	2.3	Nd-27
Soft drink	12	1.7	Nd-8

[1] Average is geometric mean
[2] Not detected at the limit of detection 1 ppb

Potential daily intakes from the use of epoxy resins as interior protective lining for food and beverage cans were estimated using average and maximum concentrations of bisphenol A, and daily intake values for the food commodities (Health Canada, Food Directorate, Health Products and Food Branch [HPFB], pers. comm., 2007 March 14, unreferenced, and are presented in Table 11. Leaching from metal closures was considered to contribute minimally to these exposures.

Table 11. Potential daily intake of bisphenol A (µg/kg-bw per day) from use of epoxy resins as interior protective lining for food and beverage cans

Canned food	1-4 year olds[3]		5-11 year olds[3]		12-19 year olds[3]		Adults[3]	
	Avg[1]	Max[2]	Avg	Max	Avg	Max	Avg	Max
Soft drinks	0.00189	0.00889	0.00216	0.0102	0.00253	0.0119	0.00181	0.00854
Evaporated milk	0.00248	0.00637	0.00106	0.00273	0.00056	0.00143	0.00057	0.00145
Soups	0.187	1.25	0.104	0.694	0.0596	0.398	0.0587	0.392
Tuna	$2.7x10^{-5}$	$3.0x10^{-4}$	$4.2x10^{-4}$	$4.7x10^{-3}$	$2.7x10^{-4}$	$3.0x10^{-3}$	$2.0x10^{-4}$	$2.3x10^{-3}$
Pastas	0.0494	0.330	0.0304	0.203	0.0189	0.126	0.00804	0.0537
Vegetables	0.00847	0.358	0.00814	0.345	0.00418	0.177	0.00309	0.131
Fruits	0.00260	0.0306	0.00132	0.0156	0.00034	0.00402	0.00056	0.00657
TOTAL	**0.252**	**1.98**	**0.147**	**1.28**	**0.0864**	**0.731**	**0.0730**	**0.596**

[1]Based on the average concentration of bisphenol A found in foods as reported in Table 10.
[2]Based on the maximum concentration of bisphenol A found in foods as reported in Table 10.
[3]Based on body weight of 14.4 kg for 1-4 year olds; 26.4 kg for 5-11 year olds; 53.8 kg for 12-19 year olds; and 60 kg for adults (Nutrition Canada 1980)

Analyses of bisphenol A in other food items are limited. Miyamoto and Kotake (2006) identified bisphenol A in noncanned foods, but attributed this to additives in ink in paper used in the food packaging. Table 9b presents concentrations of bisphenol A found in aquatic biota. Seafood purchased in a Singapore market was analysed by Basheer et al. (2004) and mean concentrations (n=5 for each product) were reported as 13.3 ng/g in prawns, 213.1 ng/g in crabs, 56.5 ng/g in blood cockle, 27.4 ng/g in white clam, 118.9 ng/g in squid, and 65.6 ng/g in carangid fish (limit of detection 1.357 ng/g). Vivacqua et al (2003) detected bisphenol A in the range of 0.25 to 1.0 ③g/g in fresh market vegetables in Italy (8/14 detects).

As there are no measured concentrations of bisphenol A in fish caught in Canada or North America, or of fish available on the Canadian market, the maximum concentration reported in fish from European countries (see Table 9b) was used to derive estimates of intake from fish consumption. Using a maximum concentration of 61.97 µg/kg as measured by Fjeld et al. (2004) and based on rates of consumption of fish for Canadians (Health Canada 1998), the estimated intake of bisphenol A from this source would range

from 0.11 µg/kg-bw per day (for 12-19 year olds) to 0.24 µg/kg-bw per day (for 1-4 year olds). Studies have also indicated that concentrations of bisphenol A tend to be higher in fish liver and other organs (Belfroid et al. 2002) so consumption of these organs may slightly increase exposure. Confidence in these estimates is low as they are based on a number of assumptions; however it is likely that they are an overestimate of actual exposure from this source.

As infant formula (ready-to-use, concentrate, powder) available on the Canadian market is packaged in cans, a separate estimate of the dietary intake of bisphenol A by infants was conducted. Due to the nature of the extracting medium, migration into liquid is considered to be greater than migration into powder and analysis therefore focussed on liquid formulations. Preliminary research conducted at Health Canada supports the conclusion that migration of BPA is significant only for liquid infant formulas (Health Canada, Food Directorate, HPFB, pers. comm., 2008 Sept 04, unreferenced). In 2007, Health Canada analyzed canned liquid infant formula to characterize residual levels of bisphenol A. Samples packaged in cans lined with epoxy-based coatings were collected in October, 2007 in Ottawa, Canada from 21 cans representing eight brands of ready-to-drink or concentrated liquid infant formulas. Bisphenol A was detected and quantified in all samples, with concentrations ranging from 2.27 to 10.2 ppb (Cao et al. 2008). These data are consistent with other data reported in the literature. For instance, EWG (2007) reported average bisphenol A concentrations of 2.4 ppb (range from limit of detection of 1 ppb to 17 ppb) in 6 cans of infant formula available on the US market. The Canadian data were considered to be the most relevant for use in the assessment. As a worst-case scenario it was assumed that liquid infant formula is the main source of food for infants in the first 18 months of their life, and that their formula intake is equal to their daily total fluid intake (i.e., formula, milk, water, juice). A dilution factor of 0.5 was applied to the concentrated liquid formulas as they would be diluted with water prior to the feeding (1 part water to 1 part concentrated formula). No dilution factor was applied to the ready-to-use infant formulas. Assumptions regarding formula intakes are based on recommendations of the Institute National de Santé Publique du Québec (INSPQ 2001). Potential daily intake of bisphenol A from liquid infant formula packaged in containers with epoxy resin interior protective lining is provided in Table 12.

Table 12. Potential daily intake of bisphenol A (µg/kg-bw per day) from liquid infant formula packaged in containers with epoxy resin interior protective lining.

Age of infants	Intake based on average bisphenol A concentration[1]		Intake based on maximum bisphenol A concentration[1]	
	Average formula intake	Maximum formula intake	Average formula intake	Maximum formula intake
0 to 1 month[2]	0.45	0.75	0.81	1.35
2 to 3 months[3]	0.50	0.69	0.96	1.31
4 to 7 months[4]	0.38	0.52	0.75	1.02
8 to 12 months[5]	0.21	0.28	0.42	0.55
12 to 18 months[6]	0.23	0.27	0.38	0.46

[1]Based on the average and maximum concentration of bisphenol A measured in twenty-one cans representing 8 brands of ready-to-drink or concentrated liquid infant formula purchased in Ottawa, Ontario (see paragraph above)) with selective grouping according to the age of use intended by the manufacturer.
[2]Based on average female infant weight of 3.9 kg (NCHS 2000) and an average formula intake of 644 g/day and maximum formula intake of 1080 g/day (INSPQ 2001).The average and maximum concentrations of bisphenol A found in products intended for use by this age group were 2.72 and 4.89 ppb respectively after accounting for dilution of concentrated formulas.
[3]Based on average female infant weight of 5.5 kg (NCHS 2000) and an average formula intake of 1080 g/day and maximum formula intake of 1470 g/day (INSPQ 2001).The average and maximum concentrations of bisphenol A found in products intended for use by this age group were 2.72 and 4.89 ppb respectively after accounting for dilution of concentrated formulas.
[4]Based on average female infant weight of 7.2 kg (NCHS 2000) and an average formula intake of 1050 g/day and maximum formula intake of 1470 g/day (INSPQ 2001).). The average and maximum concentrations of bisphenol A found in products designed for this age group were 2.70 and 5.12 ppb respectively after accounting for dilution of concentrated formulas.
[5]Based on average female infant weight of 9.0 kg (NCHS 2000) and an average formula intake of 735 g/day and maximum formula intake of 960 g/day (INSPQ 2001).The average and maximum concentrations of bisphenol A found in products intended for use by this age group were 2.70 and 5.12 ppb respectively after accounting for dilution of concentrated formulas.
[6]Based on average female infant weight of 10.6 kg (NCHS 2000) and an average formula intake of 750 g/day and maximum formula intake of 900 g/day (INSPQ 2001).). The average and maximum concentrations of bisphenol A found in products intended for use by this age group were 3.10 and 5.44 ppb respectively after accounting for dilution of concentrated formulas.

Infants can also be exposed to bisphenol A through the consumption of human breastmilk, however no Canadian data on concentrations of bisphenol A in breastmilk were identified. In a survey of 20 U.S. lactating women with no known occupational exposure, Ye et al. (2006) identified concentrations of total bisphenol A (free + conjugate) ranging from the limit of detection (1 ng/ml) to 7.3 ng/mL (7.1 ppb – assuming breastmilk has a density of 1.03 g/mL (Health Canada 1998)), with a mean concentration of 1.9 ng/mL (1.8 ppb). Sun et al. (2004) reported a mean bisphenol concentration in breastmilk of 0.61 ng/ml (range 0.28 to 0.97ng/ml) in a survey of 23 Japanese women (limit of detection 0.11 ng/ml). In another Japanese study, Otaka et al. (2003) quantified levels ranging from the limit of detection (0.09 ng/g) to 0.70 ng/g (ppb) of bisphenol A in the breastmilk of three women. Based on the U.S. data (Ye et el. 2006), potential daily intakes for infants exposed to bisphenol A through breastmilk are provided in Table 13.

Table 13. Potential daily intake of bisphenol A (µg/kg-bw per day) from consumption of human breastmilk containing either average or maximum bisphenol A concentrations.

Infant age group	Average Concentration of bisphenol A (1.8 ppb)[1]	Maximum concentration of bisphenol A (7.1 ppb)[1]
0 to 1 month[2]	0.28	1.09
2 to 3 months[3]	0.21	0.84
4 to 7 months[4,5]	0.19	0.73

[1]Average and maximum concentrations of bisphenol A as measured in breastmilk from 20 lactating women in the United States (Ye et al. 2006).

[2]Based on average female infant weight of 3.9 kg (NCHS 2000) and an estimated breast milk intake of 596 g/day (Arcus-Arth et al. 2005).
[3]Based on average infant weight of 5.5 kg (NCHS 2000) and an estimated breast milk intake of 649 g/day (Arcus-Arth et al. 2005).
[4]Based on average infant weight of 7.2 kg (NCHS 2000) and an estimated breast milk intake of 744 g/day (Arcus-Arth et al. 2005).
[5]Health Canada recommends exclusive breastfeeding of infants from 0-6 months, at which time they would be introduced to solid foods. Therefore intake from this source was not estimated past seven months of age.

ii) Repeat-use Containers

Migration of small amounts of bisphenol A from polycarbonate repeat-use containers such as baby bottles, drinking bottles, pitchers and carboys can contribute to oral exposure. Numerous studies have reported on migration of bisphenol A from polycarbonate bottles into water or milk simulant under different conditions (Brede et al. 2003; Biedermann-Brem et al. 2007; Biles et al. 1997; Cao and Coriveau (2008); Ehlert et al. 2008; Kawamura et al. 1998; Le et al. 2008; Maragou et al. 2007; Mountfort et al. 1997; Environmental Defence, 2008; Sun et al. 2000; Takao et al. 1999; Wong et al. 2005, D'Antuono et al. 2001, Miyamoto and Kotake 2006) and data have been summarized by others (EFSA 2006; ECB 2003; NTP 2007). These studies were conducted under diverse conditions using food simulants such as water, 10% ethanol, 50% ethanol and 3% acetic acid. In considering these results, it is important to differentiate between study designs intended to simulate realistic exposure scenarios versus those designed to characterize maximum concentration that may migrate from the product under extreme conditions or over the life of a container.

Five studies of bottles obtained from the Canadian market are available. In 2000, Health Canada conducted a series of limited migration studies (Page et al. 2006). No bisphenol A was detected in milk simulant (50% ethanol/water) following storage in polycarbonate baby bottles for up to 7 days at 4 or 22^{o}C (detection limit of <0.1 μg/kg). In additional trials, bottles were subjected to the following treatments: (i) storage for 7 days at 4^{o}C then storage for an additional 7 days at 22^{o}C, followed by 6 days at 70^{o}C; (ii) storage for 7 days at 22^{o}C then storage for 7 days at 4^{o}C, followed by 6 days at 70^{o}C C; (iii) storage for 6 days at 70^{o}C. In these 3 trials, aliquots of simulant were collected after 1, 2, 3 and 6 days at 70^{o}C and analyzed for bisphenol A. For all three trials, bisphenol A concentrations in the simulant on day 1 were 0.4 to 1 ppb, and concentrations increased on subsequent days of incubation at 70^{o}C. Sustained incubation at 70^{o}C is not considered a meaningful study design for characterization of migration under realistic use conditions.

A second study also measured the migration of bisphenol A from polycarbonate baby and drinking bottles into water. Cao and Corriveau (2008) tested five polycarbonate bottles, three baby bottles and two refillable drinking bottles, bought in Ottawa, Canada in 2007. The bottles were filled to capacity with boiling water and then left at room temperature for 24 hours. Bisphenol A concentrations in the water ranged from 1.7 to 4.1 μg/L (ppb).

Preliminary raw data are available from a study conducted by the Health Canada in 2008 (Health Canada, Safe Environments Programme, Healthy Environments and Consumer

Safety Branch (HECSB), pers. comm., 2008 March 6, unreferenced). Migration was characterized by filling 14 brands of baby bottles available in Canada with water to simulate migration to aqueous and acidic foods, and a 50% ethanol/water solution to simulate migration to fatty foods such as infant formula. The bottles were incubated for 8, 24 or 240 hours at 40°C to simulate use at room temperature, as per recommendations from the USFDA (2007). The 240-hour scenario (10 days) was included to estimate migration from both repetitive use and worst-case scenarios. Average migration for these tests ranged from 0.095 µg/L (ppb) in water incubated for 8 hrs, to 2.05 µg/L in the 50:50 ethanol/water blend incubated for 240 hours. The scenario considered to represent the most realistic use consisted of filling bottles with the 50:50 ethanol/water blend and incubating them for 8 hours. This scenario resulted in average concentrations of 0.15 µg/L.

In another study of polycarbonate baby bottles on the Canadian market (Environmental Defence 2008), new baby bottles (n=9) were filled with water, sealed and allowed to sit for 24 hours; initially at room temperature and then in a subsequent trial at 80^{o}C. The study investigators specify that the 80^{o}C treatment was considered to simulate repeat washing of bottles (i.e., approximately 60-100 washes). As such, the 80^{o}C trials are not considered to represent a realistic migration from a single use. Results from the room temperature trials showed that bisphenol A levels ranged from below the limit of detection, i.e. 0.05 to 0.063 ng/mL (ppb). Results from the 80^{o}C trial ranged from 4.294 to 8.323 ppb.

Most recently, the migration of bisphenol A from various types of new and used baby bottles into 3.25% milk and apple juice was analyzed under normal use conditions (INSPQ pers. comm., 2008 September 8, unreferenced). Thirty bottles were washed in a dishwasher, filled with milk and refrigerated at 4°C for 16 hours. Bottles were then heated in a microwave oven for 30 seconds to 37^{o}C before the milk was tested for bisphenol A. The same bottles were then rewashed and placed under similar experimental conditions to test migration into apple juice; the only difference in protocol was that the juice was brought to room temperature. The concentration range of bisphenol A measured in milk migrating from new, hard polycarbonate bottles ranged from 0.44 to 0.53 µg/L (n=10) and was reported to be 0.29 µg/L in used bottles (n=5). The migration concentrations measured in apple juice ranged from 0.29 to 0.46 µg/L in new bottles (n=10) and was 0.43 µg/L when measured in the used bottles (n=5). For both liquids, bisphenol A concentrations from the disposable plastic bags and glass bottles were below the detection limit (0.2 µg/L).

Maragou et al. (2007) assessed migration potential from 31 new polycarbonate baby bottles (from 6 different brands) available on the Greek market under a variety of conditions, including those which study investigators considered to be representative of actual use. To determine the impact of the repeated cleaning of bottles, either with the dishwasher or with brushing, the bottles were cleaned using either method, rinsed and sterilized prior to being filled with water and incubated at 70^{o}C for 2 hours. This series of treatments did not lead to detectable bisphenol A migration with a reported detection limit of 2.4 ppb. Migration was only detected when bottles were filled with boiling water

(100°C). Specifically, 5 repeat cycles of cleaning the bottles by brushing with detergent, sterilizing in boiling water for 10 minutes, then filling with boiling water (100°C) and leaving at ambient temperature for 45 minutes resulted in an average bisphenol A concentration of 10 ppb (ranged from limit of detection, 2.4ppb, to 14.3 ppb).

Additionally, EFSA (2006) summarizes two studies conducted on commercially available baby bottles, conducted under experimental conditions designed to represent realistic conditions of use, which measured concentrations of up to approximately 50 μg/L (ppb) of bisphenol A in the food simulant contents. In a study of bottles filled with boiling water and kept overnight at room temperature Hanai (1997) measured bisphenol A migration varying from 3 to 55 μg/L (detection limit of 2 μg/L). Earls et al. (2000) detected bisphenol A in 5 out of 12 bottles filled with either boiling water or 3% acetic acid, placed in a refrigerator for 24 hours, and then heated to approximately 40°C by immersion in boiling water for approximately 2 minutes. Bisphenol A concentrations in detected samples ranged from 20 to 50 μg/L (detection limit of 10 μg/L).

However, the Norwegian Food Safety Authority (Biedermann-Brem et al. 2007) investigated the effect of migration of bisphenol A from polycarbonate under extreme washing conditions such as washing using very strong alkali detergents (80°C for 1 hour, followed by drying of unrinsed bottles at 90°C for 30 minutes). They concluded that even under aggressive conditions, concentrations of bisphenol A in contents are unlikely to exceed 10 μg/L (ppb).

A recent study investigated migration behaviour of bisphenol A into water during microwaving of polycarbonate baby bottles obtained from the European market (Ehlert et al. 2008). Polycarbonate bottles filled with water were heated to 100°C during 3 microwave cycles. Migration of bisphenol A into water was shown to be in the range of <0.1 to 0.7 μg/L (ppb).

Miyamoto and Kotake (2006) reported bisphenol A concentrations of 0.05 to 3.9 ppb (limit of detection 0.05 ppb) in new unwashed polycarbonate bottles, which were exposed to water at 95°C for 30 minutes.

Polycarbonate carboys can be used to store drinking water. Biles et al. (1997) measured bisphenol A in a 5-gallon carboy by filtering a 1 L aliquot of water through an SPE cartridge (flow rate: 3 ml/min) followed by a DDH_20 wash (2x20ml), with analysis by GC-MSD. The range of bisphenol A was 0.1 to 4.7 ng/L (0.0001 to 0.0047 ppb) (detection limit < 0.05 ng/L).

Le et al. (2008) measured bisphenol A migration from polycarbonate drinking bottles used for consumption of water and other beverages. New and used polycarbonate bottles were filled with water and left for up to 7 days at room temperature (22°C). Samples were collected on days 1, 3, 5 and 7. On day 1, the calculated mean concentration of bisphenol A detected in the water was 0.24 ng/mL (ppb). Mean concentrations across all sampling days, for both new and used polycarbonate containers, ranged from 0.08 to1.33 ng/mL (ppb). In general, the concentration of bisphenol A released from polycarbonate bottles

into water at room temperature increased with time, but no significant difference was observed between the concentrations resulting from the use of new versus used bottles. Repeating the study using boiling water (100°C) and leaving the samples for 24 hr, during which time the water samples slowly cooled, increased the amount of bisphenol A migration from 15-fold to 55-fold.

Directions for preparation of concentrate and powder formula typically specify that water be boiled for sterilization purposes and then be cooled before adding to the bottle. For infants 0-18 months it was considered appropriate to estimate bisphenol A intake from the use of polycarbonate baby bottles for both the recommended room temperature use and plausible high temperature use (boiling water) scenarios. Results calculated from Le et al (2008) indicate that filling polycarbonate bottles with room temperature water, could result in migration of approximately 0.24 ppb of bisphenol A into the contents of the bottle. This is supported by preliminary data from a migration study conducted by Health Canada indicating an average concentration of 0.15 ppb bisphenol A (Health Canada, Safe Environments Programme, HECSB, pers. comm., 2008 March 6, unreferenced). To estimate migration of bisphenol A from addition of boiling water [100°C] directly to the baby bottle, the results of Maragou *et al.* (2007), in which boiling water was added to polycarbonate bottles and cooled for 45 minutes, support a concentration of 10 ppb bisphenol A. As a worst-case scenario it was assumed that liquid infant formula is the main source of food for infants in the first 18 months of life, and so formula intake is considered to be equal to their daily total fluid intake (i.e., formula, milk, water, juice). Exposure estimates are provided in Table 14.

Table 14. Contribution of use of polycarbonate baby bottles to potential daily intake (PDI) of bisphenol A (µg/kg-bw per day) for infants.

	PDI of bisphenol A (µg/kg-bw per day)			
Infant age group	**Concentration of bisphenol A resulting from filling bottles with room temperature water (0.24 ppb)[1]**		**Concentration of bisphenol A resulting from filling bottles with boiling water (10.0 ppb)[2]**	
	Average formula intake	**Maximum formula intake**	**Average formula intake**	**Maximum formula intake**
0 to 1 month[3]	0.040	0.066	1.65	2.77
2 to 3 months[4]	0.047	0.064	1.95	2.67
4 to 7 months[5]	0.035	0.049	1.46	2.00
8 to 12 months[6]	0.020	0.026	0.82	1.07
12 to 18 months[7]	0.017	0.020	0.71	0.85

[1]Based on an average concentration of bisphenol A detected in new and used polycarbonate bottles that were filled with room temperature liquid and left for 24 hours (Le et al. 2008). This value is also supported by an average concentration of 0.15 ppb reported from filling bottles with liquid at room temperature and

leaving for 8 hours. (Health Canada, Safe Environments Programme, HECSB, pers. comm., 2008 March 06, unreferenced).
[2]Based on an average concentration of bisphenol A resulting from filling polycarbonate baby bottles with boiling water and leaving at room temperature for 45 minutes (Maragou et al. 2007).
[3]Based on average female infant weight of 3.9 kg (NCHS 2000) and an average formula intake of 644 g/day and maximum formula intake of 1080 g/day (INSPQ 2001).
[4]Based on average female infant weight of 5.5 kg (NCHS 2000) and an average formula intake of 1080 g/day and maximum formula intake of 1470 g/day (INSPQ 2001).
[5]Based on average female infant weight of 7.2 kg (NCHS 2000) and an average formula intake of 1050 g/day and maximum formula intake of 1470 g/day (INSPQ 2001).
[6]Based on average female infant weight of 9.0 kg (NCHS 2000) and an average formula intake of 735 g/day and maximum formula intake of 960 g/day (INSPQ 2001).
[7]Based on average female infant weight of 10.6 kg (NCHS 2000) and an average formula intake of 750 g/day and maximum formula intake of 900 g/day (INSPQ 2001).

No studies of activity-use patterns for repeat use containers are available to help determine frequency and method of use of polycarbonate repeat-use bottles by other segments of the population (i.e., children aged 1-4 years, 5-11 years, 12-19 years and adults). Therefore exposure estimates were based on a migration of 0.24 ppb of bisphenol A as calculated from Le et al. (2008), resulting from the room temperature use of polycarbonate bottles, as it was assumed that contents would typically not be heated prior to serving for these age groups. This value is supported by preliminary results of a study conducted by Health Canada (Health Canada, Safe Environments Programme, HECSB, pers. comm., 2008 March 6, unreferenced), and represents an overestimate of concentrations reported in water carboys by Biles et al. (1997). It was considered, conservatively, that all drinking water consumed by these age groups was from polycarbonate containers (e.g., repeat use drinking bottles, pitchers and carboys). Exposure estimates for this use are presented in Table 15.

Table 15. Contribution of use of polycarbonate drinking containers to potential daily intake of bisphenol A (µg/kg-bw per day) for children (aged 1+ years) and adults

Age group	Potential daily intake of bisphenol A (µg/kg-bw per day)[1]
1–4 years[2]	0.012
5–11 years[3]	0.010
12–19 years[4]	0.005
Adults[5]	0.006

[1]Based on a calculated average bisphenol A concentration of 0.24 ppb (Le et al. 2008), assuming contents would not be heated prior to serving.
[2]assumed to weigh 14.4 kg (Nutrition Canada 1980) and to drink 0.7 L of water per day (Health Canada 1998)
[3]assumed to weigh 26.4 kg (Nutrition Canada 1980) and to drink 1.l L of water per day (Health Canada 1998)
[4]assumed to weigh 53.8 kg (Nutrition Canada 1980) and to drink 1.2 L of water per day (Health Canada 1998)
[5]assumed to weigh 60.0 kg (Nutrition Canada 1980) and to drink 1.5 L of water per day (Health Canada 1998)

Another potential source of exposure to bisphenol A is through the use of polycarbonate tableware and storage containers. Kawamura et al. (1998) measured the migration of bisphenol A from tableware items commercially available in Japan (i.e., measuring cups, mugs and bowls) using either 20% ethanol maintained at 60°C degree C for 30 minutes (n=9) or water at 95°C degree C for 30 minutes (n=9). Under both sets of conditions, migration was below the limit of quantification (0.6 ppb) in 7 of 9 samples. In the 4 samples with detectable concentrations of bisphenol A, concentrations ranged from 1.7 to 4.5 ppb. Due to limited data on migration from polycarbonate tableware and storage containers, the lack of information on availability of these products on the Canadian market, and use patterns by the general population, exposure estimates cannot be derived. However, based on available information, under normal use conditions exposure from this source is expected to be limited.

Environmental Media

Many recent reviews have summarized bisphenol A concentrations in environmental media (Willhite et al. 2008; Vandenburg et al. 2007; NTP 2007; Kang et al. 2006b).

Data on concentrations of bisphenol A in Canadian waters are summarized in Table 9a. The only published Canadian drinking water values were measured by Chen et al. (2006) in Alberta at the Bearspaw (on the Bow River) and the Glenmore (on the Elbow River) water treatment plants with bisphenol A concentrations of 0.00045 and 0.00076 µg/L respectively (no detection limit presented). These values fall within the range reported by other countries, with concentrations between 300 pg/L to 2 ng/L (0.0003 to 0.002µg/L) (Kuch and Ballschmiter 2001) in Germany, and from below detection (0.01µg/L) to 0.06µg/L in Japan (Nakanishi et al. 2007). Boyd et al. (2003) was the only other Canadian study identified and although bisphenol A was detected (LOD 0.1 ng/L), it was not quantifiable, making this study unsuitable for deriving estimates of bisphenol A intake for the Canadian population.

No Canadian data were identified for ambient or indoor air. Although bisphenol A is released to air, due to its low vapour pressure it is more likely to partition to soil or water rather than remain in the air, where it has a half life of a few hours (see Environmental Fate section of Ecological Exposure Assessment). Concentrations in ambient air have been measured in two pilot studies conducted in 1997 (Wilson et al. 2001, 2003) and in a 2000-2001 survey (Wilson et al. 2007) of outside residences and daycare centres in North Carolina and Ohio. In the 2000-2001 survey, bisphenol A was detected in ambient air outside residences in 31% of samples in North Carolina, ranging from below the limit of detection (0.9 ng/m^3) to 44.6 ng/m^3 (50th percentile 0.9 ng/m^3), and 34% of samples in Ohio, ranging from the limit of detection to 19.0 ng/m^3 (50th percentile 0.920 ng/m^3) (Wilson et al. 2007). Concentrations of bisphenol A measured in ambient air outside daycare centres, ranged from below the limit of detection (0.01 ng/m^3) to 51.5 ng/m^3 (50th percentile below detection) in North Carolina (detected in 38% of samples), and below detection to 6.94 ng/m^3 (50th percentile below detection) in Ohio (detected in 44% of samples). In deriving intake estimates for the Canadian population, it was considered

appropriate to use the maximum and fiftieth percentile ambient air concentration in North Carolina (44.6 ng/m^3, 0.9 ng/m^3), taking into consideration the residential location and larger sample size (n=127).

Concentrations of bisphenol A in indoor air were measured by Wilson et al. (2001, 2003, 2007) in 42 daycare centres and 153 residences across North Carolina and Ohio in 2000-2001. In Ohio residences, bisphenol A was detected in 63% of the samples within a range of concentration from below the limit of detection (0.01 ng/m^3) to 30.3 ng/m^3 (50^{th} percentile 0.980ng/m^3). In North Carolina, this range was extended to include a maximum concentration of 193 ng/m^3 (50th percentile 1.82 ng/m^3) with bisphenol A detected in 68% of samples. For daycare centres, indoor air concentrations ranged from below the detection limit (0.01 ng/m^3) to 7.42 ng/m^3 in Ohio, and 8.99 ng/m^3 in North Carolina, with bisphenol A detected in 73% and 45% of the samples, respectively. In another survey of 120 homes in Cape Cod, Massachusetts, conducted by Rudel et al. (2003), concentrations in indoor air were below the reporting limit (18 ng/m^3). In an earlier study, Rudel et al. (2001) measured bisphenol A in air in the range of 0.002 to 0.003 µg/m^3 (2-3 ng/m^3) in offices and residential locations (n=5). The maximum and fiftieth percentile indoor air concentrations in North Carolina (193 ng/m^3, 1.82 ng/m^3) were considered the most appropriate for use in deriving estimates of intake based on the residential location and sample size (n=127).

No Canadian data were identified for soil. One study in the United States analyzed soil in four daycare facility play areas, and reported bisphenol A concentrations that ranged from 0.005 to 0.007 µg/g (mean of 0.006 µg/g, n=2), and in the vicinity of nine homes with levels ranging from 0.004 to 0.014 µg/g (mean of 0.007 µg/g, n=9) in North Carolina (detection limit 0.001 µg/g)(Wilson et al. 2003). The maximum and mean concentrations in soil (0.007 µg/g; 0.006 µg/g) from residential locations were considered most appropriate for use in deriving estimates of intake.

Preliminary raw data are available for Phase 1 of the Canadian House Dust Study. Based on air-dried vacuum samples collected from 260 Canadian homes, median concentrations of bisphenol A in dust were reported at 1.60 µg/g dust (ranged from less than the method reporting limit [0.17 µg/g] to 23.84 µg/g). Bisphenol A was detected in 99% of homes (Health Canada, Environmental Health Science and Research Bureau, pers. comm., 2008 Feb 7, unreferenced). These results are consistent with concentrations reported in dust from homes in other countries. In a survey of 118 homes in Cape Cod, Massachusetts, Rudel et al. (2003) identified a maximum value of 17.6 µg/g (mean of 1.65 µ/g) with 86% of samples above the reporting limit. Wilson et al. (2007) also reported dust levels in residences in North Carolina and Ohio. In North Carolina, 25% of homes had detectable levels, with a maximum value of 707 ng/g (50th percentile was reported as the limit of detection). In Ohio, 72% of homes had detectable levels, with a maximum value of 589 ng/g (50^{th} percentile is below detection limit). The maximum and median concentrations (23.84 µg/g; 1.60 µg/g) identified in dust measured in homes in Canada were considered most appropriate for use in deriving estimates of intake.

Tables 16 and 17 present mean and upper bounding estimates of intake for each age group in the general population of Canada based upon concentrations of bisphenol A identified in environmental media. Dust and soil concentrations have been summed for the purposes of the intake table.

Table 16. Average estimates of potential daily intake of bisphenol A by the general population in Canada from environmental media.

Route of exposure	Estimated intake (µg/kg-bw per day) of bisphenol A by various age groups					
	0–7 months[1]	8–12 months[2]	1–4 years[3]	5–11 years[4]	12–19 years[5]	20+ years[6]
Ambient air[7]	4×10^{-5}	1.2×10^{-4}	7.3×10^{-5}	6.2×10^{-5}	3.3×10^{-5}	3.0×10^{-5}
Indoor air[8]	5.6×10^{-4}	1.6×10^{-3}	1.0×10^{-3}	8.7×10^{-4}	4.7×10^{-4}	4.3×10^{-4}
Drinking water[9]	NA[10]	NA[10]	3.7×10^{-5}	3.2×10^{-5}	1.7×10^{-5}	1.9×10^{-5}
Soil and dust[11,12,13]	8.1×10^{-3}	1.8×10^{-2}	1.1×10^{-2}	4.0×10^{-3}	9.0×10^{-4}	8.0×10^{-4}
Total intake	8.7×10^{-3}	2.0×10^{-2}	1.2×10^{-2}	4.9×10^{-3}	1.4×10^{-3}	1.3×10^{-3}

[1] Assumed to weigh 5.9 kg (NCHS 2000), to breathe 2.1 m^3 of air per day and ingest 30 mg of soil per day (Health Canada 1998).

[2] Assumed to weigh 9.0 kg (NCHS 2000), to breathe 9.3 m^3 of air per day and to ingest 100 mg of soil per day (Health Canada 1998).

[3] Assumed to weigh 14.4 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[4] Assumed to weigh 26.4 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[5] Assumed to weigh 53.8 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[6] Assumed to weigh 60.0 kg (Nutrition Canada 1980) , 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 (Health Canada 1998).

[7] Wilson et al. (2007) reported that the fiftieth percentile ambient air concentration as measured in samples taken outside residences in North Carolina, U.S.A, was below the detection limit of 0.0009 µg/m^3 (detected in 31% of samples, n=127). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[8] Wilson et al. (2007) reported that the fiftieth percentile indoor air concentration as measured in samples inside residences in North Carolina, U.S.A, was 0.00182 µg/m^3 (detected in 68% of samples, n=127). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[9] The only published Canadian values for bisphenol A in drinking water were 0.00045 and 0.00076 µg/L measured at two water treatment plants in March 2003 in Alberta, Canada (Chen et al. 2006) (sample size unknown, no detection limit presented). The maximum concentration value 0.00076 µg/L was used in generating the estimated average intake due to the lack of an average value presented in this reference.

[10] NA – not applicable. Reported concentrations in drinking water (0.00076 µg/L) are significantly lower than those reported in liquid infant formula.

[11] The estimated intake for soil and dust is based on the sum total of the average concentration identified in each medium..

[12] The average concentration in soil of 7 µg/kg is based on a survey of 9 residences in North Carolina, U.S.A as part of a study by Wilson et al. (2003) which also included day care play facilities (detection limit of 1 µg/kg).

[13] The median concentration in dust of 1600 µg/kg was identified in the preliminary data of the Phase 1 Canadian House Dust Study of 260 homes (Health Canada, Environmental Health, Science and Research Bureau, pers. comm., 2008 Feb, unreferenced).

Table 17. Upper-bounding estimates of potential daily intake of bisphenol A by the general population in Canada from environmental media.

Route of exposure	Estimated intake (µg/kg-bw per day) of bisphenol A by various age groups					
	0–7 months[1]	8-12 months[2]	1–4 years[3]	5–11 years[4]	12–19 years[5]	20+ years[6]
Ambient air[7]	2.0×10^{-3}	5.8×10^{-3}	3.6×10^{-3}	3.1×10^{-3}	1.6×10^{-3}	1.5×10^{-3}
Indoor air[8]	6.0×10^{-2}	1.8×10^{-1}	1.1×10^{-1}	9.3×10^{-2}	5.0×10^{-2}	4.6×10^{-2}
Drinking water[9]	NA[10]	NA[10]	3.7×10^{-5}	3.2×10^{-5}	1.7×10^{-5}	1.9×10^{-5}
Soil and dust[11,12,13]	1.2×10^{-1}	2.6×10^{-1}	1.7×10^{-1}	5.9×10^{-2}	1.3×10^{-2}	1.2×10^{-2}
Total intake	1.8×10^{-1}	4.4×10^{-1}	2.8×10^{-1}	1.6×10^{-1}	6.4×10^{-2}	5.9×10^{-2}

[1] Assumed to weigh 5.9 kg (NCHS 2000), to breathe 2.1 m^3 of air per day and to ingest 30 mg of soil per day (Health Canada 1998).

[2] Assumed to weigh 9.0 kg (NCHS 2000), to breathe 9.3 m^3 of air per day and to ingest 100 mg of soil per day (Health Canada 1998).

[3] Assumed to weigh 14.4 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[4] Assumed to weigh 26.4 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[5] Assumed to weigh 53.8 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[6] Assumed to weigh 60.0 kg (Nutrition Canada 1980), 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 (Health Canada 1998).

[7] Wilson et al. (2007) reported the maximum ambient air concentration as measured in samples taken outside residences in North Carolina, U.S.A., as 0.0446 µg/m^3 (detected in 31% of samples, n=127). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

[8] Wilson et al. (2007) reported the maximum indoor air concentration as measured in samples inside residences in North Carolina, U.S.A., as 0.193 µg/m^3 (detected in 68% of samples, n=127). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

[9] The only published Canadian values for bisphenol A in drinking water were 0.00045 and 0.00076 µg/L measured at two water treatment plants in March 2003 in Alberta, Canada (Chen et al. 2006) (sample size unknown, no detection limit presented). The maximum concentration value 0.00076 µg/L was used in generating the estimated upper-bounding intake.

[10] NA – not applicable. Reported concentrations in drinking water (0.00076 µg/L) are significantly lower than those reported in liquid infant formula.

[11] The estimated intake for soil and dust is based on the sum total of the maximum concentration identified in each medium.

[12] The maximum concentration in soil of 14 µg/kg is based on a survey of 9 residences in North Carolina, U.S.A., in a study by Wilson et al. (2003) which also included day care play facilities (detection limit of 1 µg/kg).

[13] The maximum concentration in dust of 23 840 µg/kg was identified in the preliminary data of the Phase 1 Canadian House Dust Study of 260 homes (Health Canada, Environmental Health, Science and Research Bureau, pers.comm., 2008 February, unreferenced).

Other Sources of Exposure

Dental materials manufactured from bisphenol A derived monomers include composite resins used to restore cavities in the teeth of children and adults and dental sealants. Sealants may be used, infrequently, to seal the biting surfaces of baby (primary) teeth but are mainly used to seal the surfaces of permanent first and second molars that erupt into the mouth at ages six and twelve respectively (Health Canada, Medical Devices Bureau, pers. comm., 2008 February 27, unreferenced)

While current Canadian data on the prevalence of dental decay in children are not available, it is known through studies of individual populations that it is a common childhood disorder, particularly in certain at-risk populations. Leake and Main (1996) found that children aged five in Ontario had 1.22 decayed, missing or filled teeth. Peressini et al. (2004) found that children aged seven in an Ontario First Nations Community had 6.20 decayed, missing or filled teeth. Leake et al. (2001) in a sample survey of the oral health of 3657 Toronto children aged five, seven or thirteen, found that 30.0% of five year olds, 41.3% of seven year olds and 39.3% of thirteen year olds children had one or more cavities.

The restoration of decayed teeth, both primary and permanent, may be accomplished using a variety of materials including dental amalgam and composite resin. While current data on the prevalence of usage of composite resins versus other restorative materials are not available, anecdotal information suggests that the use of composite resin is increasing and is currently used more frequently than other materials to restore primary and permanent teeth in children.

Santerre (2007) has stated the three sources of bisphenol A derived from dental materials are unpolymerized monomer on the surface of the restoration or sealant; hydrolyzed polymers of bisphenol-derived monomers in the material and fine particulate polymer produced by abrasion of the restoration. Santerre (2007) further states that BisGMA, one of the most commonly used bisphenol A-derived monomers used in the manufacture of dental restorative materials and sealants, shows no capacity to be hydrolyzed back into bisphenol A under normal oral conditions.

A number of investigators have shown that placement of composite resin restorations and sealants can result in acute, transient exposures to bisphenol A (Fung et al. 2000; Joskow et al. 2006; Sasaki et al. 2005)

Fung et al. (2000) collected saliva following the application of 8 mg (applied to one surface) and 32 mg (8 mg applied to four surfaces) of a dental sealant to a group of 18 and 22 adults, respectively. Concentrations of bisphenol A in saliva ranged from 5.8 to 105.6 ppb (detection limit of 5 ppb) at 1 hr and 3 hrs following treatment but was not

detected immediately after treatment or at other time intervals (24 hr, 72 hrs and 120 hrs) post-treatment.

More recently, Joskow et al. (2006) measured concentrations of bisphenol A in saliva of 14 adults before and after the application of between 39.0 to 42.5 mg of two dental sealants. Mean concentrations of bisphenol A before treatment, immediately following treatment, and an hour post-treatment were reported as 0.22 ng/ml, 0.54 ng/ml, and 0.24ng/ml in five patients treated with one sealant and 0.30 ng/ml, 26.5 ng/ml and 5.12 ng/ml in nine patients treated with the other sealant.

Sasaki et al. (2005) measured bisphenol A concentration in saliva collected from 21 patients before and after dental treatments using 9 different commercial composite resins. The concentration of bisphenol A in saliva for patients treated with bis-GMA monomer-based composite resins (and bonding agents) labelled A (n=4) measured in the range of 0.3 to 2.0 ng/ml (mean 0.87ng/ml) prior to treatment, 21.0 to 60.1 ng/ml (mean 32.1 ng/ml) following treatment and 1.6 to 4.7 ng/ml (mean 3.1 ng/ml) after gargling for 30 seconds with water at 37^{o}C. Patients treated with the composite labelled F (n=3) had the highest concentration of bisphenol A in saliva post-treatment of (100 ng/ml; range 60 to 100 ng/ml) and after gargling (19 ng/ml; range 5 to 19 ng/ml). The concentration of bisphenol in saliva following the use of the other composites labelled C (n=2), G (n=2), H (n=2), and I (n=2) ranged from 10 to 45 ng/ml.

Azarpazhooh and Main (2008) observed that no dental sealants that carried the Seal of the American Dental Association [product recognition program, now discontinued] in 2007 released detectable amounts of BPA and continued with recommendations for simple clinical procedures [commonly followed] to reduce the possibility of unpolymerized BPA-derived monomer remaining on the surface of the tooth following sealant placement.

A method to extrapolate from concentrations in saliva to daily estimates of exposure was not identified. However, consistent with the data presented above, other international assessments have characterized exposure to bisphenol A as a result of dental treatments as an acute event (ECB 2003) or as nominal relative to other oral sources of exposure (Nakanishi 2007).

Consumer products are also a potential source of exposure. Miyamoto and Kotake (2006) characterized exposure to bisphenol A for infants from contact with consumer products such as toys. The contact time was established using a survey of mothers who observed mouthing behaviour in a total of 50 infants (Tanimura 1999) and video recordings of 25 infants in which time spent mouthing toys was monitored (Tanimura 2000). A minimum migration rate (of 0 µg/cm^2/min (for products that do not contain bisphenol A) and a maximum migration rate 0.0162 µg/cm^2/min identified in the Japanese literature [Kanagawa 2000] were used. The estimated intake of bisphenol A was 0.026 µg/kg per day (0-5 month old boys) and 0.069 µg/kg per day (6-11 month old boys). The authors noted that only a few toys are made of bisphenol A-based polymers and, as such, these are likely to be overestimates of exposure. Similarly, few toys on the Canadian market

are expected to be made of bisphenol A-based polymers and, additionally, these hard plastics tend to have a lower migration rate than would be expected from soft plastic toys (Health Canada, Consumer Product Safety Bureau, pers. comm., 2008 March 17, unreferenced) and therefore contribution to exposure among infants and children is expected to be limited.

The Household Products Database (National Institutes of Health 2007) indicates that bisphenol A may be found as a residual monomer in epoxy resins used in the manufacture of epoxy adhesives. The resins may be present in the adhesive products at concentrations ranging from 0.1%– 100%. However, only trace quantities of bisphenol A are likely to be present in the resins with a predicted residual level of 1 ppm (identified in ECB 2003). An estimate of exposure to bisphenol A from epoxy adhesives predicts air concentrations during use to range from 3.82×10^{-5} μg/m^3 to 6.08×10^{-5} μg/m^3 (Table 18). The chosen scenarios correspond to gluing a handle on a coffee mug or gluing a large vase. However it is expected that the majority of exposures will occur at the lower end of this range. Dermal exposure may also result from the use of this product and was estimated at 0.0167 μg/kg-bw per use (Table 18). Confidence in these estimates is low as they are based on a number of assumptions; however it is likely that they overestimate actual exposures from this source.

Table 18. Upper-bounding estimates of potential exposure to bisphenol A from consumer products

Consumer product scenarios	Assumptions	Estimated exposure
Two component epoxy adhesive– gluing the handle of a coffee mug[1]	**Inhalation** - Used ConsExpo model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release (RIVM 2006) - Assume saturation conditions (i.e. select "limit air concentration to vapour pressure of pure substance" check box) - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.0001% residual bisphenol A monomer in epoxy resins (ECB 2003) - Assume amount of product used is 0.5 g/event to cover a surface area of 2 cm^2, and an application duration of 5 minutes - Assume a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuirs method and a molecular weight matrix of 3000 g/mol (RIVM 2007).	Mean event concentration = 0.0000382 μg/m^3
Two component epoxy	**Inhalation** - Used ConsExpo model version 4.1, exposure to vapour: evaporation from an increasing area as mode of release	Mean event concentration = 0.0000608

Consumer product scenarios	Assumptions	Estimated exposure
adhesive–gluing a large vase[1]	(RIVM 2006). - Assume saturation conditions (i.e. select "limit air concentration to vapour pressure of pure substance" check box). - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.0001% residual bisphenol A monomer in epoxy resins (ECB 2003). - Assume amount of product used is 20 g/event to cover a surface area of 500 cm^2, an application duration of 30 minutes, a room volume of 20 m^3, exposure duration of 240 minutes, a ventilation rate of 0.6 times/hr, a mass transfer rate based on Langmuirs method and a molecular weight matrix of 3000g/mol (RIVM 2007).	µg/m^3
	Dermal - Used ConsExpo model version 4.1, direct dermal contact with product: instant application as mode of release (RIVM 2006). - Based on a reported weight fraction of 0.1 for epoxy resins in epoxy adhesives (Emerson and Cuming 2004) and assuming 0.0001% residual bisphenol A monomer in epoxy resins (ECB 2003). - Assume the exposed area of skin is 43 cm^2, and an applied amount of 0.1 grams of product is applied (RIVM 2007). - Assume adult exposed weighs 60.0 kg (Nutrition Canada 1980). - Assume 100% uptake.	Acute dose per event = 0.00167 µg/kg

[1] Possible exposure of teenagers (12–19 years old) and adults (20+). Scenarios were completed for adults only.

It has been reported to Health Canada that polymers manufactured with bisphenol A may be used in the production of cosmetic products, such as lipsticks, eye makeup, face makeup and nail lacquers (Health Canada, Cosmetics Division, pers. comm., 2008 March 18, unreferenced). Residual bisphenol A in these products are not known but are expected to be low and are not expected to contribute significantly to the overall exposure to the general population.

Aggregate Exposure from Dietary and Non-dietary sources

For exposure among formula fed infants aged 0 to 18 months, exposures from multiple sources (food packaging of infant formula, migration from polycarbonate bottles, and through environmental media) were aggregated and are presented in Tables 19a and 19b.

Table 19a. Aggregated average estimates of potential exposure for formula fed infants aged 0 to 18 months (µg/kg-bw per day).

Age group	Intake from infant formula[1,2]	Intake from environmental media[6]	Intake from migration from polycarbonate bottles[3,4]	Total estimated dietary intake[4,5] (bottles + formula)	Total estimated intake (dietary intake + media)	
					Boiling water	Room temp. water
0 to 1 month	0.45	0.009	1.65	2.1	2.11	0.50
2 to 3 months	0.50	0.009	1.95	2.450	2.46	0.56
4 to 7 months	0.38	0.009	1.46	1.840	1.85	0.42
8 to 12 months	0.21	0.02	0.82	1.03	1.05	0.25
12 to 18 months	0.23	0.02	0.71	0.94	0.96	0.27

[1] Based on the average concentration of bisphenol A as measured in liquid infant formula (Health Canada, Food Directorate, HPFB, pers. comm., 2007 Dec 14, unreferenced) and an average formula intake for each age group (see Table 12).

[2]If drinking water is used to dilute the infant formula during preparation, it may affect the overall bisphenol A concentrations. However as concentrations of bisphenol A measured in drinking water were significantly lower than those measured in liquid infant formula, that source of exposure was not included in these estimates.

[3]Intakes from room temperature water are minimal compared to boiling water and are not presented here (see Table 14).

[4] Based on the average concentration of bisphenol A measured in water, 10 ppb, that resulted from filling polycarbonate bottles with boiling water (Maragou et al. 2007) (see Table 14).

[5] Heath Canada recommends that solid food be introduced to infants after 6 months of age. For this assessment it was assumed that an infants main source of food is infant formula, however if infants consume other canned foods this may increase their total dietary exposure to bisphenol A.

[6] Based on average concentrations measured in various environmental media (see Table 16).

Table 19b. Aggregated maximum estimates of potential exposure for formula fed infants aged 0 to 18 months (µg/kg-bw per day).

Age group	Intake from infant formula[1,2]	Intake from environmental media[6]	Intake from migration from polycarbonate bottles[3,4]	Total estimated dietary intake[4,5] (bottles + formula)	Total estimated intake[2] (dietary intake + media)	
					Boiling Water	Room temp. water
0 to 1 month	1.35	0.18	2.77	4.12	4.30	1.60
2 to 3 months	1.31	0.18	2.67	3.98	4.16	1.55
4 to 7 months	1.02	0.18	2.00	3.02	3.20	1.25
8 to 12 months	0.55	0.44	1.07	1.62	2.06	1.02
12 to 18 months	0.46	0.44	0.85	1.31	1.75	0.92

[1] Based on the maximum concentration of bisphenol A as measured in liquid infant formula (Health Canada, Food Directorate, HPFB, pers. comm., 2007 Dec 14, unreferenced) and the maximum formula intake for each age group (see Table 12).
[2]If drinking water is used to dilute the infant formula during preparation, it may affect the overall bisphenol A concentrations. However as concentrations of bisphenol A measured in drinking water were significantly lower than those measured in liquid infant formula, that source of exposure was not included in these estimates.
[3]Intakes from room temperature water are minimal compared to boiling water and are not presented here (see Table 14).
[4] Based on the average concentration of bisphenol A measured in water, 10 ppb, that resulted from filling polycarbonate bottles with boiling water (Maragou et al. 2007) (see Table 14).
[5] Heath Canada recommends that solid food be introduced to infants after 6 months of age. For this assessment it was assumed that an infants main source of food is infant formula, however if infants consume other canned foods this may increase their total dietary exposure to bisphenol A.
[6] Based on maximum concentrations measured in various environmental media (see Table 17).

For exposure among breastfed infants aged 0 to7 months, exposures from multiple sources (breast milk and through environmental media) were aggregated and are presented in Table 20.

Table 20. Aggregate estimate of potential exposure for breastfed infants aged 0 to 7 months (µg/kg-bw per day)[1].

Age group	Intake from consumption of breastmilk[2]		Overall intake from environmental media[3]		Total estimated intake	
	Average	Maximum	Average	Maximum	Average	Maximum
0 to 1 month	0.28	1.09	0.009	0.18	0.29	1.27
2 to 3 months	0.21	0.84	0.009	0.18	0.22	1.02
4 to 7 months	0.19	0.73	0.009	0.18	0.20	0.91

[1] If infants are fed pumped breastmilk via polycarbonate bottles, this may add to their overall exposure to bisphenol A.

[2]Based on the average and maximum concentrations of bisphenol A identified in breastmilk by Ye et al. (2006) (see Table 13).
[3]Based on the average and maximum concentrations of bisphenol A identified in various environmental media (see Tables 16 and 17)

For exposure among children and adults (aged 1+ years), exposure from multiple sources (food packaging of canned food and beverages, migration from polycarbonate drinking bottles and through environmental media) were aggregated and are presented in Table 21.

Table 21. Aggregate estimate of potential exposure for children (aged 1+ years) and adults (µg/kg-bw per day).

Age group	Intake from consumption of canned food[1]		Intake from migration from polycarbonate bottles[2]	Overall intake from environmental media[3]		Total estimated intake	
	Average	Maximum	Average	Average	Maximum	Average	Maximum
1 to 4 years	0.25	1.98	0.012	0.012	0.28	0.27	2.27
5 to11 years	0.15	1.28	0.010	0.005	0.16	0.17	1.45
12 to 19 years	0.09	0.73	0.005	0.001	0.06	0.10	0.80
Adults	0.07	0.60	0.006	0.001	0.06	0.08	0.67

[1] Based on the average and maximum concentrations of bisphenol A identified in canned food (EWG 2007) (see Tables 10 and 11)
[2] Based on the calculated average concentration of bisphenol A detected in water, 0.24 ppb, that resulted from the room temperature use of polycarbonate bottles (Le et al. 2008) (see Table 15).
[3]Based on the average and maximum concentrations identified in various environmental media (see Tables 16 and 17).

In a limited study, Wilson et al. (2003) reported aggregate exposure estimates for nine children aged 2-5 year olds from concentrations of bisphenol A reported in indoor and ambient air, floor dust, play area soil and solid and liquid food collected at two daycare centres and nine households in North Carolina. Mean exposure was 42.981 ng/kg-bw per day and maximum exposure was 71.124 ng/kg-bw per day. The aggregate exposure was based on the following assumptions: 100% absorption, that a child spends 12 hours a day at the daycare centre, ingests soil and dust at a rate of 100 mg/day (Stanek and Calabrese 1995a,b), and inhales air at a rate of 8.3 m^3/day (EFH 2000). In an expanded study by Wilson et al. (2007), 257 children aged 1.5 to 5 years old were surveyed in daycare centres and homes located within North Carolina and Ohio using the approach described above. A 50^{th} percentile aggregate exposure of 71.4 ng/kg-bw per day and a maximum of 1570 ng/kg-bw per day was reported in North Carolina. A 50th percentile aggregate exposure of 60.8 ng/kg-bw per day and maximum of 775 ng/kg-bw per day was reported in Ohio (an assumption of 50% absorption was made).

Concentrations in biological tissues and fluid have been reported by a number of investigators and are summarized in Vandenburg et al (2007), Dash et al. (2006) NTP (2007) and Dekant and Volkel (2008). Tissues and fluid analyzed include semen, amniotic fluid, placental tissue and serum. Urine is considered the most appropriate body fluid for quantifying exposure to bisphenol A. Several studies have analyzed bisphenol A in urine. Most recently, bisphenol A (free and conjugated) was an analyte of the 2003-2004 National Health and Nutrition Examination Survey (NHANES) .The NHANES results are reported by Calafat et al. (2008) and present results of bisphenol A analysis (free and conjugated) in 2517 individuals aged 6 years and older in the United States. Using these data, Lakind and Naiman (2008) have derived estimates of daily intake of bisphenol A, assuming steady state excretion. Fiftieth and ninety-fifth percentiles for the following subpopulations of the U.S. (6–11 years, 12–19 years, 20–39 years, 40–59 years and 60+ years) have been derived based on standard values for urinary output and adjusted for individual bodyweights. For all individuals, the 50th percentile exposure estimate is 50.5 ng/kg-bw per day (the 95th percentile exposure estimate is 274.2 ng/kg-bw per day). For children aged 6 to 11, the 50th percentile exposure estimate is 67.4 ng/kg-bw per day (the 95th percentile exposure estimate is 310.5 ng/kg-bw per day).

Confidence in the exposure assessment is considered to be moderate. Canadian multimedia data are very limited. Biomonitoring data indicates that exposures may be less than those derived from aggregating exposure estimates based on concentrations in different media, but the absence of biomonitoring data for a key segment of the population (infants) precludes use of biomonitoring data to characterize risk. Additionally, applying precaution, derivation of exposure estimates based on concentrations in media captures exposures in the most exposed individuals. Furthermore, there are uncertainties associated with the use of spot urine samples from one point in time to predict daily exposure estimates.

Health Effects Assessment

The European Chemicals Bureau (ECB) has classified bisphenol A as a Category 3 reproductive toxicant; that is a substance which causes concern for human fertility based on sufficient evidence of reproductive toxicity in experimental animals (ECB 2003). In general, bisphenol A is considered to have low acute oral toxicity in animals (ECB 2003). The European Union reported that bisphenol A is not a skin irritant, but may cause eye or respiratory irritation in experimental animals (ECB 2003). Extensive literature is available regarding effects on various organ systems in adult or developing animals; encompassing acute, short-term and long-term durations of exposure and different routes of exposure. A critical review of all hazard data on bisphenol A is beyond the scope of this screening assessment. Key toxicokinetics and metabolism data are summarized; as is the carcinogenicity and genotoxicity literature. Analysis of the recent literature, and recent assessments by other organizations, confirmed that reproductive and developmental endpoints were the critical effects, and the focus of the screening assessment is therefore on these effects.

Toxicokinetics and metabolism

With respect to metabolism of bisphenol A, it is considered that free bisphenol A, not the glucuronide conjugate, is the biologically active moiety. The route of exposure is significant as it affects the circulating levels of free bisphenol A. Following oral exposure, the glucuronidation of bisphenol A by hepatic uridine diphosphate glucuronyltransferase (UDPGT), appears to be a major *in vivo* metabolism pathway in rats (specifically the isoform, UGT2B1) (Pottenger et al. 2000; Yokota et al. 1999), non-human primates (Kurebayashi et al. 2002), and humans (Volkel et al. 2002). The UGT isoform(s) which may be involved in metabolism of bisphenol A in humans is/are not known (NTP 2008). In a recent draft, the European Food Safety Authority (EFSA) acknowledged glucuronidation as the major pathway of bisphenol A metabolism in adult humans and animals while sulfation was suggested as a minor pathway in humans and rats (EFSA 2008). The United States Food and Drug Administration (USFDA) also recognized glucuronidation as a major metabolic pathway in rodents, monkeys and humans, but the possibility of bisphenol A sulfation during metabolism was not sufficiently reviewed (USFDA 2008).

In humans and other non-human primates, bisphenol A administered orally enters first-pass metabolism in the gut wall and the liver and is quickly metabolized to bisphenol A-monoglucuronide, which has no endocrine activity and is rapidly excreted in urine with a half-life of less than 6 hours (Tominaga et al 2006; Volkel et al. 2002). Due to rapid elimination and plasma protein binding of bisphenol A, it is expected that very low concentrations of free bisphenol A would be available for receptor binding in humans (EFSA 2006).

In rats, bisphenol A administered orally also undergoes glucuronidation, but the resulting bisphenol A-glucuronide is excreted from liver into bile. In the gut, the bisphenol A-glucuronide is then cleaved into bisphenol A and aleuronic acid and bisphenol A is reabsorbed into the blood. This enterohepatic recirculation may cause slow elimination of bisphenol A in rodents (Pottenger et al. 2000; Snyder et al. 2000). An overview of toxicokinetics or pharmacokinetics of bisphenol A by the EFSA and USFDA elaborated the similar stages of bisphenol A metabolism in rodents, non-human primates and humans (EFSA 2008; USFDA 2008).

Additionally, the toxicokinetics and metabolism of bisphenol A in pregnant animals, fetuses or neonates may be different to that of non-pregnant adults. The absorption and distribution of bisphenol A was rapid in maternal F344 rat organs following a single oral exposure to a high dose of 1 g/kg, reaching the fetus by crossing the placenta within 20 minutes of exposure; the fetal bisphenol A concentration exceeded that of maternal blood 40 minutes after exposure (Takahashi and Oishi 2000). Also, in humans, bisphenol A was present in serum and follicular fluid of pregnant women, as well as fetal serum and amniotic fluid, demonstrating placental transfer. Bisphenol A (presumably bound and free) concentrations in amniotic fluid, mid-term, were 5-fold higher as compared to

serum and follicular fluid (Ikezuki et al. 2002). These data indicate that repeated maternal exposures could lead to an accumulation of fetal circulating levels of free bisphenol A and correspondingly elevated *in utero* exposures (Ikezuki et al. 2002; Welshons et al. 2006).

Free bisphenol A in human fetal plasma has also been reported to be 0.2 – 9.2 ng/mL (mean 2.9 ng/mL) and the mean bisphenol A plasma levels in the male human fetus was reported as 3.5 ng/mL; significantly lower levels of bisphenol A were reported in female fetal plasma with a mean of 1.7 ng/mL (Schönfelder et al. 2002). In women, bisphenol A has been detected in biological fluids/tissue including breastmilk, colostrum and adipose tissue in parts per billion concentrations (Fernandez et al 2007; Kuruto-Niwa et al 2007; Sun et al 2004). A careful evaluation of biologically active or free bisphenol A concentration in various tissues of a sensitive population was previously identified as a research need and has also recently been identified as being of critical importance by the USFDA (2008).

A reduced UGT2B1 activity was seen in pregnant rats as compared to non-pregnant females. The UGT2B1 enzyme was not present in the fetus, its activity was slow in neonates, and reached the adult level of activity within three weeks after birth (Matsumoto et al. 2002). It has been suggested that an increase in glucuronidation capacity during pregnancy may result in negligible fetal exposure to xenobiotics (EFSA 2008). Human data show that glucuronide enzyme activity may be induced during pregnancy as it was evidenced by an increased clearance of orally administered lorazepam, paracetamol and lamotrigine in pregnant women (Miners et al 1986; Papini et al 2006; Pennell et al 2008). It is important to note that based on the limited evidence of selective glucuronidation and considering other factors including individual variation, tissue localization, and substrate-specificity of these enzymes in animals, it cannot be assumed that glucuronidation activity would be increased in pregnant women following exposure to bisphenol A.

Limited activity of glucuronidation enzymes in the human fetal liver has also been demonstrated (Ring et al. 1999). In human liver microsomes, most of the UGT isozymes were not expressed prenatally. A full complement was present at three months after birth; however, levels were substantially reduced compared to the adult (Coughtrie et al. 1988). Studies indicate that, in humans, sulfotransferase (SULT) enzymes are fully functional at birth and it has been suggested that sulfoconjugation of bisphenol A may overcome the absence of or very low glucuronidation activity in newborns (Benedetti and Baltes 2003; EFSA 2008; Richard et al. 2001).

Some *in vitro* data showed that SULT enzymes may have the ability to metabolize some phenolic or estrogen-like compounds including bisphenol A in cell cultures (Nishiyama et al 2002; Shimizu et al 2002; Suiko et al 2000). This limited data needs to be interpreted carefully as different liver cells were studied under controlled conditions using different protocols. Whether the sulfotransferase activity reported in these studies would be sufficient to efficiently metabolize the bisphenol A in *in vivo* is not known at this time. A study conducted using post-mortem human (fetal, term and adults) liver

microsomes, in general, showed reduced UDPGT activity towards some phenolic compounds, which were structurally similar to bisphenol A, in fetal and term samples as compared to adults. Also, the human fetal liver sulphotransferase activity was found to be less than 3% of that present in non-human primate fetal liver (unpublished work – Leakey). The authors suggested that glucuronic acid or sulphate conjugation pathway may not be efficient in human perinate against phenolic compounds (Leakey et al 1987).

It is therefore not clear, based on the data of Leaky et al. (1987) whether sulfotransferases would act as a major metabolic enzyme system in human neonates following exposure to bisphenol A. Together, the toxicokinetics and metabolism differences suggest that the developing fetus and neonate may be more sensitive to bisphenol A due to reduced clearance, increased half-life of free bisphenol A (Welshons et al. 2006) and their inability to efficiently glucuronidate bisphenol A (Ring et al. 1999; Coughtrie et al. 1988).

Conversely, some evidence suggests that there were no significant differences between pregnant (at different stages of gestation) and non-pregnant Sprague-Dawley rats in the toxicokinetics and metabolism of orally administered bisphenol A (10 mg/kg single dose), and fetal bisphenol A elimination half-life appeared to be dependent on maternal bisphenol A elimination (Domoradzki et al. 2003). It was reported that, in developing Sprague-Dawley rats, dose-dependent metabolism of 1 or 10 mg/kg (gavage) bisphenol A to its glucuronide conjugate occurred as early as postnatal day 4 through postnatal day 21 and no significant sex-related differences were noted in the metabolism and pharmacokinetics in neonatal to weanling rats (Domoradzki et al. 2004).

In the absence of fully developed physiologically-based pharmacokinetic models to quantitatively characterize absorption, distribution, metabolism and excretion of bisphenol A and its metabolites in test animals and humans via different routes and at different life stages, it is considered appropriate to consider the pregnant woman/fetus and infant as potentially sensitive subpopulations.

Carcinogenicity

A lifetime (103-week) bisphenol A chronic toxicity/carcinogenicity study in male (0, 74 or 148 mg/kg/d) and female (0, 74 or 135 mg/kg per day) F344 rats reported reduced body weight gain in all exposed animals which was correlated with reduced feed consumption. A marginal increase in the incidence of leukemia and testicular interstitial tumors in male rats was considered statistically non-significant due to failure to meet the Bonferoni inequality criterion; the incidence of both tumor types was more common in the high-dose groups. Male and female B6C3F1 mice were administered doses of 0, 120 or 600 mg/kg-bw per day or 0, 650 or 1300 mg/kg-bw per day, respectively. Reduced body weight gain was observed in male and female B6C3F1 mice that received bisphenol A doses of 600 mg/kg per day or 650 or 1300 mg/kg per day respectively for 103 weeks. There was an increase in the combined incidence of leukemia and lymphoma in male mice, which was not considered dose-related. Overall, it was concluded that there was no

convincing evidence that dietary exposure to bisphenol A causes carcinogenicity in rats or mice of either sex (NTP 1982). Some debate exists regarding the biological significance of the NTP (1982) findings. Specifically, it has been argued that the marginal increases in leukemias of rats and the combined incidence of lymphomas and leukemias in male mice should be considered to be bisphenol A related. It has been proposed as well that the observed testicular effects should also be considered as some evidence for carcinogenic activity (Huff 2001; 2002). However, others maintain that the 2-year study correctly concluded that the results demonstrate equivocal evidence of carcinogenicity in male rats and no evidence of carcinogenicity in female rats and mice of both genders (Haighton et al. 2002; Munro et al. 2002a; 2002b). It was noted that the incidence of malignancies observed in the bisphenol A exposed groups of rats and mice were within the historical control ranges for the strains and species tested (Haighton et al. 2002). In support of the NTP (1982) conclusions, Tyl et al. (2002) observed no increase in cancer incidence in a three-generation assessment of bisphenol A toxicity in male and female Sprague-Dawley rats exposed to doses ranging from 0.001 to 500 mg/kg-bw per day (Tyl et al. 2002). The available evidence suggests that bisphenol A is not a carcinogen following adult exposure (Keri et al. 2007).

Recent reports have suggested that prenatal and/or neonatal exposure to bisphenol A in rats at doses of 25 or 250 ng/kg-bw (via osmotic pumps implanted into pregnant dams) and ranging from 2.5 µg/kg-bw per day to 1.0 mg/kg-bw per day (administered via maternal subcutaneous injection) during development, may increase susceptibility to neoplastic transformation in the prostate and mammary gland in adult rats (Ho et al. 2006; Murray et al. 2007; Durando et al. 2007; Markey et al. 2003, 2005; Munoz-de-Toro et al. 2005). However, the limited evidence is insufficient to demonstrate that early bisphenol A exposure, acting independently, could lead to neoplastic events (Newbold et al. 2007; Prins et al. 2007; Ho et al. 2006; Keri et al. 2007; Ichihara et al. 2003). Further research is needed on the role of early life exposures to bisphenol A, in particular via routes most relevant to human exposure, in the process of carcinogenesis (Keri et al. 2007

Genotoxicity

In vitro genotoxicity studies demonstrated a lack of mutagenic activity; however, it was noted that bisphenol A has aneugenic potential and induced morphological transformation and micronuclei formation in the absence of metabolic activation in cultured Syrian hamster embryo cells and Chinese hamster V79 cells, respectively (NTP 2007; ECB 2003; Haighton et al. 2002). In contrast, a large number of standard genotoxicity assays, including the *in vivo* mammalian dominant lethal assay and the mouse micronucleus assay, provided no evidence of mutagenic or clastogenic potential of bisphenol A (ECB 2003; Haighton et al. 2002). Using the ^{32}P-postlabeling technique, bisphenol A has been shown to form DNA adducts *in vivo* in the rat liver; the major adducts were not further characterized and the relevance to human health is unknown. Based on a review of the literature and the lack of significant tumour induction in animal studies, the European Union concluded that "it does not appear that bisphenol A has significant mutagenic potential *in vivo*" (NTP 2007; ECB 2003).

The aneugenic potential of bisphenol A was further investigated following the observation of a spontaneous increase in oocyte meiotic abnormalities in mice attributed to inadvertent exposure to bisphenol A from damage to caging materials (Hunt et al. 2003). The authors subsequently investigated the impact of short-term bisphenol A exposure on meiotic processes during oogenesis. Oral bisphenol A administration to juvenile (20-22days old) female C57BL/6 mice (0, 20, 40, or 100 µg/kg-bw per day) for 6 to 8 days preceding oocyte collection induced a significant increase in chromosome congression failure (1.7%, 5.8%, 7.5% and 10.9% for 0, 20, 40, and 100 µg/kg-bw per day, respectively) and a dose-related increase in meiotic abnormalities (Hunt et al. 2003). Subsequent examination of the effects of bisphenol A on female and male germ cells and somatic cells did not confirm aneugenic potential. There was no evidence of increased hyperploidy or polyploidy, alterations on the timing of meiotic progression or micronuclei induction following bisphenol A exposure via drinking water (7 daily doses of 0.04 mg/kg or for 7 weeks at a concentration of 0.5 mg/L) to C57Bl/6 female mice or via gavage (0, 0.002, 0.02, 0.2 mg/kg) to (102/ElxC3H/E1) F1 male mice (Pacchierotti et al. 2008). Contrary to the induction of aneuploidy, it has been suggested that oocytes from bisphenol A exposed mice respond to disturbances in spindle formation by initiating meiotic arrest (Eichenlaub-Ritter et al. 2008). Thus, the lack of direct evidence of aneugenic induction *in vivo* and very limited data *in vitro* suggests that bisphenol A has no significant aneugenic potential (ECB 2003).

Reproductive and Developmental Toxicity

Multigeneration reproductive toxicity studies in Sprague-Dawley rats and CD-1 mice were evaluated by various jurisdictions and were considered to be valid (ECB 2008; Willhite et al. 2008; NTP 2007; Nakanishi et al. 2007; EFSA 2006; ECB 2003). Reproductive and developmental endpoints were examined following dietary exposure to bisphenol A in rats (0.001, 0.02, 0.30, 5, 50 and 500 mg/kg-bw per day) and mice (0, 0.003, 0.03, 0.3, 5, 50, 600 mg/kg-bw per day) (Tyl et al. 2002; 2007). NOAELs of 5 mg/kg-bw per day and 50 mg/kg-bw per day were identified for adult systemic effects and reproductive and developmental toxicity in rats and mice, respectively. The NOAEL of 5 mg/kg-bw per day for adult systemic effects was based on significantly reduced body weight and reduced body weight gain, reduced absolute and increased relative organ weights in rats, and an increased incidence of minimal to mild hepatocyte hypertrophy in adult male and female mice. The NOAEL of 50 mg/kg-bw per day for reproductive and developmental toxicity was based on effects on the offspring at the highest doses tested. These effects included reduced weanling body weight, exposure-related changes in absolute and relative organ weights in male and female rats, and hypoplasia of seminiferous tubules and delayed acquisition of preputial separation, as well as a slight increase in the incidence of undescended testes in weanling male mice. No changes of toxicologic significance were seen within the dose range of 0.001-5.0 or 0.003-5.0 mg/kg-bw per day in adult or developing rats and mice respectively (Tyl et al. 2002; 2007). The three-generation reproductive toxicity study by Tyl et al. (2002) in rats did not include an estrogenic reference control against which the negative results could be

evaluated. However, the most recent multigeneration report in mice incorporated a dietary 17β-estradiol reference group (Tyl et al. 2007). Developmental toxicity in CD-1 mice and CD rats has been demonstrated to occur following prenatal exposure during major periods of organogenesis (gestational days 6-15), through gavage, at high doses of bisphenol A. Measures of developmental toxicity included percentage resorptions, number of live fetuses per ratio, sex ratio, average fetal body weight per litter and percentage of malformed fetuses. No developmental effects were observed following administration of 640 mg/kg-bw per day (highest dose reported due to severe maternal toxicity at 1280 mg/kg-bw per day) or 1000 mg/kg-bw per day in rats and mice, respectively. Bisphenol A was not teratogenic at any of the administered doses (Morrissey et al. 1987).

Recent studies have shown that chemicals that alter endocrine function, including bisphenol A, can alter the cell function at levels below NOAELs identified in these standard toxicology studies (reviewed in Welshons et al. 2003; vom Saal and Welshons 2006; Welshons et al. 2006). These studies have been described as 'low dose studies'. Effects observed are not necessarily manifested following a linear dose-response relationship and, in several instances, have been found to follow a non-monotonic response curve. Bisphenol A has been considered as a weak environmental estrogen, based on traditional bioassays, as it binds to the estrogen receptor alpha and beta (ERα and ERβ) (Gould et al. 1998; Kuiper et al. 1998; Pennie et al. 1998) with affinity, which is about 10 000 to 100 000-fold weaker than that of 17β-estradiol (Vandenberg et al. 2007). A mode-of-action analysis is beyond the scope of this screening assessment; however, exposure to low doses of bisphenol A has been demonstrated to produce disruptive effects in endocrine organs including the androgen or estrogen responsive tissues, immune system, thyroid hormone function, and developing nervous system (reviewed in Richter et al. 2007; Vandenberg et al. 2007; Wetherill et al. 2007). Evidence suggests that bisphenol A can stimulate the aforementioned cellular responses at very low concentrations through genomic (nuclear estrogen receptor) or non-genomic (membrane-associated or intracellular transduction) mechanisms, with effects on cellular function at doses as low as 1 pM or 0.23 pg/ml (Anway et al. 2005, 2006; Wozniak et al. 2005, Zoeller et al. 2005) (reviewed in Wetherill et al. 2007). Specifically, it has been demonstrated that some of the effects of bisphenol A may be mediated through the cell surface estrogen receptor (GPR30) being equipotent with 17β-estradiol and diethylstilbestrol (Alonso-Magdelena et al. 2005).

There are many studies in the peer-reviewed literature that describe effects in experimental animals resulting from exposure to bisphenol A administered at doses below the NOAELS established in standard toxicological studies for systemic and reproductive/developmental endpoints. Effects observed include changes in prostate growth and development, mammary gland organization, protein induction in the uterus, organization of sexually dimorphic circuits in the hypothalamus, onset of estrus cyclicity, early puberty, body weight, genital malformations and others (reviewed in Richter et al. 2007; Wetherill et al. 2007). Thorough overviews of these studies have been summarized in several recent reviews (NTP 2007; Richter et al. 2007; Willhite et al. 2008). For purposes of the screening assessment, the primary focus will be placed on identification

of alterations considered potentially 'adverse' for the purposes of human health risk assessment.

It should be noted that, due to the finding by Taylor et al. (2008) that the differences between oral and subcutaneous injection toxicokinetics in adults are not likely conserved in neonates, those studies delivering bisphenol A during fetal development and/or early postnatal periods via the subcutaneous (sc) injection route were evaluated for the current assessment (Kato et al. 2003; 2006; Ho et al. 2006; Honma et al. 2002; Nakamura et al. 2006; Suzuki et al. 2002). The neonatal data, using sc injection permits the evaluation of possible effects of ecposure during the early stages of development. While informative, these studies were not the basis for hazard characterization of bisphenol A for human health.

A number of reproductive and developmental studies provide evidence that *in utero* and/or neonatal exposure to doses below the established reproductive/developmental NOAEL of 50 mg/kg-bw per day may result in altered reproductive function and developmental endpoints. Prenatal exposure from gestational day 11 to 17, of CF-1 mice to 0, 2 or 20 µg/kg-bw per day bisphenol A administered orally, resulted in an increase in prostate size in male offspring beginning at 2 µg/kg-bw per day (Nagel et al. 1997), reduced epididymal weight and decreased daily sperm production at doses of 2 and 20 µg/kg –bw per day, respectively (vom Saal et al. 1998). It also resulted in increased postnatal growth in both males and females and early onset of sexual maturation in female offspring, observed following exposure to 2.4 µg/kg-bw per day (Howdeshell et al. 1999). Additionally, CD-1 mice exposed to 10 µg/kg-bw per day, from gestational day 14 to 18, displayed disrupted development of the prostate as shown by an increase in the number and size of the prostate ducts and an increase in the overall volume of the prostate; a malformation of the urethra was also observed (Timms et al. 2005). Honma et al. (2002), using subcutaneous injections of 0, 2 or 20 µg/kg-bw per day bisphenol A to ICR/Jcl mice from gestational day 11 to 17, demonstrated that these low doses administered via a non-oral route produced common alterations. Specifically, they produced altered postnatal growth and early vaginal opening at 20 µg/kg-bw per day. However, female reproductive function was not affected at the first breeding. Furthermore, oral exposures of pregnant and nursing Long-Evans rat dams from gestational day 12 to postnatal day 21 to 2.4 µg/kg-bw per day altered plasma luteinizing hormone levels and decreased testosterone levels in adulthood. This suggests that bisphenol A-dependent effects on androgen biosynthesis by adult leydig cells occurred as a result of targeting a sensitive period during perinatal development. Chronic exposure from weaning at postnatal day 21 to adulthood, representing adolescent exposure, also suppressed androgen biosynthesis by adult leydig cells at doses as low as 2.4 µg/kg-bw per day bisphenol A (Akingbemi et al. 2004). A LOAEL for the reproductive effects of bisphenol A was observed to be 2 µg/kg-bw per day in the aforementioned subset of studies. A non-monotonic (inverted-U) dose-response was observed in several instances.

Conflicting results have been described in various additional reports. Oral bisphenol A exposure to 0.2, 2, 20 or 200 µg/kg-bw per day from gestational day 11 to 17 did not produce reproductive toxicity in studies assessing outcomes in CF-1 mice (Cagen et al.

1999a; Ashby et al. 1999). Nor was there an effect on sperm density or male reproductive organ development following bisphenol A exposure of estrogen-sensitive C57Bl/6N mice during various life stages (Nagao et al. 2002). Notably, in the studies by Cagen et al. (1999a) and Ashby et al. (1999), the responses of the positive control did not differ from either the negative control or bisphenol A. There were no treatment-related effects on progeny following maternal drinking water exposure to 0.01, 0.1, 1.0 or 10 ppm bisphenol A among female Wistar albino rats. The authors conclude that bisphenol A should not be considered a selective reproductive or developmental toxicant (Cagen et al. 1999b). A 2-generation reproduction study using Crj: CD(SD) IGS rats administered bisphenol A orally at doses between 0.2 and 200 µg/kg-bw per day also found no significant adverse treatment-related changes in the multiple reproductive and developmental endpoints assessed (Ema et al. 2001); this study also lacked a positive control for interpretation of negative data. Most recently, assessing the impact of bisphenol A exposure in the male Long Evans hooded rat following oral dosing with 2, 20 or 200 µg/kg-bw per day from gestational day 7 to postnatal 18, Howdeshell et al. (2007) found no significant effect on any male reproductive endpoint investigated. These included male reproductive development, reproductive hormone levels or sperm production.

It is recognized that a number of experimental variables may account for divergent results in response to bisphenol A exposure at low doses: specifically, species and strain differences; variable responses depending on the tissues and/or endpoint(s) assessed; variability in feed with respect to amounts of estrogenic contaminants; inappropriate use or lack of positive controls; as well as the consideration of exposure-related effects that present in a non-monotonic dose-response curve (vom Saal and Hughes 2005; vom Saal et al. 2005a; Richter et al. 2007). Additionally, the dosing period or time of exposure with respect to critical developmental windows and the dosing regimen are important considerations, particularly when assessing alterations resulting from developmental exposures. Furthermore, the nature of the effects are such that it is difficult to characterize the degree to which they would be considered potentially “adverse” and, hence, form the basis of a human health risk assessment.

Developmental Neurotoxicity

Recently, expert panel assessments of the current status of bisphenol A toxicity have identified neurodevelopmental and behavioural alterations as an endpoint of concern. The U.S. National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) (NTP 2007) concluded there was “some” concern that pregnant women, fetuses, infants and children may be susceptible to bisphenol A disruption for neural and behavioural endpoints. “Some” concern for these effects was based on the finding that the bisphenol A literature regarding neural and behavioural effects consistently produced more “positive” studies, as compared to the reproductive and developmental studies, although the endpoints assessed differed between investigators. The level of concern was expressed relative to estimates of exposure for the general population in the United States (NTP 2007). Recently, the NTP finalized its evaluation

of bisphenol A and confirmed some concerns for neurobehavior effects in fetuses, infants, and children at the current level of human exposure (NTP 2008) Additionally, based on existing evidence, the Chapel Hill bisphenol A expert panel states with confidence "that low doses of bisphenol A during development have persistent effects on brain structure, function and behaviour in rats and mice" (vom Saal et al. 2007). Confidence was defined as research areas where the expert panel concluded that there was an agreement of findings from multiple papers from multiple labs. Given these expert panel conclusions, as part of the screening assessment it was considered appropriate to further consider the weight of evidence associated with neurodevelopmental and behavioural studies investigating effects of low dose bisphenol A exposure. These studies are presented in Appendix D and are discussed in further detail below.

Neural development is a complex process beginning in early embryonic development and continuing through different life stages. Precise functioning of the nervous system is critical for all mental, sensory and motor activities, and regulates homeostasis through interaction with the endocrine system (Clancy et al. 2001). An array of behavioural tests has been conducted to evaluate the effect of low dose bisphenol A exposure. Some tests were among those recommended by the recently adopted OECD Developmental Neurotoxicity Study Guideline # 426 (OECD 2007). A number of developmental neurotoxicity endpoints were examined, including locomotor and exploratory activity, learning, social, sexual and maternal behaviour, as well as brain morphology, with a range of exposures from 0.2 to 400 000 µg/kg-bw per day [reviewed in NTP 2007; Richter et al. 2007; Willhite et al. 2008; ECB 2008].

Evaluation of several pivotal studies on neural development and behaviour effects of bisphenol A in rodents showed that *in utero,* perinatal or postnatal exposure to bisphenol A, at levels below the established NOAELs of 50 mg/kg-bw per day for reproductive/developmental effects and 5 mg/kg-bw per day for systemic toxicity in rats and mice reported by Tyl et al. (2002; 2007), which were used in the most recent derivations of reference concentrations of 16-50 µg/kg-bw per day (EFSA 2006; Willhite et al. 2007), may produce some effects on neurobehavioral development in fetal or early postnatal life in rodents. The lowest observed effect in the neurodevelopmental literature was 0.02 µg/kg-bw per day based on changes in estrogen receptor mRNA expression, however, no effects were observed at 2 µg/kg-bw per day; this is suggestive of an inverted U shaped (non-monotonic) dose response phenomenon (Nishizawa et al. 2003; 2005a; 2005b).

While this inverted non-monotonic dose-response relationship is considered to be mediated by both positive and negative feedback effects on estrogenic receptors (Welshons et al. 2003; 2006) or related to physiological responses to estrogenic activity of bisphenol A via the feedback mechanism of the endocrine system of the animals, the issue of non-monotonic dose response curves remains an area of ongoing research with efforts directed at the replication of perturbations at levels of exposure below those demonstrated to have no effects. Furthermore, it has been noted that the shape of the dose-response curves for effects of various estrogenic compounds differs depending on

the endpoint assessed and the dosing regime applied (Melnick et al. 2002). As such, the significance of the LOEL of 0.02 µg/kg-bw per day for bisphenol A to human health risk assessment, however, is difficult to ascertain, particularly in light of the fact that it was the only dose level tested below the NOEL of 2 µg/kg-bw per day and some of the effects were not consistently observed throughout the study periods. In addition, since the studies (exposure period and endpoints measured) were carried out only up to certain embryo development stages, the relevance to the postnatal developmental period for newborns and infants is unknown. An additional study that examined substance-induced changes in brain receptors noted a fluctuating increase in the number of neurons expressing ERα and ERβ after oral administration of 2 µg/kg-bw per day bisphenol A to ICR mice from gestational day 11 to 17. Increases were observed at 5 and 13 weeks, but not at 9 weeks (Kawai et al. 2007). Oral administration of Sprague Dawley rats with 40 µg/kg-bw per day bisphenol A from postnatal day 23–30, thereby targeting the period of juvenile development, resulted in a transient and gender-specific increase in ERα levels in the ventromedial nucleus of the hypothalamus. Changes were noted at postnatal day 37, but not at postnatal day 90, in females only (Ceccarelli et al. 2007). Although these effects may be considered biomarkers of exposure to bisphenol A, and potential precursor events to adverse effects, the biological relevance of these effects for purposes of human health risk assessment is not known.

Volumetric changes of sexually dimorphic regions of the brain have been used as a biomarker for developmental disruption by endocrine-active substances [reviewed in Patisaul and Polston 2008]. Following subcutaneous injection of 100 mg/kg-bw per day to Sprague-Dawley rat pups on postnatal day 1 and 2, no bisphenol A-induced changes in the volumes of the sexually dimorphic nucleus of the pre-optic area (SDN-POA) or the anterioventral periventricular nucleus of the hypothalamus was observed (Patisaul et al. 2006; 2007). Although bisphenol A was shown to disrupt neuronal phenotype by demasculinization of tyrosine hydroxylase (TH) immunoreactive cells and defeminization of ERα/TH double labelled cells in male and female rats, respectively, no functional changes were observed by examination of gonadotropin-releasing hormone (GnRH) neurons (Patisaul et al. 2006; 2007). Thus, neuroanatomical and expression changes detected by immunohistochemistry may not always translate into disruption of neuronal function [reviewed in Patisaul and Polston 2008]. Examination of GnRH neurons as an index of feminization of the AVPV is an indirect means to determine bisphenol A-induced alterations in this sexually dimorphic region of the brain. Assessing the ability of exposed females to generate an LH surge would have been more informative regarding AVPV feminization. Oral administration of 12 – 60 mg/kg- bw per day bisphenol A to male pups from 5 days to 3 weeks of age led to reduced tyrosine hydroxylase immunoreactivity in the midbrain at 7 weeks of age. This occurred concomitantly with an increase in TUNEL-positive cells in the substantia nigra, possibly reflecting neurodegeneration, and reduced mesencephalic dopamine transporter expression (Ishido et al. 2007). Oral exposure to doses of bisphenol A ranging from 3.2 to 320 mg/kg-bw per day also failed to induce volumetric changes to the SDN-POA in female Sprague Dawley rats exposed during gestation and lactation (Kwon 2000). A reversal of gender differences in the volume of the locus coeruleus, a nucleus in the brainstem involved in stress and panic responses, was observed following administration of drinking water at

0.03 and 1.5 mg/kg-bw per day, respectively (Kubo et al. 2001; 2003). A non-monotonic dose response was reported as the extent of reversal was greater at 0.03 mg/kg-bw per day than at 0.3 mg/kg-bw per day (Kubo et al. 2003). Similarly, the normal gender difference in numbers of corticotrophin releasing hormone (CRH) neurons was disrupted in the bed nucleus of the stria terminalis and preoptic area in Wistar rats following gestational and lactational exposure in drinking water to 2.5 mg/kg–bw per day bisphenol A (Funabashi et al. 2004). Homologous sexually dimorphic regions exist in the human brain (Balthazart and Ball, 2007; MacLusky and Naftolin, 1981), however, the relevance to human health risk assessment is uncertain.

Brain receptor expression and immunohistochemical investigations are key for providing mechanistic information, and are useful biomarkers, but relevance to human health risk assessment is uncertain. This is consistent with interpretations in the draft updated Risk Assessment of bisphenol A by the European Union (ECB 2008).

Behavioural testing was used to characterize the effect of bisphenol A exposure on general locomotor and exploratory activity, anxiety and learning and memory in rodents. At 10 µg/kg-bw per day, CD-1 mice exposed via drinking water during perinatal development showed altered maternal behaviour. Interestingly, the differences in nursing behaviour were observed following prenatal or adult exposure, but not following continuous exposure (Palanza et al. 2002). Reduced D-amphetamine-related reinforcing effects in females (Laviola et al. 2005) and decreased or eliminated sex-related behavioural differences (Gioiosa et al. 2007), were also demonstrated in CD-1 mice exposed orally during gestation to 10 µg/kg-bw per day suggesting that exposure to bisphenol A at doses which are well below established NOAEL of 50 mg/kg-bw per day for reproductive/developmental effects may lead to organizational effects during critical periods of brain development in rodents. However, these studies, though, were limited to a single exposure level precluding the evaluation of dose-response. The lowest dose leading to bisphenol A-induced organizational effects in the brain was 10 µg/kg-bw per day in CD-1 mice. It should be recognized that studies were conducted using the same outbred strain of mice (CD-1), the same experimental dosing protocol (single dose, no positive control) and by the same group of researchers in one research institute.

Effects of gestational exposure to 40 µ/kg-bw per day bisphenol A have been noted in rats, including statistically significant gender-specific changes in sexual performance (Farabollini et al. 2002), effects on active and passive maternal behaviour of treated rats (Della Seta et al. 2005), marginally diminished intergroup differences in pain response (Aloisi et al. 2002), altered novelty seeking and impulsive behaviour in females and males, respectively (Adriani et al. 2003), as well as altered play behaviour in female rats (Porrini et al. 2005). In addition, in Sprague-Dawley rats, pubertal exposure to oral doses of 40 µg/kg-bw per day altered behaviour of male rats (Della Seta et al. 2006). These studies, again conducted by a common group of researchers, provide convincing evidence of bisphenol A-induced effects at 40 µg/kg-bw per day and illustrate the implementation of a comprehensive approach. Replication of the aforementioned results by independent researchers is needed.

The effect of bisphenol A exposure on open field behaviour (i.e., an assessment of general locomotor and exploratory activity, grooming and anxiety) (ECB 2008), was not consistent among the available studies. Kubo et al. (2001;2003) administered bisphenol A to Wistar rats during gestation and lactation at 0.03 or 0.3 mg/kg-bw per day in drinking water and noted slightly reduced anxiety-related behaviour in male rats. This behaviour was somewhat increased in females. Rearing behaviour, indicative of exploratory behaviour, observed by Fujimoto et al. (2006), also reflected opposing effects in male and female Wistar rats following 15 μg/kg-bw per day bisphenol A from gestational day 13 to birth. Increased duration of rearing was observed in males and was slightly reduced in females, suggesting that the sex difference in rearing activity had been abolished. No effects on open field behaviour were reported in additional studies assessing the effects of oral bisphenol A exposure during the prenatal and neonatal periods with doses ranging from 40 μg/kg-bw per day to 400 mg/kg-bw per day (Adriani et al. 2003; Negishi et al. 2003; 2004). Notably, the 2-generation study in Sprague Dawley rats by Ema et al. (2001), also reported no effects of oral bisphenol A exposure (0.2, 2, 20, 200 μg/kg-bw per day) on the behavioural endpoints tested in F1 Crj: CD(SD)IGS rats (in open field and water-filled T-maze). It was acknowledged in the report that differences in results to comparative studies may have been due to possible discrepancies in experimental conditions (Ema et al. 2001). However, this large study, though, did not provide data from behavioural measures preventing assessment of the relationship between exposed and control groups.

Some studies have investigated the effect of prenatal and neonatal bisphenol A exposure on anxiety-related behaviour using the hole board test, elevated maze test, forced swimming test and/or light-dark preference chamber (Farabollini, 1999; Negishi et al. 2004; Fujimoto et al. 2006; Ryan and Vanderbergh 2006). Farabollini et al. (1999) found that oral administration of 400 μg/kg-bw per day bisphenol A from gestational day 14 to postnatal day 6 increased anxiety-related behaviour in male and female rats using the hole board test. However, decreased anxiety-related behaviour was noted in males using the elevated plus maze. No effects were evident following administration of 40 μg/kg-bw per day. Ryan and Vanderbergh (2006) reported increased anxiety in females (males not tested) after administration of 200 μg/kg-bw per day bisphenol A from gestational day 3 to postnatal day 21, but not after 2 μg/kg-bw per day, in the light-dark preference chamber. No differences in spatial memory tests were observed. No changes were observed in additional studies assessing the same endpoints. Specifically, applying the elevated plus-maze test in rats, Fujimoto et al. (2006) observed no anxiety-related effects of bisphenol A following drinking water exposure to 15 μg/kg-bw per day from gestational day 13 to birth. Male and female offspring were tested. Negishi et al. (2004) also found no effects on female offspring exposed to 100 μg/kg-bw per day bisphenol A from gestational day 3 to postnatal day 20 (males not tested). Together, these findings illustrate the variable responses observed across gender and species in anxiety-related behavioural endpoints following a range of bisphenol A exposures.

Further research into the effects of bisphenol A exposure focused on disturbances in cognitive function. Of those studies examining bisphenol A-induced effects on learning and memory, no effects were observed by water-filled T-maze following gestational and

lactational exposure to 0.2, 2, 20, 200 µg/kg-bw per day bisphenol A (Ema et al. 2001) (2-generation study in Sprague Dawley rats). Nor were effects observed using passive avoidance testing in Wistar rats after late gestational exposure via drinking water (15 µg/kg-bw per day) (Fujimoto et al. 2006). Interestingly, in the same study, one week of bisphenol A exposure (gestational day 13 to postnatal day 0) altered the normal sex differences in struggling behaviour in the forced swimming test observed in control rats. Exposure increased the immobility of male rats in the forced swimming test, which is indicative of depression-like behaviour called behavioural despair. Male rats appeared to be more sensitive to the effects of bisphenol A on depressive response (Fujimoto et al. 2006). Kubo et al. (2001), assessing the impact in rats of 1.5 mg/kg-bw per day bisphenol A, also administered via drinking water, found that the sexually dimorphic pattern of avoidance behaviour was abolished in exposed animals. Males showed enhanced avoidance memory while that of females was reduced. The authors therefore suggest that this exposure results in demasculinization of males with a corresponding defeminization of females. Using similar tests, Negishi et al. (2003) found no consistent effects on active avoidance following exposure to 4, 40 or 400 mg/kg-bw per day bisphenol A from gestational day 10 to postnatal day 20. Responses were variable and did not follow a dose-related pattern. Further assessment of male F344 rats exposed to 100 µg/kg-bw per day from gestational day 3 to postnatal day 20 showed fewer avoidance responses in trials 1 to 3 of 4 in the active avoidance;. However, no differences were observed between bisphenol A-exposed and control groups in passive avoidance (Negishi et al. 2004). Carr et al. (2003) exposed F344 rats to 100 or 250 µg/kg-bw per day bisphenol A from postnatal day1 to 14 and reported that the normal gender-dependent pattern of maze performance acquisition in the Morris water maze test was disrupted after the low dose only. Exposure to the higher dose significantly reduced spatial information retention in females.

Additionally, a number of studies have been conducted to investigate bisphenol A-induced behavioural alterations in response to pharmacological challenge; specifically, D-amphetamine (Laviola et al. 2005; Adriani et al. 2003), methamphetamine- (Suzuki et al. 2003) or morphine-induced (Mizuo et al. 2004a; 2004b; Narita et al. 2006; 2007) behavioural changes. These studies, using standard testing paradigms, provide evidence for altered stimulated responses following bisphenol A administration and are outlined in Appendix D. Prenatal exposure of CD-1 mice from gestational day 11 to 18 with 10 µg/kg-bw per day bisphenol A eliminated D-amphetamine-induced conditioned place preference in females suggesting exposure-related impairment of brain reward pathways; males were unaffected (Laviola et al. 2005). In rats, the D-amphetamine-induced increment activity in the open field test was significantly reduced in males exposed to 40 µg/kg-bw per day throughout gestation and lactation; in this case, females were unaffected (Adriani et al. 2003). Pharmacological challenge studies are suggestive of potential organizational alterations of the neural system following perinatal bisphenol A exposure. The details of additional studies are not elaborated on as the doses that resulted in significant effects on the neurochemical systems were above the established NOAEL of 50 mg/kg-bw per day for reproductive/developmental effects; altered behaviour was observed following administration of 250 or 400 mg/kg bw per day.

Weight of Evidence Summary of Developmental Neurotoxicity Findings

Several organizations have recently evaluated the developmental neurotoxicity dataset (ECB 2008; EFSA 2006; NTP 2007; NTP 2008; USFDA 2008; Willhite et al. 2008). Specifically, the EU in the draft Updated Risk Assessment of bisphenol A concluded that "overall, taking together the low confidence in the reliability of the developmental neurotoxicity studies and the lack of consistency in the results of behavioural testing, no conclusions can be drawn from these studies" (ECB 2008). Other jurisdictions concluded that the scientific evidence cited supports the conclusion of some concern for neural and behavioural effects of bisphenol A in potentially vulnerable populations (NTP 2007; NTP 2008).

It was considered appropriate to characterize the weight of evidence supporting neurobehavioral effects in rodents following low-dose exposures to bisphenol A from the following perspectives: rigour, power, corroboration/consistency, biological plausibility/coherence.

The rigour of the neurobehavioral dataset was assessed based on use of suitable test methodology, endpoints monitored, and analysis used to report results. A majority of the studies assessing the effect of bisphenol A on neurobehavioral endpoints used acceptable methodology. All studies were published in the peer-reviewed literature. One study (Ema et al, 2001) declared compliance with good laboratory practices (GLP). However, the rigor of several studies was limited by small sample size, incomplete reporting and inadequate statistical analysis. Additionally, only a few studies reported use of concurrent positive controls. There were few common endpoints across studies and it was difficult to evaluate whether related endpoints that are indicative of anxiety, hyperactivity, avoidance, and so forth, respond in a similar manner. As such, the overall rigour of the neurobehavioral dataset is considered limited.

The statistical power of the studies comprising the dataset was considered. Ema et al. (2001) conducted a 2-generation study in rats using the largest number of animals per exposure group. This study may have had sufficient power to detect subtle changes in the endpoints evaluated, however, no effects were observed between exposed and control groups. The majority of other studies used fewer animals per exposure group which may not be sufficient to detect the neurobehavioral alterations associated with exposure to bisphenol A. Diverse study designs and lack of reporting of data, in many cases where similar study designs were followed, precluded meta-analysis methodology. As such, the overall power of the neurobehavioral dataset is considered limited.

With respect to corroboration/consistency (i.e., the replication of findings among similar studies and observation of similar effects under relevant conditions), the limited data preclude characterization of consistency with regard to the qualitative direction of neurobehavioral changes regardless of the statistical significance of reported alterations. Furthermore, apparent inconsistencies in results may be a function of design and/or the behavioural bioassays used to evaluate the potential developmental alterations (e.g., different tests of the same underlying functions, age of testing). For instance,

inconsistencies in the effects of bisphenol A on anxiety-related behaviours should consider that holeboard, light-dark test (emergence test) and elevated-plus mazes all provide measures of anxiety but are also differentially sensitive to other concurrent neurobehavioural effects such as motor effect. The same applies to active and passive avoidance tests (active avoidance is more susceptible to motor effects). Thus, the apparent absence of a consistent pattern of effects may indicate that other factors (such as motor effects) may play a role in the discrepant results. As such, a lack of consistent effects when comparing these measures does not indicate that bisphenol A does not affect anxiety per se. In addition, not only does the comparison between hole board and elevated plus maze appear to include differences in the actual test, but the doses and dosing regimes used in these tests were different: doses of 15, 100 or 400 μg/kg per day bisphenol A with exposure periods from gestational day 13 to birth, gestational day 3 to postnatal day 21 or gestational day 14 to postnatal day 6, respectively. Variations in the dosing period, especially perinatal dosing, can itself have a substantial impact on subsequent effects. As such, there are sufficient methodological differences between these studies to preclude drawing firm conclusions regarding lack of effects of bisphenol A. A consistent finding among studies was that exposure during gestation and/or during early postnatal life consistently represented periods of sensitivity to bisphenol A-induced alterations. Additionally, a consistency in the reported effects regarding alterations of sexually dimorphic behaviours appears to be emerging in rodents. From the current database, it seems likely that the more stongly sexually dimorphic traits are more likely to be disrupted by bisphenol A, and moreover, are those most likely to be detected given the measurements used. The degree of corroboration demonstrated in the dataset is considered limited.

Finally, biological plausibility is an important consideration when considering the weight of evidence. Biological plausibility is informed by investigations of mechanism(s) of action. Bisphenol A produces estrogenic effects via interactions with estrogen receptors (ER). The estrogen receptor family includes the classic ERα, ERβ, and their splice-variants, extranuclear estrogen receptors associated with cell membranes and neuronal synapses (Woolley et al. 2007). Bisphenol A was found to have limited binding affinity with ERα, but it showed a nearly tenfold higher affinity for ERβ. Specifically, the relative binding affinity (RBA) of bisphenol A for ERα and ERβ was 0.05 and 0.33 respectively, whereas RBA for 17b-estradiol was 100 (Kuiper et al., 1997). Strikingly, these chemicals are equally potent at inducing effects through cell membrane ER (Quesada et al. 2002). It is possible that bisphenol A preferentially affects ERβ-containing tissues including the ovary, cardiovascular system and brain (Harris 2007) and those with cell membrane receptors. Importantly, estrogen is a key regulator of organizational and activational processes in the brain of both males and females. Note that the relative contribution of estrogen and androgen to sexually dimorphic behaviours has been demonstrated to differ between species. Specifically, it is generally held that the estrogen-signalling pathway predominates in rodents, while the androgen-signalling pathway plays a more predominate role in humans and non-human primates (Li et al. 2008). Thus, the relative significance of the estrogenic mode of action of bisphenol A in rodents with respect to human relevance requires further investigation.

Typically, demonstration of a dose-response relationship supports biological plausibility. The dose-response relationship following exposure to bisphenol A at doses below the established NOAEL of 50 mg/kg-bw per day for reproductive/developmental effects is complex and not yet completely understood. This is in large part due to a lack of studies consistently assessing multiple endpoints following administration of 3 or more incremental doses of bisphenol A. Regarding the neurobehavioral dataset, a very limited number of studies assessed more than one dose. Therefore, a dose-response relationship could not be established. An attempt was made to compare and evaluate bisphenol A-related changes at similar doses between similar experiments. However, this was not possible due to a number of the aforementioned design limitations. In a few studies which included multiple doses, bisphenol A-related effects were seen at some doses, but not at others (Kubo et al. 2003; Narita et al. 2006; Tando et al. 2007). Further characterization of the dose-response and examination of the significance and relevance of non-linear dose-response relationships are needed for a comprehensive understanding of neurodevelopmental effects associated with bisphenol A exposures in the µg/kg-bw per day range. The weight of evidence for biological plausibility is considered limited.

Overall, taking into consideration rigour, power, corroboration/consistency, and biological plausibility/coherence, the weight of evidence supporting neurobehavioral effects in rodents following exposures to bisphenol A at exposures below established NOAELs for reproductive/developmental toxicity is limited.

An emerging trend from the developmental neurotoxicity studies is that prenatal and/or neonatal bisphenol A exposure may cause organizational effects in the brain leading to disruptions in the sexually dimorphic behaviours in mice and rats. Although the mode of action, and thus biological plausibility, of the reported effects of bisphenol A is not clear, it is not deemed necessary for risk assessment if the evidence indicates an adverse effect (Li et al. 2008). Detailed mechanistic information can reduce uncertainty regarding the relevance of rodent findings to humans, but is not crucial for general toxicity screening. Thus, as highlighted by the NTP (2007), it is not clear whether the reported changes constitute critical adverse toxicological responses, however, the uncertainties associated with the results from neurodevelopmental and behavioural testing warrant concern with respect to human health, in particular during certain sensitive life stages.

Epidemiology Investigations

Epidemiology studies have investigated cohorts exposed to bisphenol A and these are summarized in Vandenberg et al. (2007). Although concentrations of bisphenol A in blood have been associated with a variety of conditions in women including obesity, endometrial hyperplasia, recurrent miscarriages, and polycystic ovarian syndrome, as well as elevated androgen hormone levels, these studies have many limitations including small sample size, potential exposure misclassification, and lack of control of potential confounding factors. These studies did not investigate neurodevelopmental and behavioural effects in the potentially sensitive subpopulations (the pregnant woman/fetus and infant).

Confidence in the toxicological database, overall, is considered moderate. Data for acute toxicity, repeated dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity are available. Although there is an extensive database from which to evaluate the effects of bisphenol A exposure, inconsistencies and experimental limitations exist among studies evaluating reproductive and developmental endpoints. Additionally, several of the studies administered a single dose precluding characterization of dose response.

Characterization of Risk to Human Health

Consistent with the assessment of the European Commission (ECB 2003), which classified bisphenol A as a Category 3 reproductive toxicant, that is a substance which causes concern for human fertility based on sufficient evidence of reproductive toxicity in experimental animals, a critical effect for characterization of risk to human health is reproductive and developmental toxicity.

Exposure estimates for the general population of Canada range from 0.08 µg/kg-bw per day to 4.30 µg/kg-bw per day. Specific exposure estimates for the most highly exposed subpopulation (i.e., infants) range from an average of 0.27 µg/kg-bw per day (maximum 1.75 µg/kg-bw per day) for infants aged 12 to 18 months to an average of 0.50 µg/kg-bw per day (maximum 4.30 µg/kg-bw per day) for infants aged 0 to 1 month. The NOAELs from the multigeneration reproductive toxicity studies in Sprague- Dawley rats and CD-1 mice of 5 mg/kg-bw per day for systemic effects (reduced body weight gain in rats and minimal to mild hepatocyte hypertrophy in adult male and female mice) and 50 mg/kg-bw per day for reproductive and developmental toxicity (Tyl et al. 2002; 2007) are considered an appropriate departure point for characterizing risk to human health from exposure to bisphenol A. Based on the NOAEL of 5 mg/kg-bw per day, margins of exposure for infants exposed to bisphenol A from consumption of infant formula, use of polycarbonate bottles and via environmental media range (Tables 19a and 19b) from 1160 to 18 520. For infants 0-7 months, exposed via the consumption of breastmilk and environmental media (Table 20), margins of exposure to the NOAEL of 5 mg/kg-bw per day range from 3940 to 25 000. For other segments of the population, exposed via the consumption of canned food, use of polycarbonate bottles and environmental media (Table 21), margins of exposure to the NOAEL of 5 mg/kg-bw per day range from 2200 to 62 500. Margins of exposure to the NOAEL of 50 mg/kg-bw per day would be 10-fold higher than those presented above. Although these margins are considered adequate to address interspecies and intraspecies differences with respect to the adverse effects on which the NOAELs are based, the dataset of neurodevelopmental and behavioural studies, though limited when subject to a weight of evidence analysis, is suggestive of potential effects at doses well below these NOAELs.

Specifically, a small number of studies in CD-1 mice reported alterations in behaviour following oral administration of 10 µg/kg-bw per day. These include altered maternal behaviour in dams exposed either as fetuses or during adulthood and decreased or

eliminated sex-related behavioural differences following gestational or gestational and lactational exposures (Palanza et al. 2002; Laviola et al. 2005; Gioiosa et al. 2007). At 40 µg/kg-bw per day, a small number of studies in rats have reported behavioural effects including gender-specific changes in sexual performance, effects on active and passive maternal behaviour, and altered novelty seeking and impulsive behaviour in both sexes in adults whose mothers were administered bisphenol A during gestation and lactation (Farabollini et al. 2002; Della Seta et al. 2005; Adriani et al. 2003). Further supporting the effect of bisphenol A exposure on altered behaviour, oral administration of 100 µg/kg-bw per day in rats during gestation and lactation reduced the number of correct avoidance responses (Negishi et al. 2004), while early postnatal exposure disrupted the normal gender-dependent pattern of maze performance acquisition in the Morris water maze (Carr et al. 2003).

While collectively these studies provide evidence that exposure to bisphenol A during gestation and early postnatal life may be affecting neural development and some aspects of behaviour in rodents, the overall weight of evidence was considered limited from the perspective of rigour (e.g., study design limitations such as conduct of behavioural assessments at a single time point); power (e.g., limited number of animals per test group), corroboration/consistency (limited consistency of studies) and biological plausibility (e.g., certain studies involve use of a single dose, lack of dose response relationship). These limitations make it difficult to determine actual significance of findings to human health risk assessment

The neurodevelopmental and behavioural dataset in rodents, though highly uncertain, is suggestive of potential effects at doses at the same order of magnitude to 1-2 orders of magnitude higher than exposures. Given that toxicokinetics and metabolism data indicate potential sensitivity to the pregnant woman/fetus and infant; and that animal studies suggest a trend towards heightened susceptibility during stages of development in rodents, it is considered appropriate to apply a precautionary approach when characterizing risk. As such, it is concluded that bisphenol A be considered as a substance that may be 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.

Uncertainties in Evaluation of Risk to Human Health and Identification of Research Needs

There are a number of uncertainties related to evaluation of risk to human health, including:

- Uncertainty in the estimation of exposure to all age groups from the use of polycarbonate repeat-use containers due to absence of Canadian use pattern information (e.g., frequency of use, method of use) as well as the availability of studies representative of actual use conditions.

- Uncertainty in the estimation of exposures to infants from the consumption of breastmilk due to lack of surveys measuring concentrations in breastmilk from Canadian women, or surveys involving larger sample sizes. Further exploration of exposures (e.g., food, environmental media) contributing to levels in breastmilk or other biomonitoring would assist in determining which sources of exposure are most important for risk management, if required.

- Uncertainty associated with actual residual levels of bisphenol A in polymers used to manufacture consumer products, such as epoxy adhesives, toys and cosmetics, and uncertainty associated with the assumptions made to calculate general population exposure from use of these products.

- Uncertainty associated with estimating intake of bisphenol A from the consumption of fresh fish and other fresh foods due to the lack of surveys measuring concentrations in Canada or elsewhere.

- The adequacy of the database on reproductive/developmental effects below the established NOAEL of 50 mg/kg-bw per day for these effects in rodents is an uncertainty. Limitations with respect to rigour, power, corroboration/consistency, and biological plausibility/coherence exist.

- Interspecies variation. Uncertainties exist regarding toxicokinetics and metabolism differences between rodents and humans. Rodents clear bisphenol A in the faeces via biliary excretion of the glucuronide (EFSA 2006). Humans, on the other hand, clear bisphenol A primarily via urine after glucuronidation (Snyder et al. 2000; Volkel et al. 2002). It has been suggested that the fetus from rats and humans have little glucuronidation activity (Matsumoto et al. 2002; Ring et al. 1999; Coughtrie et al. 1988). Evidence suggests that the human fetus metabolizes bisphenol A less extensively as compared to the rat fetus. Thus, the human fetus may be more prone to effects of bisphenol A (Elsby et al. 2001). These important differences in toxicokinetics and metabolism introduce uncertainty in extrapolating from rodents to humans. Uncertainties also exist regarding relevance to humans of potential effects of bisphenol A on brain function in rodents. Species differences in brain development are important (Seegal 2001). The brain of a newborn rat pup is comparable to that of a human fetus nearing the third trimester of pregnancy. Conversely, the human newborn might be compared with a 2- to 3-week-old rat pup (Morreale et al. 2004). The mechanism(s) by which bisphenol A exerts estrogenic effects depends on many factors, including species, and this is an additional uncertainty with respect to interspecies extrapolation.

- With regards to intraspecies variation, available data indicate that the pregnant female/fetus and infant are potentially sensitive populations. Actual levels of free bisphenol A in the fetus however remains an uncertainty. Uncertainty also exists with respect to critical windows of susceptibility during in utero and postnatal development and potential subsequent long-term effects.

Research needs include the following:

- Canadian monitoring data for certain environmental media (e.g., air, soil, drinking water) are lacking or limited. Such data would decrease uncertainty regarding the contribution of these media to exposure among the general population.

- Biomonitoring data for the general population of Canada (including pregnant women and children younger than 6 years old) would decrease uncertainty regarding the exposure assessment. Investigations into accuracy of spot urine samples in predicting daily exposures are needed.

- Studies investigating the underlying process of migration from polycarbonate would inform risk management. To date, studies in this area report inconsistent results, with some study investigators indicating that migration rates will decrease with use and others indicating that migration rates remain relatively constant throughout the life of the container.

- Epidemiological studies are needed to establish relationships between bisphenol A exposure and health outcomes for sensitive subpopulations.

- Further exploration of mechanisms by which low dose exposure to bisphenol A may induce alterations in the developing reproductive system in males and females.

- Further exploration of molecular mechanisms by which low doses of bisphenol A may disrupt the estrogen and thyroid hormone homeostasis, as well as the impact on the central nervous system during critical windows of development.

- Dose response studies using environmentally relevant levels of bisphenol A and investigation of mechanisms responsible for various dose-response curves (linear versus non-monotonic dose response relationships) and its relevance to human health risk assessment.

- Studies on the effects of bisphenol A on the sexual differentiation of the brain and neurobehavioural endpoints conducted in accordance to OECD guidelines for developmental neurotoxicity.

- Investigation of the effects of bisphenol A exposure during precise age windows that correspond with specific aspects of *in utero* and early postnatal development of the neuraxis that are the most critical to the development of neurobehavioural features. For example, sensory and motor differences are generally brainstem, anxiety-related activity involves mid-brain and lower telencephalon, species-typical behaviour patterns are most likely lower telencephalon and learning and memory differences involve the cortex.

- Further assessment of bisphenol A-induced changes on the reproductive and nervous system during early and later stages of development including adolescence and adulthood.

- Further research is needed to identify the doses and ages or windows of sensitivity that are the most effective in producing developmental disturbances.

- Assessment of tissue levels of bisphenol A following repeat low dose exposures via oral or parenteral routes to characterize the actual versus administered dose.

- Comprehensive evaluation of the potential of bisphenol A to initiate or promote carcinogenicity from exposure during sensitive stages of development.

- An emphasis on research to establish more precisely the magnitude of effect to better understand the impact of bisphenol A exposures is required.

Conclusion

Based on the information presented in this screening assessment, and applying a precautionary approach, it is concluded that bisphenol A is entering or may be 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.

Based on the information presented in this screening assessment, and applying a precautionary approach, it is concluded that bisphenol A be considered as a substance that may be 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 bisphenol A does meet the criteria in paragraphs 64(a) and 64(c) of CEPA 1999.

References

Aarab N, Lemaire-Gony S, Unruh E, Hansen PD, Larsen BK, Andersen OK, Narbonne JF. 2006. Preliminary study of responses in mussel (*Mytilus edulis*) exposed to bisphenol A, diallyl phthalate and tetrabromodiphenyl ether. Aquat Toxicol 785:586-592.

[ACD] ACD/pKa batch. [Estimation Model]. 2005. Version 9.04. Toronto (ON). Advanced Chemistry Development. Available from: www.acdlabs.com

Adriani W, Seta DD, ssi-Fulgheri F, Farabollini F, Laviola G. 2003. Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A. Environ Health Perspect 111(4):395-401.

[AIES] Artificial Intelligence Expert System. 2003-2005. Version 1.25. Ottawa (ON): Environment Canada. Model developed by Stephen Niculescu. Available from: Environment Canada, Existing Substances Division, New Substances Division, Ottawa, K1A 0H3.

Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. 2004. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. Endocrinology 145(2):592-603.

Alexander HC, Dill DC, Smith LW, Guiney PD, Dorn P. 1988. Bisphenol A: Acute aquatic toxicity. Environ Toxicol Chem 7(1):19-26.

Aloisi AM, Della SD, Rendo C, Ceccarelli I, Scaramuzzino A, Farabollini F. 2002. Exposure to the estrogenic pollutant bisphenol A affects pain behavior induced by subcutaneous formalin injection in male and female rats. Brain Res 937(1-2):1-7.

Alonso-Magdalena P, Laribi O, Ropero AB, Fuentes E, Ripoll C, Soria B, Nadal A. 2005. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic alpha-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. Environ Health Perspect 113(8):969-977.

Anway MD, Cupp AS, Uzumcu M, Skinner MK. 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308(5727):1466-1469.

Anway MD, Skinner MK. 2006. Epigenetic transgenerational actions of endocrine disruptors. Endocrinology 147(6 Suppl):S43-S49.

[AOPWIN] Atmospheric Oxidation Program for Windows [Estimation Model]. 2000. Version 1.91**.** Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from www.epa.gov/oppt/exposure/pubs/episuite.htm

Arcus-Arth A, Krowech G, Zeise L. 2005. Breast milk and lipid intake distributions for assessing cumulative exposure and risk. J Exposure Anal Environ Epidemiol 15:357-365.

Aronson D, Boethling R, Howard P, Stiteler W. 2006. Estimating degradation half-lives for use in chemical screening. Chemosphere 63: 1953-1960.

Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. QSAR Comb Sci 22(3): 337-345.

Ashby J, Tinwell H, Haseman J. 1999. Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. Regul Toxicol Pharmacol 30(2 Pt 1):156-166.

[ASTER] Assessment Tools for the Evaluation of Risk [Internet]. 1999. Duluth (MN): US Environmental Protection Agency, Mid-Continent Ecology Division. Available from: http:www.epa.gov/med/Prods_Pubs/aster.htm Restricted access.

Azarpazhooh A, Main PA. 2008. Is There A Risk of Harm or Toxicity in the Placement of Pit and Fissure Sealant Materials? A Systematic Review. J Canadian Dental Association 2008;74(2):179-183

Balthazart J, Ball G. 2007. Topography in the preoptic region: Differential regulation of appetitive and consummatory male sexual behaviors. Front Neuroendocrinol 28(4): 161-178.

Basheer C, Lee HK, Tan SK. 2004. Endocrine dsrupting alkylphenols and bisphenol-a in coastal waters and supermarket seafood from Singapore. Marine Pollution Bulletin. 48: 1145-1167.

Bayer AG. 1988. Manufacturers Safety Data Sheet [cited in European Chemical Bureau 2003].

Bayer AG. 1999a. Fish, prolonged toxicity test (*Brachydanio rerio*) 14 day study of Bisphenol-A. Study Number 707 A/98 Fl. Leverkusen, Germany [cited in Staples et al. 2002].

Bayer AG. 1999b. Fish, juvenile growth test (*Oncorhynchus mykiss*) of Bisphenol-A. Study Number 707 A/98FF. Leverkusen, Germany [cited in Staples et al. 2002].

[BCFWIN] BioConcentration Factor Program for Windows [Estimation Model]. 2000. Version 2.15**.** Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Biedermann-Brem S, Grob K, Fjeldal P. 2007. Release of bisphenol A from polycarbonate baby bottles: mechanisms of formation and investigation of worst case scenarios. Norwegian Food Safety Authority. Available from: http://matportalen.no/Matportalen/artikler/2007/11/taateflasker_av_polykarbonat_er_trygge_i_bruk

Belfroid A, van Velzen M, van der Horst B, Vethaak D. 2002. Occurrence of bisphenol A in surface water and uptake in fish: evaluation of field measurements. Chemosphere 49: 97-103.

Benedetti, BM, Baltes EL. 2003. Drug metabolism and disposition in children. Fund Clin Pharmacol. 17:281-299.

Biles JE, McNeal TP, Begley TH. 1997. Determination of Bisphenol A migrating from epoxy can coatings to infant formula liquid concentrates. J Agric Food Chem. 45(9): 4697-4700.

[BIOWIN] Biodegradation Probability Program for Windows [Estimation Model]. 2000. Version 4.02**.** Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: http: www.epa.gov/oppt/exposure/pubs/episuite.htm

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. Chemosphere 30(4):741-752.

Bonnell Environmental Consulting. 2001. Conducting the multi-media exposure assessment of new substances in Canada. Report submitted to Environment Canada, New Substances Division, Hull, Quebec.

Boyd GR, Reemtsma H, Grimm DA, Mitra S. 2003. Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. SCi Total Environ 311(1-3):135-149.

Boyd GR, Palmeri JM, Zhang S, Grimm DA. 2004. Pharmaceuticals and personal care products (PPCPs) and endocrine disrupting chemicals (EDCs) in stormwater canals and Bayou St. John in New Orleans, Louisiana, USA. 2004. Sci Total Environ 333:137-148.

Brede C, Fjeldal P, Skjevrak I, Herikstad H. 2003. Increased migration levels of bisphenol A from polycarbonate baby bottles after dishwashing, boiling and brushing. Food Add Contam 7:684-689.

Brennan SJ, Brougham CA, Roche JJ, Fogarty AM. 2006. Multi-generational effects of four selected environmental oestrogens on *Daphnia magna*. Chemosphere 64:49-55.

Brian JV, Harris CA, Scholze M, Kortenkamp A, Booy P, Lamoree M, Pojana G, Jonkers N, Marcomini A, Sumpter JP. 2007. Evidence of estrogenic mixture effects on the reproductive performance of fish. Environ Sci Technol 4:337-344.

Calafat AM, Ye X, Wong L-Y, Reidy JA, Needham LL. 2008. Exposure of the U.S. Population to Bisphenol A and 4-tertiary-Octylphenol:2003-2004. Environmental Health Perspectives 116(1): 39-44

Cagen SZ, Waechter JM, Jr., Dimond SS, Breslin WJ, Butala JH, Jekat FW, Joiner RL, Shiotsuka RN, Veenstra GE, Harris LR. 1999a. Normal reproductive organ development in CF-1 mice following prenatal exposure to bisphenol A. Toxicol Sci 50(1):36-44.

Cagen SZ, Waechter JM Jr, Dimond SS, Breslin WJ, Butala JH, Jekat FW, Joiner RL, Shiotsuka RN, Veenstra GE, Harris LR. 1999b. Normal reproductive organ development in Wistar rats exposed to bisphenol A in the drinking water. Regul Toxicol Pharmacol. 30(2 Pt 1):130-9.

Campbell PM, Fernandez MP, Royston S, Smith JL, van Poppelen P, Ikonomou MG, Devlin RH. 2006. Male coho salmon (*Oncorhynchus kisutch*) exposed to a time-course of urban sewage effluent exhibit a sporadic low incidence of sex reversal and intersex. Water Qual Res J Can 41(3):235-243.

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, c. 33, Canada Gazette. Part III. vol. 22, no. 3. Available from: http://canadagazette.gc.ca/partIII/1999/g3-02203.pdf

Canada. 2000. *Canadian Environmental Protection Act: Persistence and Bioaccumulation Regulations,* P.C. 2000-348, 23 March, 2000, SOR/2000-107, Canada Gazette. Part II, vol. 134, no. 7, p. 607−612. Available from: http://canadagazette.gc.ca/partII/2000/20000329/pdf/g2-13407.pdf

Canada, Dept. of the Environment, Dept. of Health. 2006. *Canadian Environmental Protection Act, 1999*: *Notice of intent to develop and implement measures to assess and manage the risks posed by certain substances to the health of Canadians and their environment*. Canada Gazette, Part I, vol. 140, no. 49, p. 4109–4117. Available from: http://canadagazette.gc.ca/partI/2006/20061209/pdf/g1-14049.pdf.

Canada, Dept. of the Environment, Dept. of Health. 2007. *Canadian Environmental Protection Act, 1999: Notice of second release of technical information relevant to substances identified in the Challenge.* Canada Gazette, Part I, vol. 141. no. 5, p. 162–165. Available from: http://canadagazette.gc.ca/partI/2007/20070203/pdf/g1-14105.pdf

Cao X, Corriveau J. 2008. Determination of bisphenol A in water by isotope dilution headspace solid phase microextraction and gas chromatography/mass spectrometry without derivatization. J AOAC Int 91:622-629.

Cao X, Dufresne G, Belisle S, Clement G, Falicka M, Beraldin F, Rulibikiye A. 2008. Levels of bisphenol A in canned liquid infant formula products in Canada and dietary intake estimates. J Agric Food Chem 10.1021/jf8008712.

Carr R, Bertasi F, Betancourt A, Bowers S, Gandy BS, Ryan P, Willard S. 2003. Effect of neonatal rat bisphenol A exposure on performance in the Morris water maze. J Toxicol Environ Health A 66(21):2077-88.

Ceccarelli I, Della SD, Fiorenzani P, Farabollini F, Aloisi AM. 2007. Estrogenic chemicals at puberty change ERalpha in the hypothalamus of male and female rats. Neurotoxicol Teratol 29(1):108-115.

Chen M, Ohman K, Metcalfe C, Ikonomou MG, Amatya PL, Wilson J. 2006. Pharmaceuticals and endocrine disruptors in wastewater treatment effluents and in the water supply system of Calgary, Alberta, Canada. Water Qual Res J Can 41(4):351-364.

Chin YP, Miller PL, Zeng L, Cawley K, Weavers LK. 2004. Photosensitized degradation of bisphenol A by dissolved organic matter. Environ Sci Technol 38: 5888-5894.

Chu SG, Shahmiri S, Ciborowski JJH, Hamaed A, Haffner GC, Drouillard KG, and Letcher RJ. 2005. Polybrominated diphenyl ethers (PBDEs), including BDE209, and tetrabromobisphenol A (TBBPA) and degradation products in sediments from Lake Erie. Poster presented at SETAC North America 26th Annual Meeting, November 13-17, Baltimore, MD.

Clancy B, Darlington B, Finlay BL. 2001. Translating developmental time across mammalian species. Neurosci 105(1):7-17.

Coughtrie MW, Burchell B, Leakey JE, Hume R. 1988. The inadequacy of perinatal glucuronidation: immunoblot analysis of the developmental expression of individual UDP-glucuronosyltransferase isoenzymes in rat and human liver microsomes.
Mol Pharmacol 34(6):729-735.

Cousins IT, Staples CA, Klečka GM, Mackay D. 2002. A multimedia assessment of the environmental fate of bisphenol A. Human and Ecological Risk Assessment (HERA). 8: 1107-1136.

[CPOPs] Canadian POPs Model. 2008. Gatineau (QC): Environment Canada, Existing Substances Division; Bourgas (BG): Laboratory of Mathematical Chemistry. [Model developed based on Mekenyan et al. 2005]. Available upon request.

D'Antuono A, Dall'Orto VC, Lo Balbo A, Sobral S, Rezzano I. 2001. Determination of bisphenol A in food-simulating liquids using LCED with a chemically modified electrode. J Agric Food Chem. 49: 1098-1101.

Dash C, Marcus M, Terry PD. 2006. Bisphenol-A: Do recent studies of health effects among humans inform the long-standing debate? Mutation Research. 613:68-75.

Dekant W, Volkel W. 2008. Human exposure to bisphenol A by biomonitoring: Methods, results and assessment of environmental exposures. Toxicol Appl Pharmacol. 228(1):114-134.

Della Seta D, Minder I, ssi-Fulgheri F, Farabollini F. 2005. Bisphenol-A exposure during pregnancy and lactation affects maternal behavior in rats. Brain Res Bull 65(3):255-260.

Della Seta D, Minder I, Belloni V, Aloisi AM, ssi-Fulgheri F, Farabollini F. 2006. Pubertal exposure to estrogenic chemicals affects behavior in juvenile and adult male rats. Horm Behav 50(2):301-307.

Dessi-Fulgheri F, Porrini S, Farabollini F. 2002. Effects of Perinatal Exposure to Bisphenol A on Play Behavior of Female and Male Juvenile Rats. Environ Health Perspect. 110 (Suppl 3):403-407.

Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O. 2005. Base-line model for identifying the bioaccumulation potential of chemicals. SAR QSAR Environ Res 16:531–554.

Dirschl H J. 1969. Foods of lesser scaup and blue-winged teal in the Saskatchewan River Delta. J. Wildl. Manage. 33: 77-87 [cited in USEPA 1993].

Domoradzki JY, Pottenger LH, Thornton CM, Hansen SC, Card TL, Markham DA, Dryzga MD, Shiotsuka RN, Waechter JM, Jr. 2003. Metabolism and pharmacokinetics of bisphenol A (BPA) and the embryo-fetal distribution of BPA and BPA-monoglucuronide in CD Sprague-Dawley rats at three gestational stages. Toxicol Sci 76(1):21-34.

Domoradzki JY, Thornton CM, Pottenger LH, Hansen SC, Card TL, Markham DA, Dryzga MD, Shiotsuka RN, Waechter JM, Jr. 2004. Age and dose dependency of the pharmacokinetics and metabolism of bisphenol A in neonatal sprague-dawley rats following oral administration. Toxicol Sci 77(2):230-242.

Dorn PB, Chou CS, Gentempo JJ. 1987. Degradation of bisphenol A in natural waters. Chemosphere 16(7):1501-1507.

Dow Chemical Canada. 2007. Submission to Environment Canada under section 70, *Canadian Environmental Protection Act*, 1999.

Dow Europe. 1993. SIDS Profile for Bisphenol A. Horgen, Switzerland [cited in Staples et al. 1998].

Duft M, Schulte-Oehlmann U, Weltje L, Tillmann M, Oehlmann J. 2003. Stimulated embryo production as a parameter of estrogenic exposure via sediments in the freshwater mudsnail *Potamopyrgus antipodarum*. Aquat Toxicol 64:437-449.

Durando M, Kass L, Piva J, Sonnenschein C, Soto AM, Luque EH, Munoz-de-Toro M. 2007. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect 115(1):80-86.

Earls AO, Clay CA, Braybrook JH. 2000. Preliminary Investigation into the Migration of Bisphenol-A from Commercially-Available Polycarbonate Baby Feeding Bottles. LGC Technical Report LGC/DTI/2000/005. [cited in EFSA 2006].

[ECB] European Chemicals Bureau. 2003. European Union Risk Assessment Report. CAS 80-05-7. 4,4'-isopropylidenediphenol (Bisphenol A). Vol. 37. European Commission, European Chemicals Bureau, Existing Substances.

[ECB] European Chemicals Bureau. 2008. European Union Risk Assessment Report Draft: Updated risk assessment of 4,4'-isopropylidenediphenol (Bisphenol A) (CAS No. 80-05-7; EINECS No. 201-245-8). European Commission, European Chemicals Bureau, Existing Substances.

[ECOSAR] Ecological Structural Activity Relationships [Internet]. 2004. Version 0.99h. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[EFH] Exposure Factors Handbook. 2000. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Washington, DC. EPA 600/P- 95/ 002Fa – c. Available online at http://www.epa.gov/ncea/efh/

[EFSA] European Food Safety Authority. 2006. Opinion of the scientific panel on food additives, flavourings, processing aids and materials in contact with food on a request from the Commission related to 2,2-bis(4-hydroxyphenyl)propane (Bisphenol A) Question number EFSA-Q-2005-100. The EFSA Journal, 428:1-75. Available from: http://www.efsa.europa.eu/en/science/afc/afc_opinions.html

[EFSA] European Food Safety Authority. 2008. Toxicokinetics of bisphenol A. Scientific opinion of the panel on food additives, flavourings, processing aids and material in contact with food (AFC) on a request from the commission on the toxicokinetics of bisphenol A. The EFSA Journal, 759:1-10. Availble from: http://www.efsa.eu.int/cs/BlobServer/Scientific_Opinion/afc_ej759_bpa_toxicokinetics_sum_en.pdf?ssbinary=true

Ehlert KA, Beumer CWE, Groot MCE. 2008. Migration study of bisphenol A into water from polycarbonate baby bottles during microwave heating. (In Press).

Eichenlaub-Ritter U, Vogt E, Cukurcam S, Sun F, Pacchierotti F, Parry J. 2008. Exposure of mouse oocytes to bisphenol A causes meiotic arrest but not aneuploidy. Mutat Res 651(1-2):82-92.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15(1): 30-38.

Elsby R, Maggs JL, Ashby J, Park BK. 2001. Comparison of the modulatory effects of human and rat liver microsomal metabolism on the estrogenicity of bisphenol A: implications for extrapolation to humans. J Pharm Exp Ther. 297(1):103-113.

Ema M, Fujii S, Furukawa M, Kiguchi M, Ikka T, Harazono A. 2001. Rat two-generation reproductive toxicity study of bisphenol A. Reprod Toxicol 15(5):505-523.

Emerson, Cuming. 2004. Material Safety Data Sheet. Product Name: ECCOBOND© 286 White, Part B. Epoxy adhesive (hardener). MSDS ID: EC180729. (last updated 20 December 2004; cited 24 January 2008). Available from: http://www.ifa.hawaii.edu/instr-shop/MSDS/Emerson%20&%20Cuming%20Eccobond%20286%20B.pdf

Environment Canada. 2007a. Data for Batch 2 substances collected under the *Canadian Environmental Protection Act*, 1999, Section 71: *Notice with respect to certain Batch 2 Challenge substances*. Data prepared by Environment Canada, Existing Substances program.

Environment Canada. 2007b. Voluntary submission of data for Batch 2 substances collected under the Government of Canada's Chemical Management Plan Challenge initiative. Prepared by: Environment Canada, Existing Substances Division.

Environmental Defence. 2008. Toxic Baby Bottles in Canada. pp 17.

[EPIWIN] Estimation Program Interface for Microsoft Windows [Estimation Model]. 2000. Version 3.12. Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[EQC] Equilibrium Criterion Model. 2003. Version 2.02. Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. Available from: www.trentu.ca/academic/aminss/envmodels/models/EQC2.html

European Communities. 1994. Technical guidance document, Part I –V, ISBN 92-827-801 [1234], as described in EC Regulation 1488/94 O.J. No L 161, 29/06/1994 p. 0003-0011.

[EWG] Environmental Working Group. Bisphenol A: Toxic Plastics Chemical in Canned Food A Survey of Bisphenol A in U.S. Canned Foods. March 5, 2007. Available online at: http://www.ewg.org/reports/bisphenola

Facciolo RM, Madeo M, Alò R, Canonaco M, Dessì-Fulgheri F. 2005. Neurobiological effects of bisphenol A may be mediated by somatostatin subtype 3 receptors in some regions of the developing rat brain. Toxicol Sci 88(2):477-84.

Farabollini F, Porrini S, ssi-Fulgherit F. 1999. Perinatal exposure to the estrogenic pollutant bisphenol A affects behavior in male and female rats. Pharmacol Biochem Behav 64(4):687-94.

Farabollini F, Porrini S, Della SD, Bianchi F, ssi-Fulgheri F. 2002. Effects of perinatal exposure to bisphenol A on sociosexual behavior of female and male rats. Environ Health Perspect 110 Suppl 3:409-14.

Fent G, Hein WJ, Moendel MJ, Kubiak R. 2003. Fate of ^{14}C-bisphenol A in soils. Chemosphere 51: 735-746.

Fernandez MF, Arrebola JP, Taoufiki J, Navalon A, Ballesteros O, Pulgar R, Vilchez JL, Olea N. 2007. Bisphenol A and chlorianted derviatives in adipose tissue of women. Repro Tox 24:259-264.

Fernandez MP. 2007. Personal communication with Environment Canada regarding clarification of environmental concentrations in Campbell et al. 2006. Electronic mail dated 28 October 2007.

Fernandez MP, Campbell PM, Ikonomou MG, Devlin RH. 2007a. Assessment of environmental estrogens and the intersex/sex reversal capacity for Chinook salmon (*Oncorhynchus tshawytscha*) in primary and final municipal wastewater effluents. Environ Int 33: 391-396.

Fernandez MP, Ikonomou MG, Buchanan I. 2007b. An assessment of estrogenic organic contaminants in Canadian wastewaters. Sci Total Environ 373:250-269.

Ferrara G, Loffredo E, Senesi N. 2006. Phytotoxic, clastogenic and bioaccumulation effects of the environmental endocrine disruptor bisphenol A in various crops grown hydroponically. Planta 223:910-916.

Fjeld E, Schlabach M, Berge JA, Eggen T, Snilsberg P, Källberg G, Rognerud S, Enge EK, Borgen A, Gundersen H. 2004. Screening of selected new organic contaminants – brominated flame retardants, chlorinated paraffins, bisphenol-A and trichlosan. Norwegian Institute for Water Research (NIVA) report for the Norwegian Pollution Control Authority (SFT), Oslo, Norway.

Fujimoto T, Kubo K, Aou S. 2006. Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. Brain Res 1068(1):49-55.

Funabashi T, Kawaguchi M, Furuta M, Fukushima A, Kimura F. 2004. Exposure to bisphenol A during gestation and lactation causes loss of sex difference in corticotropin-releasing hormone-immunoreactive neurons in the bed nucleus of the stria terminalis of rats. Psychoneuroendocrinology 29(4):475-485.

Fung EYK, Ewoldsen NO, St. Germain HA, Jr. Marx DB, Miaw C-L, Siew C, Chou H-N, Gruinger SE, Meyer DM. 2000. Pharmokinetics of Bisphenol A Released from a dental sealant. J Am Dent Association 2000; 131:51-58.

Furuya M., K. Adachi, S. Kuwahara, K. Ogawa and Y. Tsukamoto. 2006. Inhibition of male chick phenotypes and spermatogenesis by Bisphenol-A. Life Sciences 78(15): 1767-1776.

Gioiosa L, Fissore E, Ghirardelli G, Parmigiani S, Palanza P. 2007. Developmental exposure to low-dose estrogenic endocrine disruptors alters sex differences in exploration and emotional responses in mice. Horm Behav 52(3):307-316.

Goto Y, Kitamura S, Kashiwagi K, Oofusa K, Tooi O, Yoshizato K, Sato J, Ohta S, Kashiwagi A. 2006. Suppression of amphibian metamorphosis by bisphenol A and related chemical substances. J Health Sci 52(2):160-168.

Gould JC, Leonard LS, Maness SC, Wagner BL, Conner K, Zacharewski T, Safe S, McDonnell DP, Gaido KW. 1998. Bisphenol A interacts with the estrogen receptor alpha in a distinct manner from estradiol. Mol Cell Endocrinol 142(1-2):203-214.

Haighton LA, Hlywka JJ, Doull J, Kroes R, Lynch BS, Munro IC. 2002. An evaluation of the possible carcinogenicity of bisphenol A to humans. Regul Toxicol Pharmacol 35(2 Pt 1):238-254.

Hanai Y. 1997. Bisphenol-A Eluted from Nursing Bottles. Unpublished Data. Environmental Science Research Center, Yokohama National University. [cited in EFSA 2006; cited in EFSA text as 1977].

Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, electronic, and steric constants. Washington (DC): American Chemical Society.

Harris HA. 2007. Estrogen receptor-beta: recent lessons from in vivo studies. Mol Endocrinol 21:1-13.

Haubruge E, Petit F, Gage MJG. 2000. Reduced sperm counts in guppies (*Poecilia reticulata*) following exposure to low levels of tributyltin and bisphenol A. Proc R Soc Lond B Biol Sci 267(1459):2333-2337.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate.

Heinonen J, Honkanen J, Kukkonen JVK, Holopainen IJ. 2002. Bisphenol A accumulation in the freshwater clam *Pisidium amnicum* at low temperatures. Arch Environ Contam Toxicol 43:50-55.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2000. Version 3.10. Washington (DC): U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Hine J, Mookerjee PK. 1975. Structural effects on rates and equilibriums. XIX. Intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J Org Chem 40(3): 292-298.

Hirano M, Ishibashi H, Matsumura N, Nagao Y, Watanabe N, Watanabe A, Onikura N, Kishi K, Arizono K. 2004. Acute toxicity responses of two crustaceans, Americamysis bahia and Daphnia magna, to endocrine disruptors. J Health Sci 50(1): 97-100.

Ho SM, Tang WY, Belmonte de FJ, Prins GS. 2006. Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. Cancer Res 66(11):5624-5632.

Honma S, Suzuki A, Buchanan DL, Katsu Y, Watanabe H, Iguchi T. 2002. Low dose effect of in utero exposure to bisphenol A and diethylstilbestrol on female mouse reproduction. Reprod Toxicol 16(2):117-122.

Honma T, Miyagawa M, Suda M, Wang RS, Kobayashi K, Sekiguchi S. 2006. Effects of perinatal exposure to bisphenol A on brain neurotransmitters in female rat offspring. Ind Health 44(3):510-24.

Howard PH 1989. Handbook of environmental fate and exposure data for organic chemicals. Volume I. Large production and priority pollutants. Chelsea (MI): Lewis Publishers.

Howdeshell KL, Furr J, Lambright CR, Wilson VS, Ryan BC, Gray LE, Jr. 2007. Gestational and lactational exposure to ethinyl estradiol, but not bisphenol A, decreases androgen-dependent reproductive organ weights and epididymal sperm abundance in the male long evans hooded rat. Tox Sci 2007 Dec 20.

Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. 1999. Exposure to bisphenol A advances puberty. Nature 401(6755):763-764.

Huff J. 2001. Carcinogenicity of bisphenol-A in Fischer rats and B6C3F1 mice. Odontology 89(1):12-20.

Huff J. 2002. Carcinogenicity of bisphenol A revisited. Toxicol Sci 70(2):281-3; author reply 283-4.

Hunt PA, Koehler KE, Susiarjo M, Hodges CA, Ilagan A, Voigt RC, Thomas S, Thomas BF, Hassold TJ. 2003. Bisphenol a exposure causes meiotic aneuploidy in the female mouse. Curr Biol 13(7):546-553.

Ichihara T, Yoshino H, Imai N, Tsutsumi T, Kawabe M, Tamano S, Inaguma S, Suzuki S, Shirai T. 2003. Lack of carcinogenic risk in the prostate with transplacental and lactational exposure to bisphenol A in rats. J Toxicol Sci 28(3):165-171.

Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. 2002. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 17(11):2839-2841.

[INSPQ] Institut National de Santé Publique du Québec. 2001. A Practical Guide to Baby Care.

Ishido M, Yonemoto J, Morita M. 2007. Mesencephalic neurodegeneration in the orally administered bisphenol A-caused hyperactive rats. Toxicol Lett 173(1):66-72.

Jagnytsch O, Krüger A, Opitz R, Lutz I, Behrendt H, Kloas W. 2006. Environmental pollution by bisphenol A: sources and fate in the Elbe basins and biological effects. In: Annual Report 2006 for the Leibniz-Institute of Freshwater Ecology and Inland Fisheries (IGB). C. Wolter and C. Grosse (eds.). Berlin, Germany.

Jobling S, Casey D, Rodgers-Gray T, Oehlmann J, Schulte-Oehlmann U, Pawlowski S, Baunbeck T, Turner AP, Tyler CR. 2004. Comparative responses of molluscs and fish to environmental estrogens and an estrogenic effluent. Aquat Toxicol 66:207-222.

Johnson I, Weeks JM, Kille P. 2005. Endocrine disruption in aquatic and terrestrial invertebrates. Final report produced by WRc NSF Ltd., Marlow, Buckinghamshire for the United Kingdom Department of Environment, Food and Rural Affairs (DEFRA). March 2005.

Joskow R, Barr DB, Barr JR, Calafat AM, Needham LL, Rubin C. 2006. Exposure to bisphenol-A from bis-glycidyl dimethacrylate-based dental sealants. J American Dental Association. 137:353-362.

Kanagawa Prefecture. 2000. The results of the survey on endocrine disrupting chemicals in FY 1999. Available from: http://www.k-erc.pref.kanagawa.jp/oldrelease/200009/ 14-01.htm (in japanese)

Kang IJ, Tokota H, Oshima Y, Tsuruda Y, Oe T, Imada N, Tadokoro H, Honjo T. 2002. Effects of bisphenol A on the reproduction of Japanese medaka (*Oryzias latipes*). Environ Toxicol Chem 21(11):2394-2400.

Kang JH, Kondo F. 2002. Bisphenol A degradation by bacteria isolated from river water. Arch Environ Contam Toxicol 43:265-269.

Kang JH, Kondo F. 2006a. Bisphenol A in the surface water and freshwater snail collected from rivers around a secure landfill. Bull Environ Contam Toxicol 76:3-118.

Kang JH, Kondo F, Katayama Y. 2006b. Human exposure to bisphenol A. Toxicology. 226:79-89.

Kang JH, Katayama Y, Kondo F. 2006c. Biodegradation or metabolism of bisphenol A: from microorganisms to mammals. Toxicology 217: 81-90.

Kato H, Ota T, Furuhashi T, Ohta Y, Iguchi T. 2003. Changes in reproductive organs of female rats treated with bisphenol A during the neonatal period. Reprod Toxicol 17(3):283-8.

Kato H, Furuhashi T, Tanaka M, Katsu Y, Watanabe H, Ohta Y, Iguchi T. 2006. Effects of bisphenol A given neonatally on reproductive functions of male rats. Reprod Toxicol 22(1):20-29.

Kawamura, Y., Koyama, Y., Takeda, Y., and Yamada, T. 1998. Migration of bisphenol A from poly-carbonate products. J. Food Hygiene. 39(3): 206-212

Kawai K, Murakami S, Senba E, Yamanaka T, Fujiwara Y, Arimura C, Nozaki T, Takii M, Kubo C. 2007. Changes in estrogen receptors alpha and beta expression in the brain of mice exposed prenatally to bisphenol A. Regul Toxicol Pharmacol 47(2):166-70.

Kawai K, Nozaki T, Nishikata H, Aou S, Takii M, Kubo C. 2003. Aggressive behavior and serum testosterone concentration during the maturation process of male mice: the effects of fetal exposure to bisphenol A. Environ Health Perspect 111(2):175-8.

Keri RA, Ho SM, Hunt PA, Knudsen KE, Soto AM, Prins GS. 2007. An evaluation of evidence for the carcinogenic activity of bisphenol A. Reprod Toxicol 24(2):240-252.

Kinney CA, Furlong ET, Zaugg SD, Burkhardt MR, Werner SL, Cahill JD, Jorgensen GR. 2006. Survey of organic wastewater contaminants in biosolids destined for land application. Environ Sci Technol 40: 7207-7215.

Klečka GM, Gonsior SJ, West RJ, Goodwin PA, Markham DA. 2001. Biodegradation of bisphenol A in aquatic environments: river die-away. Environ Toxicol Chem 20(12): 2725-2735.

Kloas W, Lutz I, Einspanier R. 1999. Amphibians as a model to study endocrine disruptors: II. Estrogenic activity of environmental chemicals in vitro and in vivo. Sci Total Environ 225:59-68.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2000. Version 1.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: A national reconnaissance. Environ Sci Technol 36:1202-1211.

Kolpin DW, Skopec M, Meyer MT, Furlong ET, Zaugg SD. 2004. Urban contribution of pharmaceuticals and other organic wastewater contaminants to streams during differing flow conditions. Sci Total Environ 328:119-130.

Koponen PS, Tuikka A, Kukkonen JVK. 2007. Effects of ultraviolet-B radiation and larval growth on toxicokinetics of waterborne bisphenol A in common frog (*Rana temporaria*) larvae. Chemosphere 66:1323-1328.

[KOWWIN] Octanol-Water Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2000. Version 1.67. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Kubo K, Arai O, Ogata R, Omura M, Hori T, Aou S. 2001. Exposure to bisphenol A during the fetal and suckling periods disrupts sexual differentiation of the locus coeruleus and of behavior in the rat. Neurosci Lett 304(1-2):73-6.

Kubo K, Arai O, Omura M, Watanabe R, Ogata R, Aou S. 2003. Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. Neurosci Res 45(3):345-56.

Kuch HM, Ballschmiter K. 2001. Determination of endocrine-disrupting phenolic compounds and estrogens in surface and drinking waster by HRGC-(NCI)-MS in the pictogram per liter range. Environ Sci Technol. 35(15):3201-3206.

Kuiper GG, Carlsson B, Grandien K, Enmark E, Häggblad J, Nilsson S, Gustafsson JA. 1997. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 138(3):863-870.

Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustafsson JA. 1998. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. Endocrinology 139(10):4252-63.

Kurebayashi H, Harada R, Stewart RK, Numata H, Ohno Y. 2002. Disposition of a low dose of bisphenol A in male and female cynomolgus monkeys. Toxicol Sci 68(1):32-42

Kuruto-Niwa R, Tateoka Y, Usuki Y, Nozawa R. 2007. Measurement of bisphenol A concentrations in human colostrum. Chemosphere 66(6):1160-1164.

Kwon S, Stedman DB, Elswick BA, Cattley RC, Welsch F. 2000. Pubertal development and reproductive functions of Crl:CD BR Sprague-Dawley rats exposed to bisphenol A during prenatal and postnatal development. Toxicol Sci 55(2):399-406.

Labadie P, Budzinski H. 2006. Alteration of steroid hormone balance in juvenile turbot (*Psetta maxima*) exposed to nonylphenol, bisphenol A, tetrabromodiphenyl ether 47, diallylphthalate, oil, and oil spiked with alkylphenols. Arch Environ Contam Toxicol 50: 552-561.

Lahnsteiner F, Berger B, Kletzl M, Weismann T. 2005. Effect of bisphenol A on maturation and quality of semen and eggs in the brown trout, *Salmo trutta f. fario*. Aquat Toxicol 75: 213-224.

LaKind, J.S. and Naiman, D.Q. 2008. Bisphenol A (BPA) Daily intakes in the United States: Estimates from the 2003-2004 NHANES Urinary BPA data. Journal of Exposure Science and Environmental Epidemiology. 1-8 (Advanced online publication)

Laviola G, Gioiosa L, Adriani W, Palanza P. 2005. D-amphetamine-related reinforcing effects are reduced in mice exposed prenatally to estrogenic endocrine disruptors. Brain Res Bull 65(3):235-240.

Leake JL, Main PA. 1996. The distribution of dental conditions and care in Ontario. Ontario Dentist 1996; 73(6):18-22.

Leake JL, Stewart H, Goettler F, Stahl-Quinlan B, Stewart H. 2001. Report of the sample survey of the oral health of Toronto children. Available from: http://www.toronto.ca/health/hsi/pdf/hsi_child_oral_health.pdf

Leakey JEA, Hume R, Burchell B. 1987. Development of multiple activities of UDP-glucuronyltransferase in human liver. Biochem J 243:859-861.

Le HH, Carlson EM, Chue JP, Belcher SM. 2008. Bisphenol A is released from polycarbonate drinking bottles and mimics the neurotoxic actions of estrogen in developing cerebellar neurons. Tox Letters 176: 149-156.

Lee HB, Peart TE. 2000a. Bisphenol A contamination in Canadian municipal and industrial wastewater and sludge samples. Water Qual Res J Can 35(2):283-298.

Lee HB, Peart TE. 2000b. Determination of bisphenol A in sewage effluent and sludge by solid-phase and supercritical fluid extraction and gas chromatography/mass spectrometry. J AOAC Int 83(2): 290-297.

Lee HB, Peart TE. 2002. Organic contaminants in Canadian municipal sewage sludge. Part I. Toxic or endocrine-disrupting phenolic compounds. Water Qual Res J Can 37(4): 681-696.

Lee HB, Peart TE, Gris G, Chan J. 2002. Endocrine-disrupting chemicals in industrial wastewater samples in Toronto, Ontario. Water Qual Res J Can 37(2):459-472.

Lee HB, Peart TE, Chan J, Gris G. 2004. Occurrence of endocrine-disrupting chemicals in sewage and sludge samples in Toronto, Canada. Water Qual Res J Can 39(1):57-63.

Lee HB, Peart TE, Svoboda ML. 2005. Determination of endocrine-disrupting phenols, acidic pharmaceuticals, and personal-care products in sewage by solid-phase extraction and gas chromatography-mass spectrometry. J Chromatogr A 1094:22-129.

Lee HC, Soyano K, Ishimatsu A, Nagae M, Kohra S, Ishibashi Y, Arizono K, Takao Y. 2004. Bisphenol A and nonylphenol bioconcentration in spotted halibut *Varaspar variegates*. Fisheries Science 70:192-194.

Leeson S and Caston LJ. 1991. Growth and development of Leghorn pullets subjected to abrupt changes in environmental temperature and dietary energy level. Poultry Science 70: 1732-1738.

Letcher RJ, Sanderson JT, Bokkers A, Giesy JP, van den Berg M. 2005. Effects of bisphenol A-related diphenylalkanes on vitellogenin production in male carp (*Cyprinus carpio*) hepatocytes and aromatase (CYP19) activity in human H295R adrenocortical carcinoma cells. Toxicol Appl Pharmacol 209:95-104.

Levy G, Lutz I, Krüger A, Kloas W. 2004. Bisphenol A induces feminization in *Xenopus laevis* tadpoles. Environ Res 94:102-111.

Lewis RJ Sr., ed. 2000. Sax's dangerous properties of industrial materials. 10th edition. New York (NY): Wiley.

Li AA, Baum MJ, McIntosh LJ, Day M, Liu F, Gray Jr LE. 2008. Building a framework for studying hormonal effects on behavior and on the development of the sexually dimorphic nervous system. Neurotoxicology 29(3):504-519.

Lindholst C, Pedersen KL, Pedersen SN. 2000. Estrogenic response of bisphenol A in rainbow trout (*Oncorhynchus mykiss*). Aquat Toxicol 48:87-94.

Lindholst C, Pedersen SN, Bjerregaard P. 2001. Uptake, metabolism and excretion of bisphenol A in the rainbow trout (*Oncorhynchus mykiss*). Aquat Toxicol 55:75-84.

Loffredo E, Senesi N. 2006. Fate of anthropogenic organic pollutants in soils with emphasis on adsorption/desorption processes of endocrine disruptor compounds. Pure Appl Chem 78(5): 947-961.

Lyman WJ, Reehl W, Rosenblatt D (eds.). 1982. Handbook of Chemical Property Estimation Methods. New York (NY): McGraw-Hill p. 7-4.

MacLusky NJ, Naftolin, F. 1981. Sexual differentiation of the central nervous system. Science 211(4488): 1294-1302.

Mandich A, Bottero S, Benfenati E, Cevasco A, Erratico C, Maggioni S, Massari A, Pedemonte F, Viganò,L. 2007. *In vivo* exposure of carp to graded concentrations of bisphenol A. Gen Comp Endocrinol 153:15-24.

Marcial HS, Hagiwara A, Snell TW. 2003. Estrogenic compounds affect development of harpacticoid copepod *Tigriopus japonicus*. Environ Toxicol Chem 22(12):3025-3030.

Maragou NC, Makri A, Lampi EN, Thomaidis NS, Koupparis MA. 2007. Food Additives and Contaminants 1-11, iFirst.

Markey CM, Coombs MA, Sonnenschein C, Soto AM. 2003. Mammalian development in a changing environment: exposure to endocrine disruptors reveals the developmental plasticity of steroid-hormone target organs. Evol Dev 5(1):67-75.

Markey CM, Wadia PR, Rubin BS, Sonnenschein C, Soto AM. 2005. Long-term effects of fetal exposure to low doses of the xenoestrogen bisphenol-A in the female mouse genital tract. Biol Reprod 72(6):1344-1351.

Matsumoto J, Yokota H, Yuasa A. 2002. Developmental increases in rat hepatic microsomal UDP-glucuronosyltransferase activities toward xenoestrogens and decreases during pregnancy. Environ Health Perspect 110(2):193-196.

Mekenyan G, Dimitrov SD, Pavlov TS, Veith GD. 2005. POPs: a QSAR system for creating PBT profiles of chemicals and their metabolites. SAR QSAR Environ Res 16(1−2):103−133.

Melnick R, Lucier G, Wolfe M, Hall R, Stancel G, Prins G, Gallo M, Reuhl K, Ho SM, Brown T, Moore J, Leakey J, Haseman J, Kohn M. 2002. Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review. Environ Health Perspect 110(4):427-31. Review.

Metcalfe CD, Metcalfe TL, Kiparissis Y, Koenig BG, Khan C, Hughes RJ, Croley TR, March RE, Potter T. 2001. Estrogenic potency of chemicals detected in sewage treatment plant effluents as determined by in vivo assays with Japanese medaka (*Oryzias latipes*). Environ Toxicol Chem 20(2):297-308.

Miners JO, Robson RA, Birkett DJ. 1986. Paracetamol metabolism in pregnanacy. Br J Clin Pharmc 22:359-362.

Miyamoto, K., and Kotake M. 2006. Estimation of daily bisphenol A intake of japanese individuals with emphasis on uncertainty and variability. Environ Sci 13(1):15-29.

Mizuo K, Narita M, Miyagawa K, Narita M, Okuno E, Suzuki T. 2004a. Prenatal and neonatal exposure to bisphenol-A affects the morphine-induced rewarding effect and hyperlocomotion in mice. Neurosci Lett 356(2):95-98.

Mizuo K, Narita M, Yoshida T, Narita M, Suzuki T. 2004b. Functional changes in dopamine D3 receptors by prenatal and neonatal exposure to an endocrine disruptor bisphenol-A in mice. Addict Biol 9(1):19-25.

Morrissey RE, George JD, Price CJ, Tyl RW, Marr MC, Kimmel CA. 1987. The developmental toxicity of bisphenol A in rats and mice. Fundam Appl Toxicol 8(4):571-582.

Morreale dE, Obregon MJ, Escobar dR. 2004. Role of thyroid hormone during early brain development. Eur J Endocrinol 151 Suppl 3:U25-U37.

Mountfort KA, Tabata J, Jickells SM, Castel L. 1997. Investigations into the potential degradation of polycarbonate baby bottles during sterilization with consequent release of bisphenol A. Food Add Contam 14: 737-740.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [Estimation Model]. 2000. Version 1.41. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Mu X, Rider CV, Hwang GS, Hoy H, LeBlanc GA. 2005. Covert signal disruption: anti-ecdysteroidal activity of bisphenol A involves cross talk between signalling pathways. Environ Toxicol Chem 24(1):146-152.

Muñoz-de-Toro M, Markey CM, Wadia PR, Luque EH, Rubin BS, Sonnenschein C, Soto AM. 2005. Perinatal exposure to bisphenol-A alters peripubertal mammary gland development in mice. Endocrinology 146(9):4138-47.

Munro IC, Haighton LA, Hlywka JJ, Lynch BS, Doull J, Kroes R. 2002a. Carcinogenicity bioassay of bisphenol A. Toxicol Sci 66(2):356.

Munro IC, Haighton LA, Hlywka JJ, Lynch BS, Doull J, Kroes R. 2002b. Carcinogenicity of bisphenol A revisited. Toxicol Sci. 70(2):author reply 283-4.

Murray TJ, Maffini MV, Ucci AA, Sonnenschein C, Soto AM. 2007. Induction of mammary gland ductal hyperplasias and carcinoma in situ following fetal bisphenol A exposure. Reprod Toxicol 23(3):383-390.

Nagao T, Saito Y, Usumi K, Yoshimura S, Ono H. 2002. Low-dose bisphenol A does not affect reproductive organs in estrogen-sensitive C57BL/6N mice exposed at the sexually mature, juvenile, or embryonic stage. Reprod Toxicol 16(2):123-30.

Nagel SC, vom Saal FS, Thayer KA, Dhar MG, Boechler M, Welshons WV. 1997. Relative binding affinity-serum modified access (RBA-SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect 105(1):70-76.

Nakamura K, Itoh K, Yaoi T, Fujiwara Y, Sugimoto T, Fushiki S. 2006. Murine neocortical histogenesis is perturbed by prenatal exposure to low doses of Bisphenol A. J Neurosci Res 84(6):1197-205.

Nakanishi J, Miyamoto K, Kawasaki H. 2007. Bisphenol A Risk Assessment Document. AIST Risk Assessment Document Series. 4:371pp

Narita M, Miyagawa K, Mizuo K, Yoshida T, Suzuki T. 2006. Prenatal and neonatal exposure to low-dose of bisphenol-A enhance the morphine-induced hyperlocomotion and rewarding effect. Neurosci Lett 402(3):249-52.

Narita M, Miyagawa K, Mizuo K, Yoshida T, Suzuki T. 2007. Changes in central dopaminergic systems and morphine reward by prenatal and neonatal exposure to bisphenol-A in mice: evidence for the importance of exposure period. Addict Biol 12(2):167-72.

NCHS] National Center for Health Statistics 2000 CDC Growth Charts United States [Internet]. 2000. Hyattsville (MD): US Department of Health and Human Services, Centers Disease Control and Prevention. [last updated 2008 March 07; cited 2008 March 13]. Available from: http://www.cdc.gov/growthcharts/

[NCI] National Chemical Inventories [database on CD-ROM]. 2006. Columbus (OH): American Chemical Society. Available from: www.cas.org/products/cd/nci/index.html

National Institutes of Health. 2007. Household products database. National Library of Medicine specialized information services. Available from: http://householdproducts.nlm.nih.gov

Negishi T, Ishii Y, Kyuwa S, Kuroda Y, Yoshikawa Y. 2003. Inhibition of staurosporine-induced neuronal cell death by bisphenol A and nonylphenol in primary cultured rat hippocampal and cortical neurons. Neurosci Lett 353(2):99-102.

Negishi T, Kawasaki K, Suzaki S, Maeda H, Ishii Y, Kyuwa S, Kuroda Y, Yoshikawa Y. 2004. Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. Environ Health Perspect 112(11):1159-1164.

Nelson AL, Martin AC. 1953. Gamebird weights. J. Wildl. Manage. 17: 36-42 [cited in USEPA 1993].

Nelson J, Bishay F, Van Roodselaar A, Ikonomou M, Law FCP. 2007. The use of *in vitro* bioassays to quantify endocrine disrupting chemicals in municipal wastewater treatment plant effluents. Sci Total Environ 374: 80-90.

Newbold RR, Jefferson WN, Padilla-Banks E. 2007. Long-term adverse effects of neonatal exposure to bisphenol A on the murine female reproductive tract. Reprod Toxicol 24(2):253-258.

Nishiyama T, Ogura K, nakano H, Kaku T, Takahashi E, Ohkubo Y, Sekine K, Hiratsuka A, Kadota S, Watabe T. 2002. Sulfation of environmental estrogens by cytosolic human sulfotransferases. Drug Metabol Pharmacokin 17(3):221-228.

Nishizawa H, Manabe N, Morita M, Sugimoto M, Imanishi S, Miyamoto H. 2003. Effects of in utero exposure to bisphenol A on expression of RARalpha and RXRalpha mRNAs in murine embryos. J Reprod Dev 49(6):539-545.

Nishizawa H, Imanishi S, Manabe N. 2005a. Effects of exposure in utero to bisphenol a on the expression of aryl hydrocarbon receptor, related factors, and xenobiotic metabolizing enzymes in murine embryos. J Reprod Dev 51(5):593-605.

Nishizawa H, Morita M, Sugimoto M, Imanishi S, Manabe N. 2005b. Effects of in utero exposure to bisphenol A on mRNA expression of arylhydrocarbon and retinoid receptors in murine embryos. J Reprod Dev 51(3):315-324.

[NITE] National Institute of Technology and Evaluation. 1977. Biodegradation and bioconcentration of existing chemicals under the Chemical Substances Control Law. Chemical Management Center. Tokyo Jpn). [updated 2005.04.01]. Available from:
http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html

[NPRI] National Pollutant Release Inventory [database on the Internet]. 2007. Gatineau (QC): Environment Canada. [cited 2007 February 28]. Available from: http://www.ec.gc.ca/pdb/querysite/query_e.cfm

[NTP] National Toxicology Program (US). 1982. Carcinogenesis bioassay of bisphenol A in F344 rats and B6C3F1 mice (feed study). No 215. Research Triangle Park (NC): National Toxicology Program.

[NTP] National Toxicology Program (US). 2007. NTP-CERHR Expert panel report on the reproductive and developmental toxicity of bisphenol-A. Research Triangle Park (NC): US Department of Health and Human Services, Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program. November 2007.

[NTP] National Toxicology Program (US). 2008. NTP-CERHR Monograph on the potential human reproductive and developmental effects of bisphenol A. Research Triangle Park (NC): US Department of Health and Human Services, Center for the Evaluation of Risks to Human Reporduction, National Institute of Environmental Health Sciences. September 2008.

Nutrition Canada. 1980. Anthropometry Report: Height, Weight and Body Dimensions of data from Nutrition-Canada Survey 1971.

[OASIS Forecast] Optimized Approach based on Structural Indices Set [Internet]. 2005. Version 1.20. Bourgas, Bulgaria: Laboratory of Mathematical Chemistry. Available from: http://oasis-lmc.org/?section=software

[OECD] Organization for Economic Co-operation and Development. 2007. OECD guideline for the testing of chemicals. Document 426. Available from: www.oecd.org/home

Oehlmann J, Schulte-Oehlmann U, Bachmann J, Oetken M, Lutz I, Kloas W, Ternes WA. 2006. Bisphenol A induces superfeminization in the ramshorn snail *Marisa cornuarietis* (Gastropoda: Prosobranchia) at environmentally relevant concentrations. Environ Health Perspect 114 (Suppl 1): 127-133.

Ortiz-Zarragoitia M, Cajaraville MP. 2006. Biomarkers of exposure and reproduction-related effects in mussels exponed to endocrine disruptors. Arch Environ Contam Toxicol 50:361-369.

Otaka H, Yasuhara A, Morita M. Determination of bisphenol A and 4-nonylphenol in human milk using alkaline digestion and cleanup by solid-phase extraction. Analytical Sciences 2003; 19: 1663-1666

Pacchierotti F, Ranaldi R, Eichenlaub-Ritter U, Attia S, Adler ID. 2008. Evaluation of aneugenic effects of bisphenol A in somatic and germ cells of the mouse. Mutat Res. 651(1-2):64-70.

Page D, Lacroix G, Lalonde PJ, Feeley M. 2006. Bisphenol A (BPA) content of commercial polycarbonate (PC) baby bottles. [abstract]. Health Canada Science Forum Book of Abstracts. Available upon request.

Palanza PL, Howdeshell KL, Parmigiani S, vom Saal FS. 2002. Exposure to a low dose of bisphenol A during fetal life or in adulthood alters maternal behavior in mice. Environ Health Perspect 110 Suppl 3:415-422.

Papini O, Bertucci C, da Cunha SP, dos Santos NAG, Lanchote VL.2006. Quantitiative assay of lorazepam an dits metabolite glucuronide by reverse-phase liquid chromatography-tandem mass spectrometry in human plasma and urine samples. J Pharm Biochem Anal 40:389-396.

Patisaul HB, Fortino AE, Polston EK. 2006. Neonatal genistein or bisphenol-A exposure alters sexual differentiation of the AVPV. Neurotoxicol Teratol 28(1):111-8.

Patisaul HB, Fortino AE, Polston EK. 2007. Differential disruption of nuclear volume and neuronal phenotype in the preoptic area by neonatal exposure to genistein and bisphenol-A. Neurotoxicology 28(1):1-12.

Patisaul HB, Polston EK. 2008. Influence of endocrine active compounds on the developing rodent brain. Brain Res Rev 57(2):352-62

[PCKOCWIN] Organic Carbon Partition Coefficient Program for Windows [Estimation Model]. 2000. Version 1.66. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. [cited yr mon date]. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Peng Z, Wu F, Deng N. 2006. Photodegradation of bisphenol A in simulated lake water containing algae, humic acid and ferric ions. Environ Pollut 144(3): 840-846.

Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, Newman M, Stowe ZN. 2008. Lamotrigine in pregnanacy: Clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 70:2130-2136.

Pennie WD, Aldridge TC, Brooks AN. 1998. Differential activation by xenoestrogens of ER alpha and ER beta when linked to different response elements. J Endocrinol 158(3):R11-R14.

Peressini S, Leake JL, Mayhall JT, Marr M, Tredeau R. 2004. Prevalence of Dental Caries among 7 and 13 year-old First Nations Children, District of Manitoulin, Ontario. Journal Canadian Dental Association. 70(6):382

[PhysProp] Interactive PhysProp Database [database on the Internet]. 2006. Syracuse (NY): Syracuse Research Corporation. Available from: http://www.syrres.com/esc/physdemo.htm

Pickford DB, Hetheridge MJ, Caunter JE, Hall AT, Hutchinson TH. 2003. Assessing chronic toxicity of bisphenol A to larvae of the African clawed frog (*Xenopus laevis*) in a flow-through exposure system. Chemosphere 53: 223-235.

Porrini S, Belloni V, Della SD, Farabollini F, Giannelli G, ssi-Fulgheri F. 2005. Early exposure to a low dose of bisphenol A affects socio-sexual behavior of juvenile female rats. Brain Res Bull 65(3):261-6.

Pottenger LH, Domoradzki JY, Markham DA, Hansen SC, Cagen SZ, Waechter JM, Jr. 2000. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicol Sci. 54(1):3-18.

Prins GS, Birch L, Tang WY, Ho SM. 2007. Developmental estrogen exposures predispose to prostate carcinogenesis with aging. Reprod Toxicol 23(3):374-82.

Quesada I, Fuentes E, Viso-Leon MC, Soria B, Ripoll C, Nadal A. 2002. Low doses of the endocrine disruptor bisphenol-A and the native hormone 17beta-estradiol rapidly activate transcription factor. CREB. FASEB J 16:1671-1673.

Richard K, Hume R, Kaptein E, Stanley EL, Visser TJ, Coughtrie WH. 2001. Sulfation of thyroid hormone and dopamine during human development: Ontogeny of phenol sulfotransfereases and arylsulfatase in liver, lung, and brain. J Clin End Metab. 86(6):2734-2742.

Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, Vandenbergh JG, Walser-Kuntz DR, vom Saal FS. 2007. *In vivo* effects of bisphenol A in laboratory rodent studies. Reprod Toxicol 24(2):199-224.

Ring JA, Ghabrial H, Ching MS, Smallwood RA, Morgan DJ. Fetal hepatic drug elimination. Pharmacol Ther. 1999. 84(3):429-445.

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2006. Consumer Exposure (ConsExpo) Model [Internet]. Version 4.1. The Netherlands: The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu). Available from: http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840

[RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2007. Do-It-Yourself Products Fact Sheet To assess the risks for the consumer. RIVM report 320104007/2007. Available from: http://www.rivm.nl/bibliotheek/rapporten/320104007.pdf

Ronen Z, Abeliovich A. 2000. Anaerobic-aerobic process for microbial degradation of tetrabromobisphenol A. Appl Environ Microbiol 66(6):2372-2377.

Rudel RA, Melly SJ, Geno PW, Sun G, Brody JG. 1998. Identification of alkylphenols and other estrogenic phenolic compounds in wastewater, septage, and groundwater on Cape Cod, Massachusetts. Environ Sci Technol 32:861-869.

Rudel RA, Brody JG, Spengler JD, Vallarino J, Geno PW, Sun, G, Yau, A. 2001. Identification of selected hormonally active agents and animal mammary carcinogens in commercial and residential air and dust samples. J. Air Waste Manage. Assoc 51:499-513.
Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. 2003. Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other endocrine-disrupting compounds in indoor air and dust. Environ Sci Technol 37(20): 4543-4553.

Ryan BC, Vandenbergh JG. 2006. Developmental exposure to environmental estrogens alters anxiety and spatial memory in female mice. Horm Behav 50(1):85-93.

Sample BE, Opresko DM and Suter II GW. 1996. Toxicological benchmarks for wildlife: 1996 revision. Prepared by the Risk Assessment Program, Health Sciences Research Division, U.S. Department of Energy, Oak Ridge, Tennessee (ES/ER/TM-86/R3). Available at http://www.esd.ornl.gov/programs/ecorisk/documents/tm86r3.pdf.

Santerre. 2007. Bisphenol A: What Dentists Should Know and Tell Their Patients. J Canadian Dental Association. 73(7):563.

Sarmah AK, Northcott GL. 2008. Laboratory degradation studies of four endocrine disruptors in two environmental media. Environ Toxicol Chem 27(4): 819-827.

Sasaki, N., Okuda, K., Kato, T., Kakishima, H., Okuma, H., Abe, K., Tachino, H., Tuchida, K. and Kubono, K. 2005. Salivary bisphenol-A levels detected by ELISA after restoration with composite resin. J Mater Sci Mater Med. 16(4): 297-300

Sax NI, Lewis RJ. 1996. Sax's Dangerous Properties of Industrial Materials. 9th edition. New York (NY): Van Nostrand Reinhold. [cited in European Communities 2003].

Schönfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, Chahoud I. 2002. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect 110(11):A703-A707.

Segner H, Caroll K, Fenske M, Janssen CR, Maack G, Pascoe D, Schäfers C, Vandenbergh GF, Watts M, Wenzel A. 2003. Identification of endocrine-disrupting effects in aquatic vertebrates and invertebrates: report from the European IDEA project. Ecotoxicol Environ Saf 54:302-314.

Seegal RF. 2001. Neurochemical effects of polychlorinated biphenyls: a selective review of the current state of knowledge. In: PCBs: recent advances in environmental toxicology and health effects (Robertson LW, Hansen LG, eds). Lexington, KY, USA:The University Press of Kentucky. 241-255.

Shimizu M, Ohta K, Matsumoto Y, Fukuoka M, Ohno Y, Ozawa S. 2002. Sulfation of bisphenol A abolished its estrogenicity based on proliferation and gene expression in human breast cancer MCF-7 cells. Toxicology in Vitro 16:549-556.

Snyder RW, Maness SC, Gaido KW, Welsch F, Sumner SC, Fennell TR. 2000. Metabolism and disposition of bisphenol A in female rats. Toxicol Appl Pharmacol 168(3):225-234.

Sohoni P, Tyler CR, Hurd K, Caunter J, Hetheridge M, Williams T, Woods C, Evans M, Toy R, Gargas M, Sumpter JP. 2001. Reproductive effects of long-term exposure to bisphenol A in the fathead minnow (*Pimephales promelas*). Environ Sci Technol 35: 2917-2925.

Solís ME, Liu CC, Nam P, Niyogi DK, Bandeff JM, Huang YW. 2007. Occurrence of organic chemicals in two rivers inhabited by Ozark hellbenders (*Cryptobranchus alleganiensis bishopi*). Arch Environ Contam Toxicol 53: 426-434.

Sosiak A, Hebben T. 2005. A preliminary survey of pharmaceuticals and endocrine disrupting compounds in treated municipal wastewaters and receiving rivers of Alberta, Alberta Environment Publication Number T/773.

Springborn Smithers. 2007. Bisphenol A – Determination of effects on seedling emergence and seedling growth (definitive test). Study number 13761.6124. Commissioned by American Chemistry Council. August 2007 [cited in ECB 2008].

SRI Consulting. 2007. Chemical Economics Handbook. Product Review. Bisphenol A

Stanek III E.J., and Calabrese E.J. 1995a. Daily estimates of soil ingestion in children. Environmental Health Perspectives. 103: 276–285.

Stanek III E.J., and Calabrese E.J.. 1995b. Soil ingestion estimates for use in site evaluations based on the best tracer method. Human Ecological Risk Assessment. 1(2): 133–156.

Staples CA, Dorn PB, Klecka GM, O'Block ST, Harris LR. 1998. A review of the environmental fate, effects, and exposures of bisphenol A. Chemosphere 36(10): 2149-2173.

Staples CA, Dorn PB, Klecka GM, O'Block ST, Branson DR, Harris LR. 2000. Bisphenol A concentrations in receiving waters near US manufacturing and processing facilities. Chemosphere 40: 521-525.

Staples CA, Woodburn K, Caspers N, Tilghman Hall A, Klěcka. 2002. A weight of evidence approach to the aquatic hazard assessment of bisphenol A. Human and Ecological Risk Assessment 8(5): 1083-1105.

Stoker C, Rey F, Rodriguez H, Ramos JG, Sirosky P, Larriera A, Luque EH, Muñoz-de-Toro M. 2003. Sex reversal effects on *Caiman latirostris* exponed to environmentally relevant doses of the xenoestrogen bisphenol A. Gen Comp Endocrinol 133:287-296.

Stuart JD, Capulong CP, Launer KD, Pan X. 2005. Analyses of phenolic endocrine disrupting chemicals in marine samples by both gas and liquid chromatography-mass spectrometry. J Chromatogr A 1079:136-145.

Suiko M, Sakakibara Y, Liu M-C. 2000. Sulfation of environmental estroge-like chemicals by human cytosolic transferases. Biochem Biophys Res 267:80-84.

Sun Y, Wada M, Al-Dirbashi O, Kuroda N, Nakazawa H, Nakashima K. 2000. High-performance liquid chromatography with peroxyoxalate chemiluminescence detection of bisphenol A migrated from polycarbonate baby bottles using 4-(4,5-diphenyl-1H-imidazol-2-yl)benzoyl chloride as a label. J Chrom B Biomed Sci Appl 749: 49-56.

Sun Y, Irie M, Kishikawa N, Wada M, Kuroda N, Nakashima K. 2004. Determination of bisphenol A in human breast milk by HPLC with column-switching and fluorescence detection. Biomed Chromatogr 18: 501–507.

Suzuki A, Sugihara A, Uchida K, Sato T, Ohta Y, Katsu Y, Watanabe H, Iguchi T. 2002. Developmental effects of perinatal exposure to bisphenol-A and diethylstilbestrol on reproductive organs in female mice. Reprod Toxicol 16(2):107-116.

Suzuki T, Mizuo K, Nakazawa H, Funae Y, Fushiki S, Fukushima S, Shirai T, Narita M. 2003. Prenatal and neonatal exposure to bisphenol-A enhances the central dopamine D1 receptor-mediated action in mice: enhancement of the methamphetamine-induced abuse state. Neuroscience 117(3):639-44.

Suzuki N, Kambegawa A, Hattori A. 2003. Bisphenol A influences the plasma calcium level and inhibits calcitonin secretion in goldfish. Zoological Science 20: 745-748.

Suzuki E, Kunimoto M, Nishizuka M, Imagawa M. 2004. Evaluation of ability of chemicals to bind frog (*Xenopus laevis*) estrogen receptor by in vitro binding assay. J Health Sci 50(6): 685-688.

Tabata A, Watanabe N, Yamamoto I, Ohnishi Y, Itoh M, Kamei T, Magara Y, Terao Y. 2004. The effect of bisphenol A and chlorinated derivatives of bisphenol A on the serum vitellogenin in Japanese medaka (*Oryzias latipes*). Water Sci Technol 50(5):125-132.

Takahashi O, Oishi S. 2000. Disposition of orally administered 2,2-Bis(4-hydroxyphenyl)propane (Bisphenol A) in pregnant rats and the placental transfer to fetuses. Environ Health Perspect 108(10):931-935.

Takahashi A, Higashitani T, Yakou Y, Saitou M, Tamamoto H, Tanaka H. 2003. Evaluating bioaccumulation of suspected endocrine disruptors into periphytons and benthos in the Tama River. Water Sci Technol 47(9):71-76.

Takao Y, Chul LH, Ishibashi Y, Kohra S, Tominaga N, Arizono K. 1999. Fast screening method for bisphenol A in environmental water and in food by solid-phase microextraction (SPME). J Health Sci. 45:39.

Tando S, Itoh K, Yaoi T, Ikeda J, Fujiwara Y, Fushiki S. 2007. Effects of pre- and neonatal exposure to bisphenol A on murine brain development. Brain Dev 29(6):352-6.

Tanimura M 1999. Omocha No Phthalate Ester No Yoshutsu Nikansuru Chosa Kenkyu - Nyuji MOUTHING Kodo No Jittai Chosa - (Research on the Migration of Phthalates from Toys – Survey on the Mouthing Behavior of Infants-). Report of Health Science Research Grants from the Ministry of Health, Labour and Welfare in Japan in FY 1998. Naibunpi Kakuran Busshitsu-tou, Seikatsu Kankyo-chu No Kagaku Busshitsu Niyoru Kenko Eikyo Oyobi Anzensei No Kakuho-to Nikansuru Kenkyu (Study on Health Effects and Safety of Chemicals such as Endocrine Disruptors in the Environment) 13-21.

Tanimura M 2000. Nyuji MOUTHING Kodo No Jittai (Mouthing Behavior of Infants.). Report of Health Science Research Grants from the Ministry of Health, Labour and Welfare in Japan in FY 1999. Kobunshi Sozai Karanaru Seikatsu Kanren Seihin Yurai No Naibunpi Kakuran Kagaku Busshitsu No Bunseki Oyobi Dotai Kaiseki (Determination and Migration of Endocrine Disrupting Chemicals in Consumer Articles Made of Polymers) 43-49.

Tatarazako N, Takao Y, Kishi K, Onikura N, Arizono K, Iguchi T. 2002. Styrene dimmers and trimers affect reproduction of daphnid (*Ceriodaphnia dubia*). Chemosphere 48: 597-601.

Taylor JA, Welshons WV, vom Saal FS. 2008. No effect of route of exposure (oral; subcutaneous injection) on plasma bisphenol A throughout 24 hr after administration in neonatal female mice. Reprod Toxicol 25(2):169-76.

Timms BG, Howdeshell KL, Barton L, Bradley S, Richter CA, vom Saal FS. 2005. Estrogenic chemicals in plastic and oral contraceptives disrupt development of the fetal mouse prostate and urethra. Proc Natl Acad Sci U S A 102(19):7014-9.

Tominaga N, Kohra S, Iguchi T, Arizono K. 2003. A multi-generation sublethal assay of phenols using the nematode *Caenorhabditis elegans*. J Health Sci 49(6):459-463.

Tominaga T, Negishi T, Miyachi A, Inoue A, Hayasaka I, Yoshikawa Y. 2006. Toxicokinetics of bisphenol A in rats, monkeys and chimpanzees by the LC-MS/MS method. Toxicology. 226:208-217.

[TOPKAT] Toxicity Prediction Program [Internet]. 2004. Version 6.2. San Diego (CA): Accelrys Software Inc. Available from: http://www.accelrys.com/products/topkat/index.html

Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, Brine DR, Veselica MM, Fail PA, Chang TY, Seely JC, Joiner RL, Butala JH, Dimond SS, Cagen SZ, Shiotsuka RN, Stropp GD, Waechter JM. 2002. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicol Sci 68(1):121-146.

Tyl RW, Myers CB, Marr MC. 2007. Two-generation reproductive toxicity evaluation of bisphenol A (BPA; CAS No. 80-05-7) administered in the feed to CD-1® Swiss mice (modified OECD 416). Research Triangle Park (NC): RTI International Center for Life Sciences and Toxicology.

[USEPA] United States Environmental Protection Agency. 1993. Wildlife exposure factors handbook. Volume 1. National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C. (EPA/600/R-93/187). Available at http://www.epa.gov/ncea/pdfs/toc2-37.pdf.

[USEPA] United States Environmental Protection Agency. 2007. Toxics Release Inventory. [cited 2007 November 27]. Available from: http://www.epa.gov/triexplorer/

[USFDA] United States Food and Drug Administration. 2007. Guidance for Industry: Preparation of Pre-market Submissions for Food Contact Substances: Chemistry Recommendations. Document prepared April 2002 and updated December 2007. Available from: http://www.cfsan.fda.gov/~dms/opa3pmnc.html

[USFDA] United States Food and Drug Administration. 2008. Draft assessment of bisphenol A for use in food contact applications. Draft version 08/14/2008. Availble from: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-0038b1_01_00_index.htm

van den Berg M, Sanderson T, Kurihara N, Katayama A. 2003. Role of metabolism in the endocrine-disrupting effects of chemicals in aquatic and terrestrial systems. Pure Appl Chem 75 (11-12):1917-1932.

Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. 2007. Human exposure to bisphenol A (BPA). Reprod Toxicol 24(2):139-177.

Vethaak AD, Lahr J, Schrap SM, Belfroid AC, Rijs GBJ, Gerritsen A, de Boer J, Bulder AS, Grinwis GCM, Kuiper RV, Legler J, Murk TAJ, Peijnenburg W, Verhaar HJM, de Voogt P. 2005. An integrated assessment of estrogenic contamination and biological effects in the aquatic environment of The Netherlands. Chemosphere 59: 511-524.

Vinogradov AP. 1953. The elementary chemical composition of marine organisms. Scars Foundation for Marine Research. Yale University.

Vivacqua A, Recchia AG, Fasanella G, Gabriele S, Carpino A, Rago V, Di Gioia ML, Leggio A, Bonofiglio D, Liguori A, Maggiolini M. 2003. The food contaminants bisphenol A and 4-nonylphenol act as agonists for estrogen receptor alpha in MCF7 breast cancer cells. Endocrine. 22:275-284.

Volkel W, Colnot T, Csanady GA, Filser JG, Dekant W. 2002. Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. Chem Res Toxicol 15(10):1281-1287.

vom Saal FS, Cooke PS, Buchanan DL, Palanza P, Thayer KA, Nagel SC, Parmigiani S, Welshons WV. 1998. A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behaviour. Toxicol Ind Health 14(1-2):239-260.

vom Saal FS, Hughes C. 2005. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environ Health Perspect 113(8):926-933.

vom Saal FS, Richter CA, Ruhlen RR, Nagel SC, Timms BG, Welshons WV. 2005a. The importance of appropriate controls, animal feed, and animal models in interpreting results from low-dose studies of bisphenol A 7. Birth Defects Res A Clin Mol Teratol 73(3):140-145.

vom Saal FS, Welshons WV. 2006. Large effects from small exposures. II. The importance of positive controls in low-dose research on bisphenol A. Environ Res 100(1):50-76.

vom Saal FS, Akingbemi BT, Belcher SM, Birnbaum LS, Crain DA, Eriksen M, Farabollini F, Guillette LJ, Jr., Hauser R, Heindel JJ, Ho SM, Hunt PA, Iguchi T, Jobling S, Kanno J, Keri RA, Knudsen KE, Laufer H, Leblanc GA, Marcus M, McLachlan JA, Myers JP, Nadal A, Newbold RR, Olea N, Prins GS, Richter CA, Rubin BS, Sonnenschein C, Soto AM, Talsness CE, Vandenbergh JG, Vandenberg LN, Walser-Kuntz DR, Watson CS, Welshons WV, Wetherill Y, Zoeller RT. 2007. Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. Reprod Toxicol 24(2):131-138.

Voordeckers JW, Fennell DE, Jones K, Häggblom MM. 2002. Anaerobic biotransformation of tetrabromobisphenol A, tetrachlorobisphenol A, and bisphenol A in estuarine sediments. Environ Sci Technol 36: 696-701.

Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect 111(8):994-1006.

Welshons WV, Nagel SC, vom Saal FS. 2006. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology 147(Suppl 6):S56-S69.

West RJ, Goodwin PA, Klecka GM. 2001. Assessment of the Ready Biodegradability of Bisphenol-A. Bull Environ Contam Toxicol 67:106-112.

Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, Watson CS, Zoeller RT, Belcher SM. 2007. In vitro molecular mechanisms of bisphenol A action. Reprod Toxicol 24(2):178-198.

Willhite CC, Ball GL, McLellan CJ. 2008. Derivation of a bisphenol A oral reference dose (RfD) and drinking-water equivalent concentration. J Toxicol Environ Health B Crit Rev 11(2):69-146.

Wilson NK, Chuang JC, Lyu C. 2001. Levels of persistent organic pollutants in several child day care centers. J Expo Analy Environ Epi 11: 449-458.

Wilson NK, Chuang JC, Lyu C, Menton R, Morgan MK. 2003. Aggregate exposures of nine preschool children to persistent organic pollutants at day care and at home. J Expo Anal Environ Epidemiol 13(3):187-202.

Wilson NK, J. C. Chuang;M. K. Morgan;R. A. Lordo;L. S. Sheldon. 2007. An observational study of the potential exposures of preschool children to entachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environ Res 103(1):9-20.

Wong KO, Leo LW, Seah HL. 2005. Dietary exposure assessment of infants to bisphenol A from the use of polycarbonate baby milk bottles. Food Additives and Contaminants. 22(3): 280-288.

Woolley CS. 2007. Acute effects of estrogen on neuronal physiology. Annu Rev Pharmacol Toxicol 47:657-680.

Wozniak AL, Bulayeva NN, Watson CS. 2005. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ Health Perspect 113(4):431-439.

[WSKOWWIN] Water Solubility for Organic Compounds Program for Microsoft Windows [Estimation Model]. 2000. Version 1.41 Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Ye X, Kuklenyik Z, Needham LL, Calafat AM. 2006. Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. J Chromatogr B. 831(0): 110-115

Ying GG, Kookana RS. 2003. Degradation of five selected endocrine-disrupting chemicals in seawater and marine sediment. Environ Sci Technol 37: 1256-1260.

Ying GG, Kookana RS, Dillon P. 2003. Sorption and degradation of selected five endocrine disrupting chemicals in aquifer material. Water Res 37: 3785-3791.

Ying GG, Kookana RS. 2005. Sorption and degradation of estrogen-like endocrine disrupting chemicals in soil. Environ Toxicol Chem 24(10): 2640-2645.

Yokota H, Iwano H, Endo M, Kobayashi T, Inoue H, Ikushiro S, Yuasa A. 1999. Glucuronidation of the environmental oestrogen bisphenol A by an isoform of UDP-glucuronosyltransferase, UGT2B1, in the rat liver. Biochem J. 340 (Pt 2):405-409.

Yokota H, Tsuruda Y, Maeda M, Oshima Y, Tadokoro H, Nakazono A, Honjo T, Kobayashi K. 2000. Effect of bisphenol A on the early life stage in Japanese medaka (*Oryzias latipes*). Environ Toxicol Chem 19(7): 1925-1930.

Zhan M, Yang X, Xian Q, Kong L. 2006. Photosensitized degradation of bisphenol A involving reactive oxygen species in the presence of humic substances. Chemosphere 63: 378-386.

Zhang S, Zhang Q, Darisaw S, Ehie O, Wang G. 2007. Simultaneous quantification of polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and pharmaceuticals and personal care products (PPCPs) in Mississippi river water, in New Orleans, Louisiana, USA. Chemosphere 66:1057-1069.

Zoeller RT. 2005. Bisphenol-A, an environmental contaminant that acts as thyroid hormone receptor antagonist *in vitro*, increases serum thyroxine, and alters RC3/Neurogranin expression in the developing rat brain. Endocrinology 146(2):607-612.

Appendix A. Robust Study Summary – Inherent Toxicity

Item	Yes	No
***Reference*:** Sohoni et al. 2001. Reproductive effects of long-term exposure to bisphenol A in the fathead minnow (*Pimephales promelas*). Environ Sci Technol 35: 2917–2925.		
Test Substance: 80-05-7 (Bisphenol A)		
***Chemical composition of the substance (including purity, by-products)**	X	
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method?**		X
Justification of the method/protocol if a non-standard method was used	X	
***GLP (good laboratory practice)**	X	
Test organisms: Fathead minnow (*Pimephales promelas*)		
Latin or both Latin and common names reported?	X	
Life cycle age/stage of test organism	X	
Sex	X	
Length and weight of test organisms	X	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation / during test)	X	
Test design/conditions		
Test type – acute or chronic: Chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls : Negative	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**	X	
Exposure media conditions (temperature, pH, electrical conductivity, hardness, total organic carbon, dissolved organic carbon, dissolved oxygen, major cations and anions; other)	X	
Was pH within 6–9 range?	X	
Was temperature within 5–28°C range?	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators/solubilizers (especially for poorly soluble / unstable substances)	Not required	
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50}- 164 d LOEC (lowest-observed effect concentration – somatic growth in adults, egg hatchability) = 0.64 mg/L; 164 d LOEC (vitellogenin [VTG] synthesis, sex cell type proportion) = 0.016 mg/L; 164 d LOEC (egg production) = 1.28 mg/L		
Other endpoints reported – e.g., bioconcentration factor / bioaccumulation factor (BCF/BAF):		
***Was toxicity value below the chemical's water solubility?**	X	
Other adverse effects (carcinogenicity, mutagenicity, etc.	X	
***Score*:** Major items – 4/5; overall score – 24/25 (96%)		
***EC Reliability code*:** 1		
***Reliability category (high, satisfactory, low)*:** High		
Comments: With respect to the chemical composition of the test substance, the source and purity of bisphenol A (BPA) were not reported; however detailed description of high performance liquid chromatography (HPLC) analysis criteria are provided and this is considered to satisfactorily confirm the identity of the test material.		

Appendix B. Robust Study Summary – Inherent Toxicity

Item	Yes	No
***Reference*:** Johnson et al. 2005. Endocrine disruption in aquatic and terrestrial invertebrates. Final report produced by WRc NSF Ltd., Marlow, Buckinghamshire for the United Kingdom Department of Environment, Food and Rural Affairs (DEFRA). March 2005.		
Test Substance: 80-05-7 (Bisphenol A)		
***Chemical composition of the substance (including purity, by-products)**		X
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?		X
Justification of the method/protocol if a non-standard method was used	X	
***GLP (good laboratory practice)**	X	
Test organisms: Amphipod (*Gammarus pulex*)		
Latin or both Latin and common names reported?	X	
Life cycle age/stage of test organism	X	
Sex	X	
Length and weight of test organisms	n/a	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation / during test)	X	
Test design/conditions		
Test type – acute or chronic: Chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls : Solvent control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**		X
Exposure media conditions (temperature, pH, electrical conductivity, hardness, total organic carbon, dissolved organic carbon, dissolved oxygen, major cations and anions; other)		X
Was pH within 6–9 range?	X	
Was temperature within 5–28°C range?	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators/solubilizers (especially for poorly soluble / unstable substances)	X	
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50}–: 14 d LOEC (lowest-observed-effect concentration – survival) = 1.0 mg/L; 14 d NOEC (no-observed-effect concentration – survival) = 0.1 mg/L		
Other endpoints reported – e.g., bioconcentration factor / bioaccumulation factor (BCF/BAF): Reproduction, moulting, markers for endocrine disruption		
***Was toxicity value below the chemical's water solubility?**	X	
Other adverse effects (carcinogenicity, mutagenicity, etc.		X
***Score*:** Major items – 2/5; overall score – 21/25 (84%)		
***EC Reliability code*:** 2		
***Reliability category (high, satisfactory, low)*:** Satisfactory		
Comments: While details relating to the composition/purity of the test substance and standard testing methods used are not included in the report, it is likely that these met acceptability criteria given that the study is part of a larger government-sponsored program and the results were submitted to the United Kingdom Department of Environment, Food and Rural Affairs. The description of test methods includes discussion of procedures for collection and analysis of chemical subsamples for the assessment of chemical stability; however, measured concentrations are not reported and results are presented in terms of nominal concentration values. Similarly, procedures for measurement of water quality parameters are described, but the numerical values are not provided in the report. Consider data generated from the study to be of acceptable quality, even though the resulting report does not fully describe all results.		

Appendix C. Robust Study Summary – Inherent Toxicity

Item	Yes	No
***Reference*:** Johnson et al. 2005. Endocrine disruption in aquatic and terrestrial invertebrates. Final report produced by WRc NSF Ltd., Marlow, Buckinghamshire for the United Kingdom Department of Environment, Food and Rural Affairs (DEFRA). March 2005.		
Test Substance: 80-05-7 (Bisphenol A)		
***Chemical composition of the substance (including purity, by-products)**		X
Persistence/stability of test substance in test system	X	
Method		
References	X	
***OECD, EU, national, or other standard method**?		X
Justification of the method/protocol if a non-standard method was used	X	
***GLP (good laboratory practice)**	X	
Test organisms (specify common and Latin names): Earthworm (*Eisenia sp.*)		
Latin or both Latin and common names reported?	X	
Life cycle age/stage of test organism	X	
Sex	X	
Length and weight of test organisms	n/a	
Number of test organisms per replicate	X	
Food type / feeding periods (acclimation / during test)	X	
Test design/conditions		
Test type – acute or chronic: Chronic		
Experiment type (laboratory or field) specified?	X	
System type (static, semi-static, flow through)?	X	
Negative or positive controls: Solvent control	X	
Number of replicates (including controls) and concentrations	X	
Exposure pathways (food, water, both)	X	
Exposure duration	X	
***Measured concentrations reported?**		X
Exposure media conditions (temperature, pH, electrical conductivity, hardness, total organic carbon, dissolved organic carbon, dissolved oxygen, major cations and anions; other)		X
Was pH within 6–9 range?	X	
Was temperature within 5–28°C range?	X	
Photoperiod and light intensity	X	
Stock and test solution preparation	X	
Use of emulgators/solubilizers (especially for poorly soluble / unstable substances)	X	
Analytical monitoring intervals	X	
Statistical methods used	X	
Results		
Toxicity values (LC_{50}, EC_{50}, or IC_{50} –: 14 d LOEC (lowest-observed-effect concentration – survival) = 100 mg/kg soil dw; 14 d NOEC (no-observed-effect concentration – survival) = 32 mg/kg soil dw		
Other endpoints reported – e.g., bioconentration factor / bioaccumulation factor (BCF/BAF): Reproduction, markers for endocrine disruption		
***Was toxicity value below the chemical's water solubility?**	n/a	
Other adverse effects (carcinogenicity, mutagenicity, etc.		X
***Score*:** Major items – 1/4; overall score – 20/24 (83%)		
***EC Reliability code*:** 2		
***Reliability category (high, satisfactory, low)*:** Satisfactory		
Comments: While details relating to the composition/purity of the test substance and standard testing methods used are not included in the report, it is likely that these met acceptability criteria given that the study is part of a larger government-sponsored program and the results were submitted to the United Kingdom Department of Environment, Food and Rural Affairs. The description of test methods includes discussion of procedures for collection and analysis of chemical subsamples for the assessment of chemical stability; however, measured concentrations are not reported and results are presented in terms of nominal concentration values. Similarly, procedures for measurement of water quality parameters are described, but the numerical values are not provided in the report. Consider data generated from the study to be of acceptable quality, even though the resulting report does not fully describe all results.		

Appendix D. Summary of Studies Investigating Neurobehavioural Effects in Rodents

Author	Species, route, dose(s)	Treatment length	Developmental neurotoxicity endpoints assessed	Critical effects
Behaviour and Receptor Expression				
Ema et al. 2001	SD rats N=25 (F0) Oral, gavage 0, 0.2, 2, 20 or 200 µg/kg per day	Two-generation study Gestation and lactation	Conventional study including behavioural endpoints: open field, water-filled T-maze.	No effects noted by authors.
Nishizawa et al. 2003	ICR mice Oral 0, 0.002 mg/kg per day	Days post coitum: 6.5–11.5 6.5–13.5 6.5–15.5 6.5–17.5	Effects of prenatal exposure on expression of retinoic acid receptors in mouse embryos.	Variable changes in retinoic acid retinoid X receptors α mRNA expression in brain, ovary and testis. Changes varied according to sex, tissue and dosing period.
Nishizawa et al. 2005 a	ICR mice Oral 0, 00002, 0.002, 0.20, 20 mg/kg per day	Days post coitum: 6.5–13.5 6.5–17.5	Effects of exposure on expression of mRNA for arylhydrocarbon and retinoid receptors in mouse embryos.	Numerous changes; varied as above. Increased mRNA expression for the arylhydrocarbon receptors in brain, testis and ovary; retinoic acid α receptor in brain, ovary and testis; retinoid X α receptor in testis and ovary.
Nishizawa et al. 2005b	ICR mice Oral 0, 00002, 0.002, 0.20, 20 mg/kg per day	Days post coitum: 6.5–13.5 6.5–17.5	Effects of exposure on expression of arylhydrocarbon receptor, related factors and metabolizing enzymes in mouse embryos.	Increased mRNA expression for arylhydrocarbon receptor, arylhydrocarbon receptor repressor, arylhydrocarbon receptor nuclear translocator in brain, testis and ovary.
Kawai et al. 2003	CD-1 mice N=7–9 Oral, micropipette 0, 2, 20 µg/kg per day	Gestational day (GD) 11–18	Aggressive behaviour in male mice at 8, 12 and 16 weeks of age: aggression scores determined by contact times with opponent.	Increased aggression scores at 8 weeks (2, 20 µg/kg per day); no effect was observed at 12 and 16 weeks.
Palanza et al. 2002	CD-1 mice N=10–12 (F0) Oral, micropipette 10 µg/kg-bw per day	GD 14–18 (F0) GD 14–18 (F1)	Maternal nursing behaviour of F1 monitored from postnatal day (PND) 2–15. Reflex responses examined in F2 offspring.	Differences in nursing behaviour observed when F1 females were exposed to BPA only prenatally or as an adult; not during both periods. No effects on F2 postnatal reflex development.
Laviola et al. 2005	CD-1 mice N=10–12 Oral, feeding from syringe 10 µg/kg-bw per day	GD 11–18	At PND 60 males and females were subjected to conditioned place preference testing following a d-amphetamine injection (d-amphetamine-reinforcing effects).	Conditioned place preference was not observed in treated females; males were unaffected.
Gioiosa et al. 2007	CD-1 mice N=14 Oral (trained to spontaneously drink) 10 µg/kg-bw per day	GD 11 to PND 8	Observed males and females at different ages to investigate explorative and emotional behaviours: novelty test (adolescents), open field and elevated plus-maze (adults).	BPA reduced or eliminated sex-related behavioural differences in novelty test, open field behaviour and elevated plus-maze.

Author	Species, route, dose(s)	Treatment length	Developmental neurotoxicity endpoints assessed	Critical effects
Fujimoto et al. 2006	Wistar rats N=6 Drinking water 15 µg/kg per day	GD 13 to PND 0	Behavioural testing in offspring: open field, elevated plus-maze, passive avoidance, forced swimming tests	In open field testing, rearing was increased in males and slightly decreased in females. Differences were observed in the forced swimming test for males and females. No effects observed in elevated plus-maze and passive avoidance tests.
Farabollini et al. 2002	SD rats N=7 Oral, micropipette 40 µg/kg-bw per day	Gestation or lactation. Cross-fostered to establish prenatal and postnatal groups.	Social and sexual behaviour assessed beginning at ~14 weeks of age; intruder test.	Statistically significant changes in sexual performance: males – reduced females – slight increase in sexual behaviour.
Aloisi et al. 2002	SD rats N=7 Oral, micropipette 40 µg/kg-bw per day	Gestation or lactation. Cross-fostered to establish prenatal and postnatal groups.	Behavioural response to pain (licking, flexing and jerking of the paw). Response to formalin injection at 22 weeks of age.	No BPA-related effect on open field behaviours. Slight inter-group differences in pain response (marginally diminished).
Adriani et al. 2003	SD rats N=9 Oral 40 µg/kg-bw per day	GD 0 to PND 23 (behaviour examined at PND 35–45; adolescence)	Novelty preference (PND 35–45; adolescence), impulsivity testing (adults), open field testing with and without amphetamine challenge.	Decreased novelty seeking in females; decreased impulsive behaviour in males. The amphetamine-induced increment activity was significantly less marked in BPA-treated male rats compared with controls. No open field differences without challenge.
Porrini et al. 2005	SD rats, females N=12 Oral, micropipette 40 µg/kg-bw per day	GD 0 to PND 21 Cross-fostered pups	Play behaviour of female offspring (PND 35, 45, 55). Identified six behaviours (principle component analysis); significant differences noted for three.	Social and non-social exploration increased (day 35 and 45); Play with males decreased (45 days); Duration of grooming behaviour decreased (day 45).
Della Seta et al. 2005	SD rats, females N=17 Oral, micropipette 40 µg/kg-bw per day	Gestation and lactation (day after mating through lactation)	Assessed maternal behaviour: the frequency, duration and latency of each element of maternal behaviour was analyzed with software (retrieving, ano-genital licking, licking-grooming, arched-back posture, lactation, on nest, nest building).	Overall significant reduction in licking-grooming behaviour. Marginal reduction in frequency of ano-genital licking and duration of arched-back posture; altered behaviour was not dependent on pup gender.
Della Seta et al. 2006	SD rats, males N=26 Oral, micropipette 40 µg/kg-bw per day	PND 23–30	Socio-sexual behaviour of juvenile males (examined on PND 45 and at PND >90). Plasma 17β-oestradiol and testosterone level were measured on PND 37 and 105.	Biting/sniffing/climbing behaviours (sexual activity) (directed at a PVC tube) were lower in BPA group (slight modifications compared to those observed with ethinylestradiol). Sexual behaviour assessment: short-term effects; latency to first intromission was reduced. Plasma testosterone levels were significantly lower (17β-oestradiol was not affected).
Negishi et al. 2004	F344 rats N=8–10 Oral, gavage 0, 100 µg/kg per day	GD 3 to PND 20	Behaviour of males: open field, spontaneous motor activity, passive avoidance, elevated plus-maze, active avoidance and monoamine-disruption tests	Fewer correct avoidance responses in active avoidance test trials 1 to 3 of 4 (suggests slower learning).

Author	Species, route, dose(s)	Treatment length	Developmental neurotoxicity endpoints assessed	Critical effects
Ryan and Vandenbergh 2006	C57/B1/6 mice N=14–16 Oral, gavage 0, 2, 200 µg/kg per day	GD 3 to PND 21	Effects on non-reproductive sexually dimorphic behaviour: ovariectomized female offspring tested in elevated plus-maze, light-dark preference chamber, radial arm maze and modified barnes maze.	Earlier onset of puberty (200 µg/kg per day). Increased anxiety (light-dark preference chamber) at 200 µg/kg per day. No differences in spatial memory tests.
Carr et al. 2003	F344 rats N=10 pups/sex Oral, gavage 0, 0.1, 0.25 mg/kg per day	PND 1–14	Neonatal exposure on Morris water maze performance (tested on PND 33)	Reduced memory retention at 0.25 mg/kg per day in males (not significant) and females (significant).
Nigishi et al. 2003	F344 rats N=8–9 Oral, gavage 0, 4, 40, 400 mg/kg per day	GD 10 to PND 20	Behavioural evaluations: spontaneous motor activity, active avoidance test, open field behaviour	Variable responses; did not follow a dose-related pattern. No effect in the open field test.
Farabollini et al. 1999	SD rats N=11 Oral, micropipette 1) 40 µg/kg-bw per day 2) 400 µg/kg-bw per day	1) 10 days prior to mating – PND 21 2) GD 14 to PND 21	Conducted between PND 85 and 87. Holeboard box, elevated plus-maze (tests to provide measure of anxiety and locomotion).	Increased anxiety-related behaviour (males and females in holeboard test) – 400 µg/kg-bw per day. Decreased anxiety-related behaviour in males in maze test (in conflict with holeboard test).
Dessi-Fulgheri et al. 2002	SD rats N=11 Oral, micropipette 1) 40 µg/kg-bw per day 2) 400 µg/kg-bw per day	1) 10 days prior to mating – PND 21 2) GD 14 to PND 6	Play behaviour observations at PND 35, 45, 55 (groups were pooled for analysis). Identified eight behaviours; significant differences noted for four.	At 40 µg/kg-bw per day: play directed to females by females increased; frequency of social interest behaviour increased in males. At 400 µg/kg-bw per day: frequency of social interest behaviour was decreased in both males and females; sociosexual exploration decreased in males (both test groups) and females.
Kawai et al. 2007	ICR mice N=18 Oral, micropipette 0, 2 µg/kg per day	GD 11–17	Expression of ERα and ERβ on male mice. Immunostaining to ERα and ERβ, serotonin and serotonin transporter at 4–5, 8–9 or 12–13 weeks of age.	Increased number of neurons expressing ERα and ERβ at 5 and 13 weeks, but not at 9 weeks.
Ceccarelli et al. 2007	SD rats N=14 Oral, micropipette 40 µg/kg-bw per day	PND 23–30	Effects of juvenile BPA exposure in brain development. ERα levels assessed in three sexually dimorphic regions of the hypothalamus (PND 37 and 90)	Increased ERα levels in ventromedial nucleus in females at PND 37; not at PND 90. No differences in males.
Facciolo et al. 2002	SD rats N=unspecified Oral 40 µg/kg-bw per day 400 µg/kg-bw per day	Pre-mating to PND 23 Cross-fostered pups	Effect on the somatostatin receptor subtype 2 (sst_2) in limbic regions of the brain (PND 10 and 23). Binding activity was examined.	The higher dose proved to be the more effective one; the most dramatic effects of BPA on sst_2 levels occurred at the low-affinity states.
Facciolo et al. 2005	SD rats N =12 Oral 40 µg/kg-bw per day 400 µg/kg-bw per day	8 days pre-mating to PND 23 Cross-fostered pups	Effect on the expression of sst_3 mRNA receptors in the limbic regions of the brain in females.	At 400 µg/kg-bw per day, mRNA levels were increased in some areas and decreased in others. Agonists for $\alpha GABA_A$ receptors enhanced responses.
Central Dopaminergic System				

Author	Species, route, dose(s)	Treatment length	Developmental neurotoxicity endpoints assessed	Critical effects
Suzuki et al. 2003	ddY mice N=? Dietary 0, 2.5, 60, 250 mg/kg per day	Gestation and lactation	In male offspring: place preference conditioning test conducted using methamphetamine; locomotor activity; G-protein activation in the limbic forebrain; expression of dopamine D1 receptor mRNA.	Methamphetamine-induced place preference (dose-dependent); hyperlocomotion by methamphetamine was dramatically potentiated (250 mg/kg per day)); increased G-protein activation and upregulated dopamine D1 receptor expression at the high dose.
Mizuo et al. 2004a	ddY mice N=? Dietary 0, 2.5, 60, 250 mg/kg per day	Gestation and lactation	In male offspring: rewarding effects, locomotion activity and receptor activity induced by morphine; G-protein activation and μ-opioid receptor mRNA expression.	Morphine-induced place preference (dose-dependent; significant at 60 and 250 mg/kg per day.) and hyperlocomotion (250 mg/kg per day.). G-protein activation and μ-opioid receptor mRNA was not changed by BPA.
Mizuo et al. 2004b	ddY mice N=? Dietary 0, 250 mg/kg per day (estimated dose levels)	Gestation and lactation	Functional changes in dopamine D3 receptors in limbic forebrain (expression measured in an RT-PCR assay)	Reduced G-protein activation by the dopamine D3 receptor agonist; decreased receptor density in brain following BPA exposure.
Narita et al. 2006	ddY mice N=? Dietary 0, 0.006, 0.06, 0.6, 100, 400 mg/kg per day	Gestation and lactation	Effects on central dopaminergic system in mouse limbic area – place conditioning, locomotion, [^{35}S]GTPγS binding assay in response to morphine.	Increased place preference (0.6, 100, 400 mg/kg per day.); hyperlocomotion (0.6 and 400 mg/kg per day.); increased dopamine-induced binding (0.006, 0.6 or 400 mg/kg per day.). [BPA may potentiate dopamine-receptor-dependent neurotransmission]
Narita et al. 2007	ddY mice N=? Dietary 0, 400 mg/kg per day	GD 0–7 GD 7–14 GD 14–20 PND 0–20	Investigate importance of exposure period with respect to morphine-induced behaviours. Male offspring: place conditioning, locomotion, [^{35}S]GTPγS binding assay in response to morphine.	Morphine associated place preference, hyperlocomotion and potentiated dopamine-induced binding at GD 7–14 and PND 0–20. Suggests organogenesis and lactation as sensitive periods for BPA-induced alternation of the dopaminergic system.
Brain Structure				
Nakamura et al. 2006	ICR/Jcl mice subcutaneous (s.c.) injection 0, 20 μg/kg per day	GD 0–16	Brain neocortex development: embryonic forebrains assessed after intraperitoneal (i.p.) injection of BrdU on either GD 10, 12, 14 or 16 (immunohistochemistry) RT-PCR analysis of various genes.	Results suggest BPA-induced acceleration of neuronal differentiation/migration. The expression of various genes was upregulated at E14.5 in the BPA-treated group.
Kubo et al. 2003	Wistar rats N=5–6 Drinking water 0, 0.03, 0.3 mg/kg per day (estimated intakes)	Gestation and lactation	Open field testing, sexual behaviour; sexually dimorphic nucleus of the preoptic area (SDN-POA) and locus coeruleus volumes; number of neurons in locus coeruleus	Open field behaviour (anxiety-related) slightly reduced in males and slightly increased in females. Gender difference in locus coeruleus volume was reversed; extent of reversal was greater at 0.03 mg/kg per day.
Kubo et al. 2001	Wistar rats N=5 Drinking water 0, 1.5 mg/kg per day (approx)	Gestation and lactation	Behaviour and brain development: open field behaviour, passive avoidance and SDN-POA and locus coeruleus volumes	Gender-related differences in open field and passive avoidance tests diminished. Gender difference in locus coeruleus volume was reversed.

Author	Species, route, dose(s)	Treatment length	Developmental neurotoxicity endpoints assessed	Critical effects
Funabashi et al. 2004	Wistar rat N=8–11 Drinking water 0, 2.5 mg/kg per day	Gestation to PND 21	Numbers of corticotrophin releasing hormone (CRH) neurones in the brain: immunohistochemistry of neurons in the bed nucleus of the stria terminalis and preoptic area.	Normal gender difference in numbers of CRH neurons not maintained; due to increase in males and decrease in females.
Tando et al. 2007	ddY mice Dietary 0, 4.5 or 1200 mg/kg per day	GD 0 to PND 21	Immunohistochemical assessment at 8–11 weeks of age: tyrosine hydroxylase, calbindin D-28 K, calretinin, parvalbumin. Cell death was assessed using TUNEL staining.	Reduced density and volume of tyrosine hydroxylase positive nuclei and fibers in substantia nigra in females at 4.5 kg per day, not at 1200 kg per day. TUNEL did not identify the presence of cell death.
Honma et al. 2006	SD rats N=6 Oral, gavage 0, 4, 40 mg/kg per day	GD 6 to PND 20	HPLC analysis of brain neurotransmitter levels at 1, 3, 6, or 9 weeks of age.	No discernable variations in neurotransmitter patterns.
Kwon et al. 2000	SD rats N=8 Oral, gavage 0, 3.2, 32, 320 mg/kg per day	GD 13 to PND 21	Sexually dimorphic nucleus of the preoptic area (SDN-POA) volume in females (immunohistochemistry)	No effects.
Ishido et al. 2007	Wistar rats N=10 (dams) Oral, 0, 600 µg/pup/day [authors indicated dose equivalent to 12–60 mg/kg per day]	Daily administration from PND 5 to 3 weeks of age	Measurements in males: Spontaneous motor activity (Supermex system) (4–5 weeks); immunohistochemistry of tyrosine hydroxylase and TUNEL; RT-PCR of dopamine transporter (7 weeks)	Increased motor activity (hyperactivity) through nocturnal phase (12-hr dark period); 1.3 times as active as controls. Tyrosine hydroxylase immunoreactivity in substantia nigra largely reduced (not quantified). Increase in TUNEL positive cells with nuclear condensation (apoptotic) in substantia nigra. Gene expression of dopamine transporter was completely inhibited. [BPA thought to contribute to the degeneration of dopaminergic neurons]
Patisaul et al. 2006	SD rats N=5–8 pups s.c. injection 100 mg/kg per day	PND 1 and 2	Development of the anterioventral periventricular nucleus of the hypothalamus (AVPV) (assessed on PND 19). Immunohistochemistry for ERα and/or tyrosine hydroxylase (TH).	TH positive cells increased in males (demasculinization); decreased TH/ERα double-labelled cells in AVPV in females (defeminization – depleted to male-typical levels). SDN or CALB-SDN volumes unaffected; AVPV volume unaffected.
Patisaul et al. 2007	SD rats N=5–8 pups s.c. injection 100 mg/kg per day	PND 1 and 2	Volumes of AVPV and SDN-POA (immunohistochemistry), calbindin, GnRH and fos immunoreactivity; assessed in adults.	Increased SDN-POA calbindin-positive nuclei (considered “hypermasculinization” of males). No other BPA-induced effects.