Government of Canada
Gouvernement du Canada

Assessment Report

Triclosan

Chemical Abstracts Service Registry Number 3380-34-5

Environment and Climate Change Canada
Health Canada

November 2016

Canada

En14-259/2016E-PDF
978-0-660-05976-1

Synopsis

An assessment of triclosan has been conducted under the *Canadian Environmental Protection Act, 1999* (CEPA) to determine if it poses a risk to Canadians and their environment. Triclosan was also scheduled for re-evaluation under Health Canada's Pest Management Regulatory Agency (PMRA) pesticide re-evaluation program pursuant to the *Pest Control Products Act* (PCPA). The preliminary assessment that preceded this assessment report included a proposed conclusion for triclosan under both CEPA and PCPA. As of December 31, 2014, the Canadian registrants voluntarily discontinued the sale of pest control products containing triclosan. Consequently, triclosan is no longer registered in Canada as a pest control product under the PCPA. Hence, this assessment does not include a conclusion under PCPA for these products.

Triclosan [phenol, 5-chloro-2-(2,4-dichlorophenoxy)] (CAS RN 3380-34-5) is used as a material preservative and as an antimicrobial agent in a wide range of products used by industry and consumers to stop the growth of bacteria, fungi and mildew and to deodorize.

Triclosan does not occur naturally in the environment. The potential sources of exposure to triclosan for Canadians include products used by consumers which are treated with or contain triclosan (including, but not limited to, cosmetics, non-prescription drugs and natural health products) as well as industrial manufacturing or formulation of products containing triclosan.

Exposure of the general population to triclosan was characterized using the available Canadian biomonitoring data for triclosan from the Canadian Health Measures Survey (CHMS) Cycle 2 (2009-2011), the Plastic and Personal-Care Product Use in Pregnancy (P4) Study, and the Maternal-Infant Research on Environmental Chemicals (MIREC) and MIREC-Child Development Plus (MIREC-CD Plus) studies. These data encompass exposure to triclosan from all potential sources and routes, and are considered the most accurate estimates of total exposure of the general population in Canada to triclosan. Similar levels were observed in the recent CHMS, Cycle 3 (2012-2013). Exposure estimates of children under the age of three were derived separately using a combination of Canadian biomonitoring data (for infants and children three to five years old) and additional estimates to account for potential exposures via breast milk, household dust and mouthing of triclosan-treated plastic products.

In examination of the toxicological database as a whole, the principal toxicity in rodents and dogs following ingestion of triclosan is mainly in the liver, with the mouse being the most sensitive species. Triclosan exposure also results in modest decreases in serum

thyroid hormone thyroxine (T_4) levels (but not triiodothyronine [T_3] or thyroid-stimulating hormone [TSH]) in rats caused by disruption in the target organ (liver) due to rodent-specific metabolism of triclosan. Critical evaluation of the overall database shows that there are no indications of adverse effects on thyroid function in the animal database and available human data show no changes in thyroid hormone levels or liver function after long-term exposure to low levels of triclosan. Further, humans have a much greater capacity to adapt to deviations in T_4 levels than do rodents. Consequently, the overall database does not support the effects of triclosan on thyroid function as a critical effect for risk characterization in humans.

Considering the current available information on the adverse effects of triclosan, an overall database no-observed-adverse-effect level (NOAEL) of 25 mg/kg bw/day was identified from a 90-day oral toxicity study in mice and was conservatively selected to be protective against a number of effects observed in multiple species at higher doses. This NOAEL was considered protective against potential liver effects, if any, that could occur in humans as well as effects in other organs and systems.

Risk to human health from exposure to triclosan is estimated by comparing estimates of exposure in humans with critical effect levels in health effects studies conducted in laboratory animals in order to derive margins of exposure (MOEs). For the general population, comparison of the estimated mean and upper-bound daily intakes with critical effect levels in mice (based on liver effects) resulted in MOEs between 416 and 5 400. For children under the age of 3 years, comparison of aggregate exposure estimates with the critical effect levels resulted in MOEs greater than 3 300. These MOEs were considered adequate to address uncertainties in the health effects and exposure databases for triclosan.

A review of all available information on the potential for triclosan to induce antimicrobial resistance (AMR) was conducted. Although there is the potential for triclosan-resistant bacteria to exist in laboratory and clinical settings, this has not been documented outside of clinical use (e.g. household settings, toothpaste use). Based on available information, induction of AMR from current levels of triclosan has not been identified as a concern for human health.

Triclosan can be released to the environment as a result of its use in many products used by consumers, or as a result of the industrial manufacture of products containing triclosan. The use in products is considered to be the major contributor to releases of triclosan down the drain. Triclosan released into wastewater reaches wastewater treatment plants[1] (WWTP), where it is partly removed from wastewater, depending on the type of treatment. Triclosan is released to aquatic ecosystems as part of WWTP effluents. Some triclosan partitions to sludge during the wastewater treatment process.

[1]The term “plants” encompasses all types of treatment facilities, including lagoons.

As a result, triclosan also reaches terrestrial ecosystems by way of biosolids amendment to agricultural land.

Triclosan degrades relatively quickly in the environment through biotic and abiotic processes. However, it is ubiquitous in the environment due to the continual release to surface water through WWTP effluents. Therefore, chronic exposure of organisms to triclosan is expected in aquatic ecosystems, especially when close to effluent sources. Exposure to soil organisms is also likely through land application of biosolids.

Triclosan is highly toxic to a variety of aquatic organisms, such as algae, macrophytes, invertebrates, amphibians and fish. Adverse effects that have been observed include reduction in growth, reproduction and survival, and there is evidence of effects on the endocrine system at environmentally relevant concentrations. Triclosan can also be highly bioconcentrated in fish, and there is evidence of bioaccumulation in algae and aquatic invertebrates. Triclosan is also highly toxic to certain soil organisms.

Based on an extensive review of the available toxicity data, a predicted no-effect concentration of 376 ng/L was derived for the aquatic compartment. This threshold includes consideration of endocrine disruptive effects in fish and amphibians.

Exposure of aquatic organisms was estimated using measured concentrations of triclosan in the receiving surface waters, including at or near WWTP effluent discharge points. Measured concentrations of triclosan in surface waters across Canada indicate that triclosan may cause harmful effects in aquatic ecosystems.

Concentrations of triclosan in soils were estimated based on the measured concentrations of triclosan in biosolids in Canada, and using parameters such as triclosan half-lives in soil and the regulated application rates for biosolids. Risk characterization that considered the high toxicity to certain soil organisms indicated that triclosan is not likely to cause harmful effects, given the low predicted soil concentrations.

The most notable transformation products of triclosan, formed through metabolism and degradation or chlorination, are methyl-triclosan and certain lower chlorinated dioxins. While most of the triclosan-derived dioxins are considered to be transient in the environment and of low toxicity, methyl-triclosan has similar properties to triclosan, such as high toxicity and bioaccumulation potential. Although chronic exposure to methyl-triclosan is likely in the environment, it has been detected at concentrations much lower than those of triclosan.

Triclosan is always present in aquatic ecosystems due to its continuous releases. It is a very potent chemical that can accumulate in organisms and cause adverse effects even at low exposure levels in the environment. Triclosan can transform to methyl-triclosan and to certain lower chlorinated dioxins. Overall, considering the potency of triclosan its

widespread occurrence and the current exposure levels observed in the Canadian environment, it is concluded that potential for harm exists from exposure to triclosan in aquatic ecosystems.

Conclusions under CEPA

Based on the adequacy of the MOEs between estimates of aggregated exposure to triclosan and critical effect levels, it is concluded that triclosan is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health; thus, it does not meet the criteria under paragraph 64(*c*) of CEPA.

Considering all available lines of evidence presented in this assessment report, there is risk of harm to organisms, but not to the broader integrity of the environment from triclosan. It is concluded that triclosan meets the criteria under paragraph 64(*a*) of CEPA as it is entering or may enter 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. However, it is concluded that triclosan does not meet the criteria under paragraph 64(*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends.

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

Even though it is continuously present in the environment, triclosan has been determined not to meet the persistence criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA. Similarly, while triclosan accumulates in organisms to levels that can cause adverse effects, it does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

Table of Contents

Tables and Figures

1. Introduction

CEPA requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that meet the categorization criteria set out in the Act to determine whether the substances present or may present a risk to the environment or to human health. A screening assessment involves an analysis of a substance using available information to determine whether the substance is harmful to human health or the environment as defined in section 64 of CEPA.

Triclosan (phenol, 5-chloro-2-(2,4-dichlorophenoxy); CAS RN 3380-34-5) is a substance on the Domestic Substances List that was identified as a priority for action under CEPA since it met the categorization criteria set out in the Act based on ecological concerns. Health Canada and Environment and Climate Change Canada conducted a scientific assessment of available information relevant to the assessment of triclosan. This assessment report provides the basis for conclusions under CEPA.

The assessment of human health effects was informed by foreign reviews conducted by the United States Environmental Protection Agency (US EPA 2008a,b,c,d; 2014), the European Union (EU) Scientific Committee on Consumer Products (SCCP 2009), the Scientific Committee on Consumer Safety (SCCS 2011), and the Australian Department of Health and Ageing National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2009).

Exposure of the Canadian population to triclosan was assessed by Health Canada using the available biomonitoring data for triclosan from the Canadian Health Measures Survey (CHMS) Cycle 2 (2009-2011), the Plastics and Personal-Care Product Use in Pregnancy (or P4) Study, and the Maternal-Infant Research on Environmental Chemicals (or MIREC) Study. These data encompass exposures to triclosan from all potential sources and routes, and are considered the most accurate estimates of total exposure of the general population in Canada to triclosan. Some deterministic exposure estimates were also conducted by Health Canada to more fully characterize the human health effects and exposure of the general population of Canada.

Data relevant to the ecological assessment of triclosan were identified in original literature, review documents, and commercial and government databases. In addition to retrieving the references from reviews and a literature database search, efforts were made to contact researchers, academia, industry and government agencies to obtain relevant information on triclosan.

Studies that form the basis of this assessment have been critically evaluated by Health Canada and Environment and Climate Change Canada. The assessment does not present an exhaustive review of all available data; rather, it presents the critical studies

and lines of evidence pertinent to the conclusions. Relevant data obtained as of April 2016 were considered in this document.

The human health and ecological portions of this assessment have undergone external written peer review or consultation. Comments on the technical portions relevant to human health were received from scientific experts who were selected and directed by Toxicology Excellence for Risk Assessment, Risk Sciences International Inc. These included ToxEcology - Environmental Consulting Ltd, Tetra Tech, and Summit Toxicology. Outcomes of the US Environmental Protection Agency's Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) panel were also taken into consideration in the development of this assessment. Comments on the technical portions relevant to the environment were received from Cecilie Rendal (Unilever), Donna Randall (US Environmental Protection Agency), Theo Traas (Dutch National Institute for Public Health and the Environment (RIVM)), and Magnus Løfstedt (Danish Environmental Protection Agency). The conclusions presented in this document are those of Health Canada and Environment and Climate Change Canada and do not necessarily reflect the opinions of the external reviewers. Additionally, a preliminary version of this assessment was subject to a 60-day public comment period. This assessment report for triclosan includes the conclusion as to whether triclosan meets any of the criteria in section 64 of CEPA.

Triclosan, as an active ingredient in pest control products, was also scheduled for re-evaluation under Health Canada's Pest Management Regulatory Agency (PMRA) pesticide re-evaluation program pursuant to the PCPA. As of December 31, 2014, pest control products containing triclosan are no longer registered in Canada under the Pest Control Products Act since the registrants voluntarily discontinued the sales of these products in Canada.

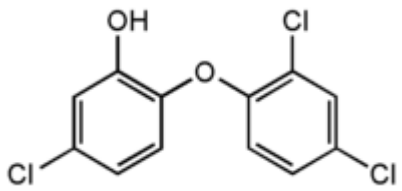
2. Substance Identity, Properties and Uses

2.1 Substance Identity

Phenol, 5-chloro-2-(2,4-dichlorophenoxy), commonly known as triclosan, is a chlorinated aromatic compound that has functional groups representative of both ethers and phenols. Information on its identity, including names and chemical structure, is presented in Table 2-1.

Table 2-1. Substance identity for triclosan

CAS RN	3380-34-5
DSL name	Phenol, 5-chloro-2-(2,4-dichlorophenoxy)
IUPAC	2,4,4′-Trichloro-2′-hydroxydiphenyl ether
Inventory names[a]	Phenol, 5-chloro-2-(2,4-dichlorophenoxy) (AICS, ASIA-PAC, NZIoC, PICCS, SWISS, TSCA) Triclosan (EINECS, PICCS, SWISS) 2,4,4′-Trichloro-2′-hydroxydiphenyl ether (ENCS) 5-Chloro-2-(2′,4′-dichlorophenoxy) phenol (ENCS) 5-Chloro-2-(2,4-dichlorophenoxy)phenol (ECL) 2′,4′,4-Trichloro-2-hydroxydiphenyl ether 2′,4,4′-Trichloro-2-hydroxydiphenyl ether 2-Hydroxy-2,4,4′-trichlorodiphenyl ether 2,2′-Oxybis(1′,5′-dichlorophenyl-5-chlorophenol) 2-Hydroxy-2′,4,4′-trichlorodiphenyl ether 3-Chloro-6-(2,4-dichlorophenoxy)phenol 4-Chloro-2-hydroxyphenyl 2,4-dichlorophenyl ether
Other names	Amicor; Aquasept; Bacti-Stat soap; Bactonix; Biofresh; Cansan TCH; CH 3565; CH 3635; DP 300; Cloxifenolum; Endure 200; Gamophen; Irgacare CF 100; Irgacare MP; Irgacide LP 10; Irgaguard B 1000; Irgaguard B 1325; Irgasan; Irgasan CH 3565; Irgasan DP 30; Irgasan DP 300; Irgasan DP 3000; Irgasan DP 400; Irgasan PE 30; Irgasan PG 60; Lexol 300; Microban Additive B; Microban B; NM 100; Oletron; Sanitized XTX; Sapoderm; SterZac; TCCP; THDP; Tinosan AM 100; Tinosan AM 110; Ultra Fresh NM 100THDP; Vinyzene DP 7000; Yujiexin; ZerZac; Zilesan UW
Chemical group	Organic
Chemical subgroup	Phenols
Chemical formula	$C_{12}H_7Cl_3O_2$

Chemical structure	
Molecular mass	289.54 g/mol
Purity/impurities	Polychlorinated dibenzodioxins and dibenzofurans

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA PAC, Asia-Pacific Substances Lists; CAS, Chemical Abstracts Service; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; IUPAC, International Union of Pure and Applied Chemistry; NZIoC, New Zealand Inventory of Chemicals; ; PICCS, Philippines Inventory of Chemicals and Chemical Substances; RN, Registry Number; SWISS, Giftliste 1 and Inventory of Notified New Substances; TSCA, US *Toxic Substances Control Act*.
[a]From NCI (2011).

2.1.1 Impurities of human health and environmental concern

Triclosan contains low levels contaminants, specifically polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs). PCDDs and PCDFs were the subject of an assessment as part of the *Priority Substances List* of CEPA 1988. These substances are considered both persistent and bioaccumulative as well as “toxic” as defined under paragraphs 11(a) and 11(c) of CEPA 1988 (Canada 1990). They are therefore considered to be Track 1 substances under the Toxic Substances Management Policy (TSMP) (Canada 1995).

In Canada, triclosan is included on Health Canada’s List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as the Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene the general prohibition found in section 16 of the *Food and Drugs Act* or a provision of the *Cosmetic Regulations* (Canada 2007). Under Canadian legislation, cosmetics that contain substances that are harmful to the user cannot be sold. The Hotlist restriction for triclosan sets a maximum concentration of 0.03% in cosmetic mouthwashes and 0.3% in other cosmetic products (Canada 2007, Health Canada 2014b). In addition, oral care products containing triclosan with polychlorinated dibenzo-p-dioxin (PCDD) and polychlorinated dibenzofuran (PCDF) impurities should not exceed 0.1 ng/g (0.1 part per billion [ppb]) for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and 2,3,7,8-tetrachlorodibenzofuran and 10 µg/g (10 parts per million [ppm]) for total other PCDD/PCDF impurities, with no individual impurity greater than 5 µg/g (5 ppm). These limits for PCDD/PCDF impurities are also expected to be respected by manufacturers/licensees of natural health products containing triclosan (NHPID 2015).

Due to the potential presence of PCDDs and PCDFs at trace levels in triclosan, the United States Pharmacopeia (USP) recommends concentration limits for certain impurities in triclosan (USP 2009). For comparison, while there may be variance on the individual impurity limits, the Canadian limits for total PCDD/PCDF impurities (of approximately 10 µg/g) do not exceed the USP recommended limits (totaled as approximately 21.5 µg/g).

The presence of TSMP Track 1 substances in pest control products is managed in accordance with Health Canada's strategy to prevent or minimize releases, with the ultimate goal of virtual elimination, as described in Regulatory Directive DIR99-03 (PMRA 1999). The relative importance of triclosan as an environmental source of PCDDs is expected to be low compared with other sources on a national scale. These other sources include large-scale burning of municipal and medical waste, production of iron and steel, backyard burning of household waste, fuel burning (including diesel), wood burning (especially if the wood has been chemically treated), electrical power generation and tobacco smoke (Health Canada 2005).

2.2 Physical and Chemical Properties

Triclosan is soluble in water and has low volatility (Table 2-2). It is not expected to volatilize from a water surface, as indicated by its Henry's law constant. It should ionize at environmentally relevant pH values (i.e., pH 6–9 for water bodies in Canada), as indicated by its acid dissociation constant (pK_a) of 8.1.

Table 2-2. Physical and chemical properties of triclosan

Property	Value	Data type	References
Melting point (°C)	54–57 54–57.3	Experimental Experimental	Sax and Lewis 2000 O'Neil 2001
Boiling point (°C)	374	Modelled	MPBPWIN 2008
VP at 20°C (Pa)	5.33×10^{-4} (4×10^{-6} mmHg)	Experimental	O'Neil 2001
WS at 20°C (mg/L)	12 (at pH 6.5); 6.5 (at pH 5)	Experimental	ECHA c2007-2014
Solubility in other solvents	Readily soluble in alkaline solutions and many organic solvents	Experimental	O'Neil 2001
HLC at 25°C (Pa·m^3/mol)	1.54×10^{-2} (HLC = VP/WS) (1.52×10^{-7} atm·m^3/mol) 5.05×10^{-4} (Bond method) (4.99×10^{-9} atm·m^3/mol)	Experimental Modelled	O'Neil 2001; Yalkowsky and He 2003 HENRYWIN 2008

Property	Value	Data type	References
log K_{ow}	4.8 (at 25°C and pH 6.7) 4.9 (at 20°C and pH 5)	Experimental	ECHA c2007-2014
log K_{oa}	9.97	Modelled	KOAWIN 2008
log K_{oc}	3.34–4.67 (pH 4–8)	Experimental	Singer et al. 2002; Wu et al. 2009; Xu et al. 2009; Karnjanapiboonwong et al. 2010
log K_d	1.00–2.45 (pH 4–8)	Experimental	Wu et al. 2009; Xu et al. 2009; Karnjanapiboonwong et al. 2010
pK_a at 20°C	8.14 (acid form)	Experimental	ECHA c2007-2014

Abbreviations: HLC, Henry's law constant; K_d, soil/water partition coefficient; K_{oa}, octanol/air partition coefficient; K_{oc}, soil organic carbon/water partition coefficient; K_{ow}, *n*-octanol/water partition coefficient; pK_a, dissociation constant; VP, vapour pressure; WS, water solubility.

2.3 Triclosan Use Patterns in Canada

Triclosan is used as a medicinal ingredient in drug products and medical devices such as sutures as well as a non-medicinal ingredient in cosmetics, natural health products and drug products (DPD 2016; LNHPD 2016; 2016 personal communications from the Consumer Product Safety Directorate, Health Canada, to the Existing Substances Risk Assessment Bureau, Health Canada, and 2015 communication from Therapeutic Products Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). As of December 31, 2014, triclosan is no longer registered in Canada as a pest control product due to voluntary withdrawal from the market (Health Canada's Pesticide Product Information Database; Health Canada 2014).

2.3.1 Cosmetic products

There were 322 cosmetic products containing triclosan notified to Health Canada, including skin cleansers (body, face and hands), moisturizers, face and eye makeups, deodorant sticks/sprays, fragrances, tanning products, shaving preparations, bath products, exfoliants, massage products, styling products, and shampoos (2016 personal communication from Consumer Product Safety Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

According to the Health Canada's Cosmetic Ingredient Hotlist, concentrations of triclosan that exceed 0.3% in all cosmetics (i.e. deodorants, creams, toothpastes, face washes, etc.) or 0.03% in mouthwashes may contravene the *Food and Drugs* or the C*osmetic Regulations*.

2.3.2 Natural health products

Triclosan is listed in the Natural Health Products Ingredients Database (NHPID) with a non-medicinal role for use as antimicrobial preservative in natural health products, provided that it does not contribute to the claim of the product (NHPID 2015). Consistent with the concentrations indicated in the Cosmetic Ingredient Hotlist, the NHPID also lists concentrations of triclosan of less than or equal to 0.03% in mouthwashes and 0.3% in topical products and dentifrices as restrictions associated with the use of triclosan in natural health products (Health Canada 2015; NHPID 2015). As a non-medicinal ingredient, triclosan is listed in the Licensed Natural Health Products Database and therefore is present in currently licensed natural health products (e.g., toothpastes, foot gels, acne treatments, body sprays, skin cleansers and lotions) (LNHPD 2016; January 2014 personal communication from Risk Management Bureau, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). There are 16 authorized natural health products containing triclosan (LNHPD 2016).

2.3.3 Drug products

Approximately 118 drug products that contain triclosan with an assigned Drug Identification Number, primarily antiseptic skin cleansers, were listed on Health Canada's Drug Product Database (DPD 2016). Health Canada's antiseptic skin cleanser monograph states that the permitted concentration of triclosan as an active ingredient can range from 0.1% to 1.0% (Health Canada 2006). Triclosan is also present as a medicinal ingredient in some tooth pastes at a maximum concentration of 0.3% and functions as an anti-gingivitis agent (DPD 2016).

2.3.4 Pest control products

The Canadian registrants voluntarily discontinued the sale of pest control products containing this active ingredient. Consequently, as of December 31, 2014, triclosan is no longer registered as a pest control product in Canada.

Commercial-class products containing triclosan and their material preservative uses (textiles leather, food contact material such as cutting boards and countertops, paper, plastic and rubber materials), registered under the PCPA as of December 2014, were considered in the assessment report.

2.3.5 Mandatory survey

A survey conducted under section 71 of CEPA requested information on the manufacture, import, use and release of triclosan in a quantity greater than 10 kg and at a concentration of 0.001% w/w or more for the year 2011. Information on triclosan contained in or used to manufacture pest control products was not requested in this survey (Canada 2013). Results from this survey indicate triclosan was not manufactured in Canada in 2011 (Environment Canada 2013). Twenty-nine companies reported importing between 10 000 and 100 000 kg of triclosan to Canada in the year 2011 as either the pure substance or in product and five companies reported exporting between 100 and 1000 kg of triclosan in manufactured products. Twenty companies reported using triclosan to manufacture formulated products. These product manufacturing facilities were located in Quebec, Ontario, Alberta and British Columbia.

An analysis of the reported data (Environment Canada 2013) revealed that formulated products containing triclosan included over the counter drugs, antibacterial soap, and toothpastes, cosmetics such as skin cleansers, make-up, deodorants, skin creams, fragrances, and cleaning products such as general all-purpose cleaners, and general purpose detergents. As mentioned in section 2.3.1, triclosan is also used in moisturizers, tanning products, shaving preparations, bath products, exfoliants, massage products, styling products, and shampoos. Triclosan is also used in dishwashing products (MSDS 2014). From the total quantity of triclosan used in Canada in 2011, 88% was used as antibacterial soaps, skin cleansers, and toothpaste (registered as drugs, cosmetics or natural health products); 6% was used for other reported products types; and for the remaining 6%, the end uses were not identified (Environment Canada 2013).

3. Human Health

3.1 Toxicology Profile of Triclosan

Reviews of the triclosan toxicological database conducted by the US EPA (2008b), the Australian Department of Health and Ageing (NICNAS 2009), which was adopted by the Organisation for Economic Co-operation and Development (OECD) at the Screening Information Data Set (SIDS) Initial Assessment Meeting (SIAM) 30 in April 2010 (OECD 2011), and the EU SCCP (2009) and SCCS (2011) were used to inform Health Canada's human health hazard evaluation. Where appropriate, secondary review references are cited. Additional review of pivotal toxicological studies was undertaken by Health Canada when deemed necessary. A review of additional toxicological studies investigating the effects of triclosan on thyroid hormones presented by the US EPA Office of Research and Development to the US FIFRA Scientific Advisory Panel (US EPA 2011a), was also considered. Furthermore, more recently published studies and reviews since the publication of the preliminary assessment (up to April 2015) were considered and incorporated into the assessment when determined relevant for risk assessment purposes.

3.1.1 Metabolism and toxicokinetics

Data available on the absorption, distribution, metabolism and elimination of triclosan in mice, rats, hamsters, rabbits, dogs and baboons suggest that there are interspecies differences in the clearance profile.

Oral metabolism studies conducted in hamsters with radiolabelled triclosan showed that 60–80% of the radioactivity was excreted in the urine, while 12–35% was excreted with feces. Compared to the low dose, administration of a single high dose or repeat dose resulted in a shift towards urine elimination and a decrease in fecal elimination. Radioactivity in fecal material was primarily parent, suggesting little metabolism prior to limited biliary excretion. Intravenous and oral administration at low doses resulted in similar patterns of elimination in male and female hamsters. At terminal sacrifice, following a single or repeated oral dose, negligible low residues were found in organs, and low amounts were noted in blood. In fact, residues at terminal sacrifice were lower following repeated dosing in comparison to single dosing, suggesting an increased clearance rate. The major urinary metabolite detected after oral and intravenous administration in hamsters was the glucuronide conjugate of triclosan, while the major fecal metabolite was parent triclosan in all oral dose groups. Distribution patterns in the orally and intravenously dosed animals were similar between the single- and repeated-dose groups, with the highest residual radioactivity found in the kidney, liver, lung and plasma. No organ demonstrated accumulation of triclosan with the highest levels of triclosan equivalent in the plasma 7 days after dosing. Urinary excretion was also found

to be a major route of elimination following oral, intravenous and intraduodenal administration in rabbits and oral administration in baboons. The major urinary metabolite in the baboon was a glucuronide conjugate (US EPA 2008b).

Following oral administration of radiolabelled triclosan in mice, rats and dogs, triclosan was rapidly absorbed and eliminated primarily through the feces via biliary excretion. Following intravenous administration in dogs, feces expressed about 60% of unchanged parent, suggesting an efficient biliary excretion. Urinary excretion was secondary to that in the gastrointestinal tract. This excretory pattern was consistent following either intravenous or intraduodenal administration in these species. Following repeated oral administration in the mouse and rat, triclosan concentrations were higher in the liver than in plasma, supporting the liver as a target organ. In fact, liver toxicity is noted to be a consistent finding in the rodent database (see below). Triclosan was found to be metabolized in rats to both glucuronide and sulfate conjugates. Although different ratios of the individual glucuronide and sulfate conjugates were observed among species, no unique species-specific metabolites have been identified to date. Repeated high-dose administration of triclosan was also shown to change the ratio of these two metabolites in hamsters, mice and monkeys, with the sulfate shown to predominate following chronic oral administration (SCCP 2009). Primary excreted compounds in the urine following single oral exposures in mice included the unmetabolized parent compound and two parent conjugates (sulfate and glucuronide conjugates of triclosan); fecal excretion was primarily that of the free parent compound, as only small amounts of glucuronide were detected, and no sulfate was detected. In addition, four conjugated metabolites (M5, M6, M8 and M9) accounting for 5% of the administered dose were detected in kidney, plasma and liver extracts in the mouse. The major biliary product in the rat was the glucuronide conjugate, with unmetabolized parent compound contributing up to 30% of residues. The major urinary metabolite in the rat after oral and intravenous administration was the glucuronide conjugate of triclosan. In the rat, the parent compound could be detected in the brain, indicating that triclosan crosses the blood–brain barrier (US EPA 2008b).Whole-body autoradiography studies in the mouse and rat showed the presence of two peak concentrations in the plasma following single or repeated dosing, indicating enterohepatic circulation. As such, these species with significant enterohepatic circulation would experience an enhanced or prolonged local exposure to triclosan in the liver and gastrointestinal tract (SCCP 2009). Consistent with this, liver toxicity was noted to be the most consistent finding in the rodent database.

In humans, triclosan is rapidly absorbed and distributed, with plasma levels increasing rapidly within 1–4 hours. Following oral and dermal administration, absorbed triclosan is nearly totally converted to glucuronic and sulfuric acid conjugates due to a pronounced first-pass effect, with only trace amounts of the parent compound detected in the plasma. Elimination is rapid, with a terminal plasma half-life of 21 hours (SCCP 2009). Similar to baboons, hamsters, monkeys and rabbits, the major route of excretion is via the kidneys (24–83%, according to Sandborgh-Englund et al. 2006), with the majority of the compound appearing as the glucuronide conjugate. Unlike the excretion pattern

noted in rodents, excretion of triclosan in the feces represents a smaller portion of the administered dose (10–30%), and triclosan is present in the feces as the free unchanged compound in humans. The human oral and dermal data provide no evidence of bioaccumulation potential (SCCP 2009).

There is sufficient evidence that the toxicokinetics of triclosan are different in humans and rodents; however, the interspecies differences are difficult to quantify based on the available toxicokinetic data. Data examining area under the plasma concentration versus time curve (AUC) and maximum concentrations in plasma (C_{max}) in rodents were typically generated with doses 10-fold higher or more than those used in humans. In general, C_{max} values were lower in humans than in rodents, but AUC data were more variable, depending on the dosing regimen as shown below:

- For a single oral dose of 2 mg/kg body weight (bw) per day in rats and mice, AUC values ranged from 63.9 µg·h/mL (rats) to 166 µg·h/mL (mice), and C_{max} values ranged from 4.77 µg/mL (rats) to 19.48 µg/mL (mice); single oral doses ranging from 0.017 to 0.17 mg/kg bw per day in adult humans yielded AUC values from 0.2 to11.2 µg·h/mL and C_{max} values from 0.023 to 0.974 µg/mL (SCCP 2009).
- For repeated doses of 2 mg/kg bw per day (14 days) in rats, an AUC value of 77.4 µg·h/mL and a C_{max} value of 4.49 µg/mL were reported. In adult humans, an AUC value of 219 µg·h/mL and a C_{max} of 0.878 µg/mL were reported after daily swallowing of a dental slurry containing 0.3 mg/kg bw per day for 14 days. Similar doses in toothpaste (expelled after brushing) resulted in an AUC of 34 µg·h/mL and a C_{max} of 0.146 µg/mL in adult humans (SCCP 2009).

In dermal absorption studies, triclosan was shown to be relatively well absorbed through the skin in all tested species. *In vivo* systemic absorption in humans following dermal application of products containing triclosan ranged from 11% to 17%, depending on the formulation, applied dose, duration of exposure, type of skin and skin occlusion (Maibach 1969; Stierlin 1972; Queckenberg et al. 2010). *In vitro* dermal absorption studies using human skin and various formulations containing triclosan showed dermal absorption values ranged from 7% to 30% (Moss et al. 2000; SCCP 2009).

In the *in vivo* dermal absorption studies in rats, the extent of dermal absorption was much more variable ranging from 4% to 93%, depending on formulation, applied dose and duration of exposure (Black and Howes 1975; Chun Hong et al. 1976; Ciba-Geigy 1976a; Moss et al. 2000; SCCP 2009). Lower absorption ranging from 4% to 28% was reported with triclosan in shampoo, soap suspension or a cream formulation. Higher absorption was observed with triclosan in an aqueous solution or in petroleum jelly (SCCP 2009). In addition, the US EPA reported *in vivo* dermal absorption in rabbits of up to 48% of an applied dose (US EPA 2008b).

3.1.2 Acute toxicity

Technical triclosan was non-toxic via oral and dermal routes and of moderate toxicity via the inhalation route in rats. It was moderately irritating to the rabbit eye and mildly to moderately irritating to the rabbit skin. Triclosan is not considered a skin sensitizer based on the results from a guinea pig test (US EPA 2008b).

3.1.3 Subchronic toxicity

In a 28-day dietary study, exposure of MAGf[SPF] mice (five of each sex per dose) to technical triclosan at a dose of 6.48 or 135.59 mg/kg bw per day in males and 8.25 or 168.78 mg/kg bw per day in females resulted in no effects on mortality, body weight or feed consumption. A no-observed-adverse-effect level (NOAEL) of 6.48 mg/kg bw per day (males) and 8.25 mg/kg bw per day (females) was established based on changes in clinical chemistry (increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase activities; significant decrease in globulin fraction) and liver pathology (an increased incidence of liver cell necrosis, hemosiderosis of Kupffer cells in the vicinity, cytoplasmic vacuoles in hepatocytes, liver cell hypertrophy) observed at the lowest-observed-adverse-effect level (LOAEL) of 135.59 mg/kg bw per day for males and 168.78 mg/kg bw per day for females (US EPA 2008b).

In a 90-day toxicity study, CD-1 mice (15 of each sex per dose) were exposed to triclosan (99.7% a.i.) in the diet at a dose of 0, 25, 75, 200, 350, 750 or 900 mg/kg bw per day. Treatment-related effects were observed at all dose levels in a dose-related manner, as evidenced by clinical pathology, organ weight changes and increased incidence or severity of histopathological lesions (especially of the liver). A statistically significant and generally dose-related reduction in measures of oxygen-carrying capacity, including reduced red blood cells, hemoglobin and hematocrit, was noted in all dose groups, reaching a level of toxicological significance at a dose of 200 mg/kg bw per day. Lower dose groups demonstrated adaptive changes in measures of red blood cells, with deficits less than 10% change from control values. Supporting evidence of a toxicological effect on the hematopoietic system was noted as a regenerative response in the spleen by an increased severity (but not incidence) of splenic hematopoiesis at doses of 200 mg/kg bw per day and greater in males and 750 mg/kg bw per day and greater in females. Statistically significant but not dose-related increases in enzymes indicative of liver injury included aspartate aminotransferase at 750 mg/kg bw per day and above, alanine aminotransferase at 350 mg/kg bw per day and above (males) and 750 mg/kg bw per day and above (females) and alkaline phosphatase (not dose related) at 200 mg/kg bw per day and above (males) and 900 mg/kg bw per day (females). An increase in triglyceride level was observed in males at 350 mg/kg bw per day and above and in females at 750 mg/kg bw per day and above. A decrease in cholesterol level (statistically significant, but not dose related) was reported at 25 mg/kg bw per day and above (NICNAS 2009; SCCP 2009). Given the known increase in peroxisomal fatty acid

β-oxidation in mice exposed to triclosan, this is not unexpected (SCCP 2009). At 25 mg/kg bw per day, a slight increase in liver/gallbladder weights in females (7% and 9%, absolute and relative to brain, respectively) was not considered significant; no change in liver/gallbladder weights in males was reported at this dose. Absolute and relative liver/gallbladder weights increased 1.3- to 3.0-fold at 75 mg/kg bw per day and above in both sexes, and the increases were statistically significant. A slight increase in the number of animals with liver lesions (vacuolization observed in 2/15 males and 1/15 females; individual cell necrosis observed in 3/15 females) was observed at 25 mg/kg bw per day (Trutter 1993). This dose level was considered a LOAEL by other agencies (NICNAS 2009; SCCP 2009)**.** Based on the observation that there was no increase in the severity of liver lesions when compared with the control group at this dose level, but a further increase in the incidence of liver lesions (including an increase in both incidence and severity of vacuolization) observed at 75 mg/kg bw per day and above, a NOAEL of 25 mg/kg bw per day was established by Health Canada for this study.

In a 90-day oral study, Sprague-Dawley rats (25 of each sex per dose) received triclosan (purity not reported) at a dietary concentration of 0, 1000, 3000 or 6000 ppm, equivalent to 0, 65, 203 and 433 mg/kg bw per day in males and 0, 82, 259 and 555 mg/kg bw per day in females. A statistically significant decrease in relative spleen weight (11–12%) and increase in relative kidney weight (12–17%) were seen at the middle dose and above in males and females, respectively. A statistically significant and dose-dependent decrease in cholesterol level in the presence of mild liver centrilobular cytomegaly was observed in males at the middle dose and above. A NOAEL of 1000 ppm (equivalent to 65 and 82 mg/kg bw per day for males and females, respectively) was established based on histopathological changes in the liver observed at the LOAEL of 3000 ppm, equivalent to 203 and 259 mg/kg bw per day in males and females, respectively (US EPA 2008b; NICNAS 2009).

In a 91-day study, Beagle dogs (three of each sex per group) were administered daily gelatin capsules containing triclosan at a dose of 0, 25, 50, 100 or 200 mg/kg bw per day. Limited hematology, clinical biochemistry and urinalysis investigations were undertaken, together with a limited histopathological examination. One female died at 25 mg/kg bw per day, two males at 100 mg/kg bw per day and four animals (two females and two males) at 200 mg/kg bw per day. Diarrhea was seen in animals at 25 mg/kg bw per day and above, and the severity and frequency increased with dose. Emesis was also seen in some animals at all doses. Body weight changes were not determined. Hematology and clinical chemistry assessment revealed a number of “abnormal” values in individual animals at 25 mg/kg bw per day and above suggestive of liver dysfunction, as were urinalysis findings of bile salts and polymorphonuclear leukocytes in the urine at all doses. Statistically significant and dose-related increases in combined male and female relative organ weights were seen only in the pancreas (35–50%), kidneys (38–44%) and adrenals (12–29%) at 100 mg/kg bw per day and above. However, histopathological changes were seen in only one of these organs, the kidney. At necropsy, focal interstitial nephritis (a kidney disorder in which the spaces between

the kidney tubules become swollen or inflamed) was seen in one female at 100 mg/kg bw per day and in one male and one female at 200 mg/kg bw per day. Additionally, “unusual” Kupffer cell activation, bile retention and/or necrosis were seen in the liver of one female, two males and two animals of each sex at 25, 100 and 200 mg/kg bw per day, respectively. In addition, pathological fat was seen in the liver of one or more male and female animals at all doses. Severe liver damage was associated with bone marrow hyperplasia and was seen in one female at 25 mg/kg bw per day, one male and one female at 50 mg/kg bw per day, two males and two females at 100 mg/kg bw per day and two females at 200 mg/kg bw per day. All of these histopathological changes were absent in control animals. Since clinical signs of toxicity, liver damage and enhanced hematopoietic activity were observed at the lowest dose tested (LOAEL of 25 mg/kg bw per day), a NOAEL was not established (NICNAS 2009; SCCP 2009).

In a 90-day study, Beagle dogs (four of each sex per group) were administered triclosan in the diet at a dose equivalent to 0, 5, 12.5 or 25 mg/kg bw per day. No deaths or effects on body weight gain, feed consumption or water consumption were seen. Pasty to thin feces were observed occasionally in all groups and were considered not treatment related. Compared with controls, no treatment-related effects were seen in hematology, clinical chemistry or urinalysis parameters at the top dose, the only dose level examined. No treatment-related histological findings or effects on organ weight were seen at any dose level. Thus, the NOAEL was determined to be 25 mg/kg bw per day in this 90-day study (NICNAS 2009). SCCP (2009) did not establish a NOAEL for this study, as the highest dose did not produce any treatment-related effects.

In a 90-day oral toxicity study, Beagle dogs were administered daily gelatin capsules containing triclosan at a dose of 0, 12.5, 25, 50 or 100 mg/kg bw per day. Body weight gain in females at 12.5 mg/kg bw per day was significantly lower in relation to untreated controls, but body weight decrements were not observed at higher doses in either sex. There were treatment-related morphological changes in the livers (including focal acidophilic to granular degeneration of the cytoplasm of hepatocytes) of most animals in the 25, 50 and 100 mg/kg bw per day dose groups. One male receiving 100 mg/kg bw per day died after 23 days on test, and another 100 mg/kg bw per day male was sacrificed in extremis after 26 days. One female receiving 50 mg/kg bw per day was sacrificed in extremis after 57 days. Each of the three animals that died or was sacrificed during the study displayed weight loss, anorexia, lethargy and symptoms of jaundice 3–5 days prior to death. Upon autopsy, histopathological examination of tissues revealed that the jaundice was a result of hepatotoxicity. A NOAEL of 12.5 mg/kg bw per day was established based on treatment-related liver morphology changes observed at the LOAEL of 25 mg/kg bw per day (US EPA 2008b).

In a 13-week study, Syrian Golden hamsters (15–20 of each sex per group) were administered triclosan in the diet at a dose equivalent to 0, 75, 200, 350, 750 or 900 mg/kg bw per day. Additional groups of 10 animals of each sex receiving 0, 75, 350 or 900 mg/kg bw per day were sacrificed at week 7 of exposure. No treatment-related

deaths were reported in the study. Polyuria (increased urination; statistically significant and dose related) was observed at 350 mg/kg bw per day and above. A slight to moderate increased incidence of blood in urine, which was statistically significant, was reported at 200 mg/kg bw per day and above, along with statistically significant decreases in urine specific gravity (2–3%) and osmolarity (31–65%). Increased coagulation times and statistically significant changes in red blood cell morphology were reported at 750 mg/kg bw per day and above. Statistically significant increases in relative liver (21–36%) and brain weights (14–38%) were observed at 750 mg/kg bw per day in the absence of histopathological changes. Dose-related nephrotoxicity (tubular casts, basophilia and dilation) was reported at 350 mg/kg bw per day and above. Significant increases in the incidence and severity of erosion to the stomach were seen at 750 mg/kg bw per day and above. Consequently, a NOAEL of 75 mg/kg bw per day was established, based on effects on urinalysis parameters together with blood in the urine in both sexes at the LOAEL of 200 mg/kg bw per day (NICNAS 2009). The SCCP considered 75 mg/kg bw per day to be a no-observed-effect level (NOEL) (SCCP 2009). It is interesting to note the absence of liver histopathology in hamsters, which is consistent with the apparent differences in toxicokinetic between hamsters and mice or rats.

In a 90-day dermal toxicity study, Sprague-Dawley rats (10 of each sex per group) were exposed to triclosan in propylene glycol by dermal application at a dose level of 10, 40 or 80 mg/kg bw per day for 6 hours/day during the study. An additional group of 10 animals of each sex per group received 80 mg/kg bw per day for 90 days followed by a 28-day recovery period. Dermal irritation was observed at the application site in all treated animals. Minor adaptive changes in hematology parameters (decrease in red blood cells, hemoglobin and hematocrit) in males and decreased triglyceride (males) and cholesterol levels (males and females) were noted at 80 mg/kg bw per day. Also, an increased incidence of occult blood in the urine (2/9 males vs. 0/10 controls, 3/9 in recovery males, 1/10 in recovery females) and a slight focal degeneration of cortical tubules (3/10 males vs. 1/10 controls) were observed at 80 mg/kg bw per day (Trimmer 1994). The NOAEL of 40 mg/kg bw per day established by the US EPA (2008b) was accepted by Health Canada. A NOAEL of 80 mg/kg bw per day (excluding dermal irritation) was determined by other jurisdictions (NICNAS 2009; SCCP 2009).

In a 21-day inhalation toxicity study, rats (nine of each sex per dose) were exposed (nose only) to triclosan (purity not reported) 5 days/week for 2 hours/day at a dose level of 0, 3.21, 7.97 or 24.14 mg/kg bw per day for males and 0, 4.51, 9.91 or 30.81 mg/kg bw per day for females. Twelve high-dose animals (five males and seven females) died during the course of the study. For females, a NOAEL of 4.51 mg/kg bw per day was established based on treatment-related effects, including slightly decreased body weight, body weight gain, feed consumption and thrombocytes, as well as increased leukocytes and alkaline phosphatase activity and a slightly increased incidence of respiratory irritation, observed at the next dose (LOAEL of 9.91 mg/kg bw per day). In males, treatment-related effects (decreased thrombocytes (platelets) and total serum

proteins, increased alkaline phosphatase activity) were observed at the lowest dose tested (Ciba-Geigy 1974). Although the US EPA established a LOAEL of 3.21 mg/kg bw per day based on the above-mentioned effects in males, given a shallow dose-response curve for the measured endpoints, Health Canada determined that the observed effects were minor, and a NOAEL of 3.21 mg/kg bw per day was established.

3.1.4 Reproductive toxicity

In a two-generation reproduction study in the rat, triclosan (99% a.i.) was administered to Sprague-Dawley rats (25 of each sex per dose) in the diet at a dose of 15, 50 or 150 mg/kg bw per day for 10 weeks prior to mating and through postnatal day (PND) 21 for both generations. No treatment-related effects were seen on mortality, clinical signs or estrous cyclicity. In the F_0 generation, there were no significant decreases in parental body weight during pre-mating. Body weight in high-dose F_0 females during lactation was significantly decreased on PND 7 (statistically significant). An increased incidence of liver discoloration in 50 and 150 mg/kg bw per day parental F_0 males was observed at necropsy, but no histopathological assessment was undertaken of any organs. No effects on reproductive performance were found in the F_0 generation. Pups of the F_0 generation (F_1 pups) showed statistically significant decreases in mean body weight on PNDs 14 and 21 at the 150 mg/kg bw per day dose. Slightly increased pup mortality was observed on PNDs 0–3 in high-dose pups, resulting in a decreased viability index (82% compared with 90% in controls), as well as an increased incidence of dilated renal pelvis at the 150 mg/kg bw per day dose in F_1 pups. In F_1 parental animals, significantly lower group mean body weights were observed during pre-mating at the 150 mg/kg bw per day dose (statistically significant). Gestational body weights in high-dose F_1 females were significantly decreased by 12% during the period of gestation, with a significant negative trend for gestational days 1, 7, 14 and 20. There were no differences in number of pregnant animals, mean gestation duration or mean precoital (pairing to insemination) interval in F_1 females. In pups of the F_1 parental generation (F_2 pups), a slight increase in number of pups found dead or missing was observed at 150 mg/kg bw per day (84% compared with 87% in controls), as well as a statistically significant, but slight (less than 10%), decrease in mean body weights in both sexes compared with controls. The weaning index was decreased at the high dose in F_2 pups, and total litter deaths were increased.

A parental NOAEL of 50 mg/kg bw per day was established based on reduced mean body weight observed at the LOAEL of 150 mg/kg bw per day. A reproductive/developmental NOAEL of 50 mg/kg bw per day was established based on reduced pup weights and reduced pup viability in both generations at the LOAEL of 150 mg/kg bw per day) (US EPA 2008b). Similar findings were reported by NICNAS (2009) and SCCP (2009).

The association between triclosan exposure and male reproductive parameters was also examined in the following studies:

In a published male pubertal study by Zorilla et al. (2009), triclosan (99.5% a.i.) was administered daily by oral gavage to weanling male Wistar rats (8-10 per group) at doses of 0, 3, 30, 100, 200, and 300 mg/kg bw per day for 31 days. No visible signs of toxicity were observed in any of treated animals following exposure to triclosan. Triclosan did not affect the age of onset of preputial separation (PPS) at any of the doses evaluated. Triclosan exposure did not significantly affect ventral prostate, seminal vesicle, levator ani plus bulbocavernosus (LABC), epididymal or testicular weights. A significant decrease in the serum testosterone level (60%) was observed at 200 mg/kg bw per day but not at 300 mg/kg bw per day. The serum and pituitary luteinizing hormone (LH) and prolactin (PRL) were not different from controls. Histological evaluation did not reveal any significant treatment-induced lesions or alterations in either testes or epididymides following triclosan exposure. The study authors measured the effect of triclosan on EROD activity as a surrogate to monitor for dioxin contamination (as dioxins activates the aryl hydrocarbon receptor, AhR). Consistent with previous reports for triclosan, no increase in hepatic EROD activity was observed following exposure to triclosan suggesting that triclosan was not contaminated with dioxins.

In a 90-week study, triclosan (99.5% a.i.) was administered in the diet to male hamsters (70 per group) (more details in section 3.1.6 Chronic toxicity) at doses of 0, 12.5, 75, and 250 mg/kg bw per day. A significant increased incidence of absent spermatozoa and abnormal spermatogenic cells and reduced numbers of spermatozoa in the epididymides was observed at a dose of 250 mg/kg bw per day in males that died and those that were sacrificed at the end of the study. An increased incidence of partial depletion of one or more generations of germ cells within the testis was also observed.

In a published study by Kumar et al. (2009), triclosan (98% a.i.) in phosphate buffer saline was administered via intubation to the male Wistar rats (8 per dose) at doses of 0, 5, 10, and 20 mg/kg bw per day for 60 days. Administration of triclosan caused a significant decrease in the weight of testis and sex accessory tissues (SATs) at 10 and 20 mg/kg bw per day. A statistically significant decrease in the activity of both the testicular steroidogenic enzymes (1□-HSD and 17□-HSD) was observed at two higher dose levels in the in vitro assay. A statistically significant decrease in the serum LH (38.5%), FSH (17%), cholesterol (35%), pregnenolone (31%), and testosterone (41%) levels was reported in males treated with a dose of 20 mg/kg bw per day. Several histopathological abnormalities were observed in cauda epididymis (CE), ductus deference and prostate from rats treated at the highest dose. Further, a 34% decrease in the daily sperm production (DSP) per gram of testis was reported in males at 20 mg/kg bw per day as compared to the control. However, concerns regarding the potential dioxin contamination in the triclosan used in this study were raised by others

(Axelstad et al. 2013). As well, there are some concerns regarding the low dosing volumes used in this study.

In a published study by Lan et al. (2013), triclosan (analytical grade) was administered via gavage in corn oil to five-week-old male Sprague-Dawley rats (8 per dose) at doses of 0, 10, 50 or 200 mg/kg bw per day for eight weeks. A statistically significant dose-responsive decrease in daily sperm production and dose-responsive increase in sperm abnormalities were observed at 50 mg/kg bw per day. Decreases in sperm production at 50 mg/kg bw per day compared to control level was approximately 20%. At 200 mg/kg bw per day, the reduction in sperm production was 46% compared with the control group. Sperm abnormalities (1000 sperm examined per dose group) included increased numbers of abnormal sperm heads and tails, reduced hook (banana head), and bent flagella in the mid (~66%) and high (~86-90%) dose groups relative to controls. Statistically significant decreases in both final body weight and ventral prostate gland weight were also observed at 200 mg/kg bw per day. Minor changes in the cauda epididymis at a high dose of triclosan included vacuolated and exfoliated epithelial cells and detached stereocilia from the epithelium. The kinetics of triclosan in the plasma of reproductive organs of male rats was also investigated. While it did not appear to accumulate in the testes or prostate, the authors hypothesized that triclosan could potentially accumulate to some degree in the epididymides based on the epididymial kinetic parameters showing that triclosan had a longer half-life, an increase mean retention time and lower clearance in this organ compared with plasma. No histopathology or organ weight measurements were reported for the liver therefore it could not be determined if the effects in the sperm parameters were secondary to liver injury.

In a published developmental study by Axelstad et al (2013), triclosan (99% a.i) was administered via gavage to Wistar rats from gestation day (GD) 7 to postnatal day (PND) 16 at doses of 0, 75, 150, and 300 mg/kg bw per day. No effects on anogenital distance, nipple retention, prostate weight or prostate histopathology were observed following exposure to triclosan. Given that these endpoints are typically affected by perinatal exposure to anti-androgenic chemicals, the study authors concluded that triclosan exposure at the tested dose levels did not affect male reproductive development.

A recent epidemiological study on men from Nanjing, China, examined 877 idiopathic infertile men and 713 fertile controls between 2005-2010 for an association between triclosan and other phenols and male infertility (Chen et al. 2013). Urinary concentrations of triclosan were measured from single samples along with semen samples obtained from study participants on the same day. Semen analysis included semen volume, sperm concentration and sperm number per ejaculate. No evidence of an association between triclosan urinary level and these semen parameters was observed, although other phenols evaluated in this study did appear to be associated with idiopathic (of unknown cause) male infertility (i.e., 3-*tert*-octylphenol, 4-*n*-

octylphenol, and 4-*n*-nonylphenol; Chen et al. 2013). Based on this one study, the limited epidemiological data do not suggest an association between exposure to triclosan and an adverse effect on sperm production in humans.

A recent retrospective study examining urinary concentrations of triclosan in 1699 Canadian women recruited between 2008 and 2011 reported that women in the highest quartile of triclosan levels (>72 ng/ml measured in the first trimester) reported a longer time to pregnancy (TTP) based on responses to a questionnaire (Vélez et al 2015). Mean maternal age was 32.8 years, more than half of the women had had at least one prior pregnancy, and 15% were obese or active smokers during the preconception period, all factors associated with TTP. Further, two thirds of the women had university degrees that may be associated with postponed childbirth. After statistical modelling accounted for maternal and paternal age, smoking, education, body mass index (BMI), and household income, increased TTP for the higher quartile of triclosan exposure was maintained. Factors such as exposures of the male partner and other lifestyle parameters that could also affect TTP were not considered and would need further investigation. Furthermore, since this was a pregnancy-based TTP study, women who were infertile and/or did not have access to infertility treatment were excluded by design from the study (Vélez et al 2015). It should be noted that results from animal studies do not show any treatment-related effects in number of pregnant animals, mean gestation duration or mean precoital (pairing to insemination, equivalent to TTP) intervals after exposure to high levels of triclosan.

The available animal studies provide conflicting results with respect to the examined reproductive endpoints, namely testicular weight, sex accessory organ weights, serum testosterone and LH levels. Further, when signs of testicular toxicity were reported, these effects were observed either at low doses of 20-50 mg/kg bw per day (Kumar et al. 2009 and Lan et al. 2013) or high doses 200-300 mg/kg bw per day (Zorilla et al. 2009 and 90-week study in hamsters). Although differences exist in the strain of rat or species used, design and the duration of each study, these differences may not be sufficient to explain the discrepancies in results between studies. However, it is possible that discrepancies in the observed effects could reflect the presence of impurities in the test substance used in each of the studies. For example, in the study by Zorilla et al. (2009), testicular toxicity occurred only after exposure to high doses of triclosan and the test substance was free of dioxin contamination as proved by measuring of EROD activity. Similar, in a 90-day study in the hamster, in which a technical grade triclosan was used, effects on reproductive parameters were observed only at the highest dose tested. For both Kumar et al. (2009) and Lan et al (2013) studies reporting triclosan effects on reproductive parameters at low doses, it is unknown if dioxins contamination was present. However, concerns regarding the potential dioxin contamination in the triclosan used by Kumar et al. (2009) were raised before (SCCS 2011; Axelstad et al. 2013) and dosing volume was extremely low.

Although, triclosan effects on sperm were not measured in the available 2-generation reproduction study in the rat, notwithstanding that rat fertility is generally resilient to modest reduction in sperm count, there is no evidence of infertility or impaired reproductive performance. Further, no correlation between triclosan urinary levels and semen parameters was observed in one available human epidemiology study (Chen et al. 2013); suggesting that human exposure to triclosan does not result in adverse effects on semen parameters.

3.1.5 Developmental toxicity

In a prenatal developmental toxicity study in rabbits, triclosan (100% a.i.) was administered by gavage to pregnant female New Zealand White rabbits (18 per group) on gestational days 6–18 at a dose level of 0, 15, 50 or 150 mg/kg bw per day. Signs of maternal toxicity at the high dose (150 mg/kg bw per day) consisted of statistically significant decreases in body weight and feed consumption and statistically significant decreases in body weight gain over the period of treatment. A maternal NOAEL of 50 mg/kg bw per day was established based on decreased body weight gain and feed consumption during treatment observed at the LOAEL of 150 mg/kg bw per day. There were no statistically significant differences in the mean number of resorptions or the resorption/implant ratio between the control and treatment groups. Fetal body weights of both sexes were comparable between the control and treatment groups. No treatment-related external, visceral or skeletal malformations or variations were observed in fetuses. A developmental NOAEL of 150 mg/kg bw per day, the highest dose tested, was confirmed by Health Canada in accordance with that established by the US EPA (US EPA 2008b; NICNAS 2009; SCCP 2009).

In a prenatal developmental toxicity study in rats, triclosan (99.8% a.i.) was administered by gavage to pregnant female Wistar rats (30 rats per group, 60 per group in controls) on gestational days (GD) 6–15 at a dose level of 30, 100 or 300 mg/kg bw per day. At 300 mg/kg bw per day, maternal toxicity consisted of transient diarrhea, statistically significant decreases in body weight gain during treatment, and reduced feed consumption and increased water consumption from onset of treatment through gestation. Based on these findings, a maternal NOAEL of 100 mg/kg bw per day (LOAEL of 300 mg/kg bw per day) was established. There was no evidence of prenatal toxicity at any dose level in this study; therefore, a developmental NOAEL of 300 mg/kg bw per day, the highest dose tested, was established (US EPA 2008b; NICNAS 2009; SCCP 2009).

In a developmental toxicity study in mice, triclosan (99% a.i.) was administered via the diet to 25 CD-1 (ICR)BR female mice at a target dose level of 0, 10, 25, 75 or 350 mg/kg bw per day from GD 6-15. The maternal toxicity appeared to be minor, with liver weight increases (7% and 17% absolute and relative to brain weight, respectively; statistically significant) and 1 out of 25 dams with a tan-coloured liver at 75 mg/kg bw

per day. The NOAEL of 25 mg/kg bw per day for maternal toxicity may represent a marginal NOAEL in view of these findings. Developmental effects were noted at 350 mg/kg bw per day as a statistically significant increased incidence of variations (characterized as irregular ossification of the phalanges). Irregular ossification of interfrontal bones (an extra bone between the frontal bones of the skull) was reported at 75 mg/kg bw per day; however, the biological significance of this finding was unclear, and incidences were within historical control ranges (NICNAS 2009). Fetal weight was decreased by 14% and 18%, respectively, at the 75 and 350 mg/kg bw per day target dose levels. The decreased fetal body weight at 75 mg/kg bw per day was considered treatment related, and a developmental NOAEL of 25 mg/kg bw per day was confirmed by Health Canada in accordance with that established by the US EPA (2008b). NICNAS (2009) determined the NOAEL to be 75 mg/kg bw per day.

3.1.6 Chronic toxicity

In a 1-year toxicity study, triclosan was administered to baboons (seven of each sex per dose) by capsule at a dose level of 0, 30, 100 or 300 mg/kg bw per day. Signs of vomiting were reported at 100 mg/kg bw per day (one female on day 196, one male on day 341) and at 300 mg/kg bw per day (one male on day 17). Failure to eat was reported at 100 mg/kg bw per day and above. Dose-related increases in incidences of diarrhea (4–6 hours after dosing or during the night) occurred within the first 90 days of exposure in 1 out of 14 animals at 30 mg/kg bw per day, in 7 out of 14 animals at 100 mg/kg bw per day and in all animals at the top dose. Statistically significant increases in mean relative kidney and liver weights were reported at 300 mg/kg bw per day and in mean absolute brain weight from 30 mg/kg bw per day (no treatment-related histopathological changes observed) (NICNAS 2009). At necropsy, an effect on the lining of the stomach was observed at the high dose. As seen in other studies, intragastric administration of triclosan via either gavage or capsule appears to cause irritation and/or enteritis, which confounded the interpretation of the study results. A systemic NOAEL of 30 mg/kg bw per day was established based on clinical signs of toxicity observed at the LOAEL of 100 mg/kg bw per day (US EPA 2008b; NICNAS 2009). The SCCP considered 30 mg/kg bw per day to be a NOEL (SCCP 2009).

In a chronic toxicity/carcinogenicity study conducted in male and female Sprague-Dawley rats (85 of each sex per dose), triclosan (99% a.i.) was administered for 104 weeks in the diet at a dose of 0, 300, 1000 or 3000 ppm (equivalent to 0, 15.3, 52.4 or 168.0 mg/kg bw per day in males and 0, 20.0, 66.9 or 217.4 mg/kg bw per day in females, according to US EPA 2008a). An additional satellite group of animals (20 of each sex) received triclosan in the diet at 415.0 mg/kg bw per day (males) or 519.3 mg/kg bw per day (females) for 52 weeks.

No treatment-related effects on mortality, clinical toxicity, ophthalmology, urinalysis or gross pathology were observed at any dose level tested. No carcinogenic potential was

demonstrated for triclosan in this study. Slightly but significantly decreased erythrocyte counts were observed in males at the middle (8%) and high doses (11%) at week 78 and at all doses (10%, 14% and 11%) by the end of the study (week 104) compared to controls. Hemoglobin concentrations at the high dose level (6%) and hematocrit at the middle and high dose levels (9%) were decreased in males at week 78, but these effects were not statistically significant at week 104 and were below 10%, and they were therefore considered adaptive. Erythrocyte counts were decreased in females at 66.9 mg/kg bw per day and above at week 78 (8% at the middle dose and 6% at the high dose), but were not statistically significant at week 104 and were below 10%, and they were therefore considered adaptive. It should be noted that hematology parameters in control animals (both male and female) dropped by 8–23% from week 13 to week 104. Minor changes in alanine aminotransferase and aspartate aminotransferase activities were noted in males at a dose of 168 mg/kg bw per day, but the changes never reached levels of biological significance. Slight changes in clinical chemistry (triglycerides, blood urea nitrogen and glucose) were noted (dosed females only) at the earliest test period of week 13. From week 26 onward, the female clinical chemistry results were comparable to those for controls, suggesting that effects noted in subchronic testing may be transient and that animals can compensate adequately with prolonged dosing. Histopathology findings were limited to 7 out of 85 males with hepatocellular hypertrophy and 12 out of 85 males with chronic progressive renal calculi (kidney stones), a common aging disease in rats. Between two and five males or females (out of 85 per group) demonstrated hepatocellular necrosis, determined to be not related to treatment by a pathology working group. The SCCP (2009) considered the NOAEL to be 12–17 mg/kg bw per day based on changes in hematology. However, these changes were considered toxicologically insignificant, and a NOAEL of 52.4 mg/kg bw per day was established based on significant decreases in body weight in male and female rats and non-neoplastic changes of the liver in males at the LOAEL of 168.0 mg/kg bw per day (US EPA 2008b). Similar findings were reported by NICNAS (2009).

In an 18-month carcinogenicity bioassay, triclosan was administered to CD-1 mice (50 of each sex per dose) in the diet at a dose level of 0, 10, 30, 100 or 200 mg/kg bw per day. An additional group of mice (20 of each sex per dose) was exposed for 6 months. There were no significant signs of clinical toxicity at any dose level and no significant effects of treatment on group mean body weight, feed consumption, ophthalmology or urinalysis. A dose-related increase in the activities of alanine aminotransferase and alkaline phosphatase was observed in male and female mice at 100 mg/kg bw per day and above in both the 6-month and 18-month dose groups. Significant decreases in both albumin and total protein levels were observed in males at 6 months and in females at 18 months at doses of 100 mg/kg bw per day and above. Serum cholesterol level was markedly reduced at all doses, including the 10 mg/kg bw per day dose, but the decrease was not considered to be adverse at this dose in the absence of frank liver toxicity. Treatment-related hematological effects included increased reticulocyte count in males and platelet count in males and females at 200 mg/kg bw per day. Mean liver weights (absolute and relative) were increased in both male and female mice at 30

mg/kg bw per day and above at 18 months and at 100 mg/kg bw per day and above at the 6-month interim sacrifice. A dose-related increase in severity of hepatocellular hypertrophy was observed in both male and female mice at 30 mg/kg bw per day and above. A statistically significant increase in the incidence of hepatocellular adenoma and/or carcinoma was observed in male and female mice at 100 mg/kg bw per day and above. The incidence was dose related in both sexes. The combined incidence of adenoma and carcinoma was 12%, 20%, 34%, 64% and 84% for males and 0%, 2%, 6%, 12% and 40% for females at 0, 10, 30, 100 and 200 mg/kg bw per day, respectively. The incidence of adenoma/carcinoma combined exceeded the historical control incidence (17% for males, 1% for females) at 10 mg/kg bw per day but became statistically significant at 30 mg/kg bw per day for males and at 100 mg/kg bw per day for females. Consequently, a NOAEL of 10 mg/kg bw per day was established, based on an increased incidence of liver neoplasms in males and females at the LOAEL of 30 mg/kg bw per day (US EPA 2008b). The SCCP did not establish a NOAEL for this study based on findings of liver effects at all doses and considered triclosan a peroxisome proliferator in mouse liver (SCCP 2009).

In a chronic toxicity/carcinogenicity study in the Bio F1D Alexander Syrian hamster, triclosan (99.5% a.i.) was administered in the diet to 70 animals of each sex per group at a target dose level of 0, 12.5, 75 or 250 mg/kg bw per day for up to 90 weeks. No treatment-related clinical signs of toxicity were observed during the first 80 weeks of the study. After this time, high-dose males showed deterioration in their general clinical condition, with signs of lethargy, hunched posture, pallor, thin appearance and unsteady gait. High-dose males had an increase in mortality after week 80, which correlated with their deteriorating condition. A statistically significant decrease was seen in body weight gain in males receiving 250 mg/kg bw per day at the end of the study (compared with controls), and a slight, although statistically significant, decrease (3%) was seen in feed consumption in females at 250 mg/kg bw per day (NICNAS 2009). At terminal sacrifice, no dose- or treatment-related gross findings were observed in males. However, in the control, low-dose, mid-dose and high-dose female groups, white nodules in the forestomach, pale kidneys and irregular cortical scarring of the kidney were observed in some animals. Microscopically, a statistically significant increase in the incidence of nephropathy was observed in high-dose males and females as compared with control animals and was considered the main factor contributing to death in animals that died before study termination. In males tested with the high dose of triclosan, statistically significant increases in the incidences of absent spermatozoa and abnormal spermatogenic cells and reduced numbers of spermatozoa were observed. An increased incidence of partial depletion of one or more generations of germ cells within the testis was also observed. The incidence of lesions in the stomach was significantly increased in high-dose males and females at termination (focal atypical hyperplasia of the fundic region in males, statistically significant increases in distended gastric glands with or without debris in females). No evidence of potential carcinogenicity of triclosan was observed in this study. A NOAEL of 75 mg/kg bw per day was established, based on decreased body weight gain, increased mortality (males), nephropathy and

histopathological findings in the stomach and testes at the LOAEL of 250 mg/kg bw per day (US EPA 2008b; NICNAS 2009).

No chronic dermal toxicity study was available at the time of the assessment report.

3.1.7 Genotoxicity

Triclosan has been tested for genotoxic activity in several assays, including two bacterial reverse mutation tests, an *in vitro* mammalian cell gene mutation test, *in vitro* mammalian chromosomal aberration tests, a mammalian bone marrow chromosomal aberration test and an unscheduled deoxyribonucleic acid (DNA) synthesis assay in mammalian cells in culture.

Triclosan was negative at all doses in both bacterial reverse mutation tests with and without metabolic activation (dose levels ranging from 0.005 to 5000 µg/plate) and the *in vitro* mammalian cell gene mutation test (dose levels ranging from 1 to 25 µg/mL), with and without metabolic activation. Nonactivated triclosan was found to induce a dose-related increase in the yield of cells with abnormal chromosome morphology in the *in vitro* mammalian chromosomal aberration test with dose levels ranging from 1 to 3 µg/mL (18-hour harvest) and at 3 µg/mL (28-hour harvest). The most frequently observed type of chromosome damage was exchange figures. However, no signs of structural chromosomal aberrations were observed in the *in vivo* bone marrow chromosomal aberration test. Triclosan was also negative in an unscheduled DNA synthesis assay in rat primary hepatocytes at the concentrations tested (US EPA 2008b).

3.1.8 Carcinogenicity potential in humans

The US EPA's Cancer Assessment Review Committee of the Office of Pesticide Programs reviewed the carcinogenic potential of triclosan based on a chronic toxicity/carcinogenicity study in hamsters, carcinogenicity studies in mice and rats, metabolism and mutagenicity studies, as well as additional documentation regarding the significance of the mouse study results for human health. The Cancer Assessment Review Committee determined that there was sufficient evidence supporting activation of peroxisome proliferator-activated receptor alpha (PPARα) as the primary mode of action (MOA) for triclosan-induced hepatocarcinogenesis in the mouse. Mutagenic and cytotoxic MOAs were ruled out based on the overall negative *in vivo* genotoxicity database for triclosan and the lack of evidence supporting a sustained regenerative cellular proliferative response, respectively.

The proposed MOA for liver tumours in mice was found to be theoretically plausible in humans. Although human cells contain PPARα, its activity is approximately 10 times

lower than that of mouse hepatocytes. Thus, the human liver would be less susceptible to peroxisome proliferation than the mouse liver. Further, peroxisome proliferators (including hypolipidemic drugs) that are known carcinogens in rodents have not been shown to be carcinogenic in other species, including humans. Consequently, based on quantitative species differences in PPARα activation and differences in toxicokinetics, triclosan-induced carcinogenicity by the proposed MOA was considered by the US EPA to be quantitatively implausible and unlikely to take place in humans. In accordance with the US EPA Final Guidance for Carcinogen Risk Assessment, the US EPA's Cancer Assessment Review Committee classified triclosan as "Not likely to be carcinogenic to humans" (US EPA 2008c).

According to the European Union and Australian classification systems, triclosan is not considered classifiable as a carcinogen (SCCP 2009, NICNAS 2009).

3.1.9 Neurotoxicity

In a 14-day neurotoxicity study in rats exposed to triclosan at a dose level of 0, 100, 300, 1000 or 2000 mg/kg bw per day, a slight inhibition of movement, decreased muscular tone, polydypsia (excessive thirst) and polyuria (increased urination) were observed at 300 mg/kg bw per day, with more pronounced signs at 1000 mg/kg bw per day. No changes in brain weights or histopathology and no changes in peripheral nerves were observed at any dose level tested (US EPA 2008b).

3.1.10 Thyroid effects

In a published short-term (4-day) study by Crofton et al. (2007), weanling female Long-Evans rats (27–29 days old) were exposed via oral gavage to triclosan at a dose of 0, 10, 30, 100, 300 or 1000 mg/kg bw per day. Decreased serum total thyroxine (T_4) concentrations and increased liver weights were reported in exposed animals. Serum T_4 concentrations were reduced in a dose-dependent manner by 28%, 34% and 53% at 100, 300 and 1000 mg/kg bw per day, respectively. No significant changes were seen at 10 or 30 mg/kg bw per day. The study authors did not report thyroid-stimulating hormone (TSH) levels. The study NOEL was 30 mg/kg bw per day, and the lower 95% confidence limit on the benchmark dose (BMDL) (calculated by the study authors) for a 20% reduction in T_4 was 35.6 mg/kg bw per day.

In a published study by Zorrilla et al. (2009), the effect of triclosan on the thyroid was investigated using the pubertal assay. Weanling male rats were dosed via oral gavage for 30 days starting on PND 23. Animals were exposed to 0, 3, 30, 100, 200 or 300 mg/kg bw per day. Mean serum T_4 concentrations were decreased in a dose-dependent manner by 47%, 50%, 80% and 81% at 30, 100, 200 and 300 mg/kg bw per day, respectively. Triiodothyronine (T_3) was affected only at 200 mg/kg bw per day, while

TSH was not affected statistically significantly at any dose. Mean liver weight in male rats was increased significantly at 100 mg/kg bw per day and above, suggestive of hepatic enzyme induction and increased clearance of thyroid hormones. However, the study noted no induction of liver uridine diphosphate-glucuronyl transferase at 3 or 30 mg/kg bw per day. In the same study, decreased serum testosterone was observed at 200 mg/kg bw per day only, although the onset of puberty (balano-preputial separation) and growth of androgen-dependent reproductive tissues (including epididymides and testis) were not altered. At the highest dose, a few animals showed testicular degeneration (multinucleated giant cells within the seminiferous tubule epithelium); however, this change was minimal and not correlated with decreased testosterone or testis weight in the individual animals. The study NOEL was 3 mg/kg bw per day, and the BMDL (calculated by the study authors) for a 20% reduction in T_4 was 7.23 mg/kg bw per day.

In a published study by Paul et al. (2010a), exposure of weanling female Long-Evans rats by oral gavage to triclosan at a dose of 10, 30, 100, 300 or 1000 mg/kg bw per day for 4 days starting on PND 27 resulted in dose-dependent decreases in thyroid hormones, more pronounced for serum T_4 than for T_3. Total T_4 decreased to 43% of control at 1000 mg/kg bw per day, and total T_3 decreased to 89% and 75% of control at 300 and 1000 mg/kg bw per day, respectively, while TSH levels remained unchanged. The study authors speculated that triclosan-induced hypothyroxinemia was likely due to the observed upregulation of hepatic enzymes (i.e., induction of cytochrome P450 2B1/2 [CYP2B1/2] and pentoxyresorufin *O*-dependentylase activity) and increased glucuronidation and sulfation of thyroid hormones. In contrast, the lack of CYP1A1 (ethoxyresorufin *O*-deethylase) induction indicated that the minor dioxin contaminants found in the triclosan sample used in this study (2,8-dichlorodibenzo-*p*-dioxin [2,8-DCDD] and 2,4,8-trichlorodibenzo-*p*-dioxin [2,4,8-TriCDD]) did not induce aryl hydrocarbon receptor–mediated effects on phase I and phase II hepatic enzymes. The NOEL was 30 mg/kg bw per day, and the BMDL (calculated by the study authors) for a 20% reduction in T_4 was 65.6 mg/kg bw per day.

Three additional studies investigated the effects of triclosan on thyroid hormone levels in pubertal and maternal animals, as well as offspring.

In a published study by Stoker et al. (2010), the effects of triclosan on thyroid hormones were investigated in a 21-day female pubertal assay and an immature rat uterotrophic assay (3-day exposure). Wistar rats were dosed orally by gavage after weaning with triclosan doses up to 300 mg/kg bw per day (PNDs 22–42 in the pubertal assay; for 3 days in the uterotrophic assay, either alone or co-treated with ethinylestradiol at 3 mg/kg bw per day). A dose-dependent decrease in thyroid hormone levels was observed at doses of 37.5–150 mg/kg bw per day following the 21-day exposure, and free serum T_4 was decreased at 75 and 150 mg/kg bw per day. There was no significant difference in the mean serum TSH concentration following a 21-day exposure. The NOEL for the decrease in total serum T_4 level was 9.4 mg/kg bw per day; the lowest-observed-effect

level (LOEL) was 18.75 mg/kg bw per day in this study (no BMDL was calculated). In the pubertal exposure study, the highest dose of triclosan (150 mg/kg bw per day) resulted in a significant earlier age of onset of vaginal opening and increased uterine weight, which, according to the authors, was indicative of an estrogenic effect. There was also a non-significant decrease in age of first estrus at the highest dose. In the uterotrophic assay measuring the estrogenicity of the compound, triclosan enhanced the uterine response to ethinylestradiol, but did not alter uterine weight or histopathology when tested alone at doses as high as 300 mg/kg bw per day.

In a published study by Paul et al. (2010b), pregnant Long-Evans rats were exposed to triclosan at a dose of 0, 30, 100 or 300 mg/kg bw per day by oral gavage from gestational day 6 through PND 22. Perinatal maternal exposure to triclosan resulted in hypothyroxinemia in dams and young neonates and a 31% and 27% decrease in serum T_4 levels in dams (PND 22) and pups (PND 4) at 300 mg/kg bw per day, respectively. No changes in serum T_4 levels were reported in pups on PND 14 or PND 21 at any dose level. TSH levels were not reported by the study authors. The NOEL was 100 mg/kg bw per day for both dams and pups. The BMDLs calculated by the study authors for a 20% reduction in T_4 were 104 mg/kg bw per day and 58 mg/kg bw per day for dams and pups, respectively.

In a subsequent study by Paul et al. (2012), pregnant Long-Evans rats were exposed to triclosan at a dose of 0, 10, 30, 100 or 300 mg/kg bw per day by oral gavage from gestational day 6 through PND 21. At 300 mg/kg bw per day serum T4 decreased approximately 30% in GD20 dams and fetuses, PND4 pups and PND22 dams. The NOEL for a decrease in serum T4 was 100 mg/kg bw per day for GD20 dams and 30 mg/kg bw per day for PND22 dams. For offspring, serum T4 was decreased by 28% in GD20 fetuses and by 26% in PND4 neonates at 300 mg/kg bw per day. The computed BMDLs for a 20% reduction in serum T4 were 33 and 61.8 mg/kg bw per day for GD20 fetuses and PND4 neonates, respectively. There was no effect on serum T4 for PND14 or PND21 neonates from any treatment group. There was no effect on T3 or TSH in samples tested. Triclosan concentrations in fetal and neonatal serum as well as liver were observed to decrease with animal age from PND 4 to PND 21, suggesting that the lack of effect on T_4 at PND 14 and PND 21 is due to lower exposures at these ages. According to the authors, the obtained data demonstrate that fetal or neonatal rats do not experience more exposure or greater effects with triclosan compared to the perinatally exposed dam. Further, the authors conclude that in the rat, triclosan is a low-potency and low-efficacy thyroid hormone disruptor.

In a published report by Axelstad et al. (2013), two studies investigating the effects of triclosan on T4 levels in rats were presented. In a first short-term (10-day) study, Wistar rat dams (10 per group) were exposed via oral gavage to triclosan (99%) in corn oil at a dose of 0, 75, 150, or 300 mg/kg-bw per day on GD 7-16. Significantly decreased T4 levels were observed in dams on GD 15 and PND 16, but no significant effects on T4 levels were observed in offspring at the end of lactation. Similar to a previous study by

Paul et al (2010), the study authors suggested that the lack of effect on T4 may have been caused by lack of triclosan entering the maternal milk. T4 levels were decreased by 59%, 72% and 72% in pregnant dams (GD15) and by 38%, 55% and 58% during lactation (PND16), respectively. Decreased body weight gain during pregnancy was observed from GD 7-21 at 300 mg/kg bw per day. Unaffected measures included gestation length, gender distribution, post-implantation loss and litter size, neonatal deaths, and offspring body weights. No effects were observed on male or female anogenital distance or nipple retention. Absolute and relative thyroid gland weights were unaffected by triclosan exposure in both dams and offspring and no histopathological effects were observed in offspring thyroids at the highest dose tested. The LOEL was 75 mg/kg bw per day for dams. The results of this study showed that exposure to triclosan at all doses tested significantly lowered T4 serum levels in dams but did not significantly affect T4 levels in the offspring at the end of the lactation period.

In a second study, male and female pups, but not dams, were dosed directly via gavage daily between PND 3-16 to 50 and 150 mg/kg bw per day of triclosan in corn oil (Axelstad et al. 2013). It should be noted that all of the control pups were from the same litter and T4 levels trended higher than those in the first study control group. A significant, dose-responsive and comparable decrease in T4 levels in both male and female offspring was observed at PND 16 at 50 (16%) and 150 mg/kg bw per day (39%). There were no signs of general toxicity or significant effects on pup body weights or weight gain. The absence of an effect in offspring exposed to triclosan indirectly via nursing compared with the presence of an effect of triclosan via direct oral exposure in the Axelstad studies supports the concept that triclosan exposure through lactation is inadequate to disrupt the thyroid system in offspring (Witorsh 2014).

The proposed adverse outcome pathway for the effects of triclosan on the thyroid hormone system includes the activation of the pregnane X receptor (PXR) and/or the constitutive androstane receptor (CAR) in rat liver by triclosan as an initiating event, leading to the effect on the circulating free T_4. The activation of these receptors was shown to result in upregulation of hepatic phase I and phase II enzymes and hepatic transporters, leading to an increased catabolism of thyroid hormones in rats (US EPA 2011a). To compensate for the movement of free T_4 into the liver, a compensatory mechanism is activated, and T_4 moves from the protein-bound state into the free pool. Due to the constant removal of T_4 from the free fraction into the liver, free T_4 concentrations remain decreased, and T_4 storage in the serum (i.e., protein-bound T_4) decreases, as manifested by a decrease in total T_4, with a subsequent potential impact on neurological development (Figure 3-1). At this time, evidence supporting an alternative mode of action for triclosan-induced decrease in the T4 level, i.e., disruption of thyroid hormone synthesis as a result of f triclosan-induced thyroperoxidase (TPO) inhibition remains elusive (Paul et al. 2013a; Paul et al. 2014).

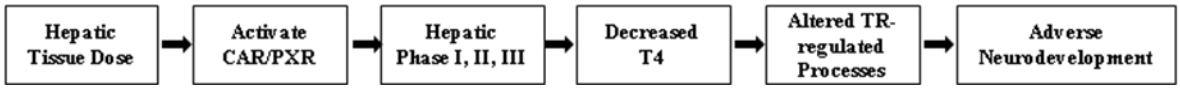


Figure 3-1. Proposed adverse outcome pathway for the effects of triclosan on the thyroid hormone system [TR = thyroid receptor]

Recently published study investigating the effect of triclosan on human, rat and mouse PXR and CAR activity *in vitro* showed that triclosan acts as an agonist for human PXR but not rat or mouse PXR. The authors concluded that failure to measure activation of rodent PXR *in vitro* may accurately reflect the *in vivo* biological response, or may be inherent to the model used or to the concentration range tested, i.e., activation of rodent PXR may require a higher concentration of triclosan than activation of human PXR. The study showed that triclosan can act as an inverse agonist for both human CAR1 and rodent CAR and as a weak agonist for human CAR3 (Paul et al. 2013b). The opposite effects of triclosan on human PXR and human CAR1 receptors are not unexpected given that similar opposite effects of xenobiotics on these orphan nuclear receptors have been previously reported (Moore et al. 2000).

Interestingly, when the study authors compared the potential human oral exposure dose estimated by them (0.13 mg/kg bw per day) to the approximate concentration required to activate human PXR *in vivo* (15 mg/kg bw per day), they concluded that it would be insufficient to activate human PXR and human CAR (Paul et al. 2013b).

There are also uncertainties as to whether the magnitude of the observed thyroid hormone alteration is sufficient to affect brain development in rats. In the existing animal database for triclosan, no neurodevelopmental effects were reported following triclosan exposure. However, these *in vivo* screens and tests were originally designed to evaluate effects of the test material on reproduction and development, and not alterations in cognitive or behavioural function. Further, a developmental neurotoxicity study with triclosan is not available. Thus, there is uncertainty associated with whether triclosan-induced alterations in T_4 levels may have an effect on brain development or cognition in rats.

In general, triclosan-induced hypothyroxinemia would be expected to manifest itself in several systemic effects. One of the early indications of a reduction of T_4 in the rat is an increase in serum cholesterol. In the rodent database with triclosan, animals were shown to demonstrate decreases in cholesterol level. Hypothyroxinemia would also have an effect on the reproduction system. In human and rodent males, thyroid hormones regulate testis development through promotion of Sertoli cell differentiation. The effect is proposed to occur through activation of thyroid receptor alpha 1 (TRα1) in both species. In general, hypothyroxinemia-induced alterations in the reproductive system, such as decreased sperm count and decreased libido, are observed in adult male laboratory animals and humans (Bourget et al. 1987; Jannini et al. 1995). Prepubertal hypothyroxinemia is associated with precocious sexual development (enlargement of the testes without virilization) and absence of libido and ejaculate in rats (Jannini et al. 1995; Longcope 2000). In adult female rats, hypothyroxinemia is generally associated with altered menstrual and estrous cycles (Fisher and Brown 2000;

Krassas 2000). Fetal hypothyroxinemia in female rats alters reproductive tract development, but a similar effect is not seen in human females. Hypothyroxinemia in the prepubertal period is associated with delayed sexual maturity in female rats and humans. However, in the rodent database with triclosan, alterations in the reproductive system either were not noted or were only observed at high doses of triclosan (e.g., chronic toxicity study with hamsters, the Stoker et al. 2010 study with rats). Thus, the paucity of clear indicators of hypothyroidism and associated clinical or histopathological indices in the rat with triclosan exposure suggests that decreases in T_4 may not be sufficient to cause overt hypothyroxinemia in the animal model.

Extrapolation of thyroid hormone data obtained in rats to human risk should be tempered by toxicodynamic and toxicokinetic differences in thyroid hormone homeostasis between humans and rats. In general, humans are considered less sensitive than rats to chemical-induced perturbation in thyroid hormone homeostasis due to the presence of high-affinity binding proteins (thyroxine-binding globulin) in human serum, which results in a longer serum T_4 half-life in humans (5–9 days in humans compared with 0.5–1 day in rats) (Glinoer 1997; Choksi et al. 2003). In rats, most T_4 in serum is bound to transthyretin, which has a lower binding affinity for T_4, resulting in a higher rate of T_4 clearance in adult rats compared with humans (Savu et al. 1987; Rouaze-Romet et al. 1992; US EPA 2011a). The increased clearance of thyroid hormones results in a higher rate of production of T_4 per unit of body weight in rats to maintain normal concentrations of T_4 (US EPA 2011a). These differences have been linked to increased susceptibility of rats to thyroid follicular tumours compared with humans (US EPA 2011a). Thus, it is likely that humans will be less responsive to any triclosan-induced changes in serum T_4 levels. As well, less than 1% of T_4 in humans is freely circulating and therefore available for destruction by liver enzymes, resulting in humans having a greater resistance than the rat model to thyroid toxicity, which occur secondary to liver enzyme activation.

Though triclosan can activate both human PXR and CAR3 *in vitro*, there is no evidence available supporting the up-regulation of Phase I and Phase II enzymes or triclosan-induced hypothyroxinemia following human exposure to triclosan (Paul et al. 2013b). The available literature reports no significant effect of triclosan on thyroid hormone homeostasis in humans.

In a published short-term (14-day) study by Allmyr et al. (2009), the effect of triclosan on thyroid hormone status was measured in 12 adult humans following exposure to triclosan-containing toothpaste. The plasma triclosan concentrations increased from 0.009–0.81 to 26–296 ng/g upon exposure. The highest serum concentration was determined to be equivalent to a triclosan dose of 0.1 mg/kg bw per day. Despite this, there were no significant changes in plasma levels of either 4β-hydroxycholesterol (indicative of CYP3A4 induction) or thyroid hormones during the exposure (Allmyr et al. 2009), demonstrating that triclosan-induced alterations in T_4 levels are unlikely to occur in healthy adult humans.

More recently, the effect of triclosan on thyroid hormone status was measured in 132 human subjects (predominantly male) with coronary heart disease (~ 61 years of age) in Brisbane, Australia, 64 of whom were exposed to triclosan-containing (0.3%) toothpaste and 68 of whom were exposed to placebo toothpaste for over four years (Cullinan et al. 2012). Serum measures of TSH, free T_4, free T_3, antithyroglobulin antibody and antithyroid peroxidase antibody were made at year 1 and year 5 of the study. Serum concentrations of triclosan were not directly measured in this study but were based on results of a previous study (Allmyr et al. 2008). No significant changes in thyroid function as indicated by changes plasma levels of thyroid hormones or antibodies were observed, except for a significantly higher level in free T_4 in the triclosan group compared to the placebo group in year 5. The study authors indicate that this result was due to a reduction in free T_4 level in the placebo group rather than a treatment related increase in T_4 in the triclosan group. Authors also evaluated haematological and clinical chemistry parameters and indicated no evidence of liver function changes, suggesting that the liver would not be a target organ in humans (Cullinan, personal communication 2014; unreferenced). Overall, triclosan exposures in this study appeared to have no adverse effect on thyroid measures. As well, the authors have reported that there were no adverse effects of triclosan exposure on human hematology, clinical chemistry, or measurements of liver function (Cullinan, personal communication 2014; unreferenced) at these exposure levels.

In another recent epidemiological study by Koeppe et al. (2013), results from 1831 subjects (≥ 12 years of age) were studied for an association between urinary biomarkers of triclosan and serum thyroid measures from 2007-2008 National Health and Nutrition Examination Surveys (NHANES) data conducted in the United States. Study participants were stratified by age (i.e., adolescents: ages 12-19; adults: ages 20+) for regression modelling. Single samples of urine and serum were obtained from each individual. Further analyses were performed with sex as a variable. Urinary biomarker concentrations of triclosan were significantly elevated in females compared with males and age was also positively associated with triclosan concentrations. The only positive association between triclosan and any thyroid measure was an interquartile range (IQR) increase in urinary triclosan associated with a 3.8% increase in total serum triiodothyronine (T_3) concentrations in the smaller sized age group of adolescents. No associations between triclosan and T_4, free T_3 or TSH levels were observed and this age group showed consistently lower urinary concentrations of triclosan compared to adults. The authors suggested that while differences in distribution kinetics or metabolism between adolescents and adults might account for small changes in total T_3, it is likely that this result might simply be the result of residual confounding or chance.

In 2011, both the EU SCCS and the US FIFRA Scientific Advisory Panel considered the effects of triclosan on thyroid hormone homeostasis in rats and their relevance to humans. In light of the evidence demonstrating that the rat as being more sensitive to

chemically induced alterations in thyroid hormone levels, the SCCS regarded a decrease in rat T_4 levels following exposure to triclosan as a biochemical marker that is not linked to an adverse effect (SCCS 2011). In consideration of the fact that the observed triclosan toxicity does not fit the typical pattern expected from perturbations of thyroid homeostasis, the FIFRA Scientific Advisory Panel recommended further revisions and refinements to the proposed adverse outcome pathway for triclosan before it could be used predictively. Although subtle perturbations of the T_4 level may have little or no effect due to the operation of homeostatic processes, the FIFRA Scientific Advisory Panel noted that additional data are needed "to determine the magnitude of perturbation of T_4 alone or in combination with other thyroid hormones that would lead to adverse neurodevelopmental effects" (US EPA 2011a).

In summary, with respect to the observed effects of triclosan on thyroid hormone system in the rat and their relevance to humans, the following can be observed:

1) a decrease in T_4 levels in rats is caused by disruption in the target organ (liver), based on rodent-specific metabolism of triclosan,
2) a decrease in T_4 levels in rats is likely to occur via up-regulation of hepatic catabolism and elimination of T_4 following exposure to triclosan,
3) there are no indications of adverse effects on thyroid function in the animal database,
4) the available human data show no changes in thyroid hormone levels or liver function after chronic, low dose exposure from toothpaste use,
5) humans have a much greater capacity to adapt to deviations in T_4 levels.

Based on the above, the overall database does not currently support effects of triclosan on thyroid function as a critical effect for risk characterization in humans. This is supported by a recent critical review of the endocrine activity of triclosan and its relevance to human exposure by Witorsch (2014). According to this review, there is little evidence that triclosan exposure, specifically through personal care product use, presents a risk of adverse health effects in humans via an endocrine mode of action.

3.1.11 Immunotoxicity

An analysis of the available information from subchronic and chronic mouse, rat, dog, and hamster studies focused on hematology, serum chemistry profiles, routine histopathology, and weight changes in specific organs in evaluating the immunotoxic potential of triclosan. No statistically significant, permanent, dose- or treatment-related findings were observed. More specifically, there were no indications of changes in white blood cell count, serum protein in combination with abnormal albumin:globulin ratios, gross findings during histological evaluations of lymphoid organs (spleen, lymph nodes, thymus, or bone marrow) or organ weights in subchronic mouse and dog as well as chronic rat and hamster studies (US EPA 2008b).

An *in vitro* study in rats monitored the level of degranulation in a mast cell model of rat basophilic leukemia cells in order to investigate the potential anti-inflammatory effect of triclosan. In response to various stimuli, mast cells degranulate, releasing allergic mediators such as histamine. The authors found that triclosan strongly dampened the release of granules from activated rat mast cells starting at 2 µM and above in a dose-responsive manner and further postulated that triclosan could be used for topical treatment for allergic skin disease (Palmer et al 2012). The overall interpretation of this study is limited.

A study by Udoji et al. (2010) examined the ability of triclosan to suppress human natural killer cell function *in vitro*. Triclosan was able to inhibit natural killer cell lytic function by 87% within 24 hours. These negative effects persisted following a brief (1-hour) exposure, indicating that the impairment of function cannot be eliminated by removal of triclosan under *in vitro* conditions. Clayton et al. (2011) investigated the association of triclosan with markers of immune function using 2003–2006 NHANES data by comparing triclosan levels with serum cytomegalovirus antibody levels and diagnosis of allergies or hay fever in US adults and children 6 years of age and older. Triclosan showed a positive association with hay fever diagnosis in the less than 18 year age group, although triclosan levels were not associated with cytomegalovirus antibody levels.

Savage et al. (2012) compared urinary levels of triclosan with IgE levels in 860 children (6-18 years of age) from the 2005-2006 NHANES data. A statistically significant increase in odds of aeroallergen sensitization with level of triclosan was observed in male subjects only, however the interaction between triclosan level and sex was not statistically significant. Also, a statistically significant increase in odds of aeroallergen and food sensitization with level of triclosan was observed when analyzed with both sexes combined. It should be noted that the allergen sensitization as an outcome was limited by lack of clinical correlation of allergic disease.
In summary, as with many epidemiological studies, it is difficult to determine a direct causal or even a reverse causal relationship between an environmental exposure and an adverse health outcome and these studies inherently have multiple limitations, such as use of general public questionnaires in lieu of medically diagnosed outcomes, cross-sectional versus prospective analysis, etc. The potential of triclosan to affect the immune system may warrant further investigation, but based on the lack of significant immune response in subchronic and chronic animal studies, triclosan-induced immunotoxicity does not appear to be demonstrated in multiple mammalian species.

3.2 Toxicological Endpoints for the Human Health Risk Assessment

3.2.1 Completeness of the database

There is high confidence in the health effects database. The database for triclosan consists of the full array of toxicity studies currently required for hazard assessment purposes and is therefore adequate to define the majority of the toxic effects that may result from exposure to triclosan.

In examination of the database as a whole, the principal toxicity in rodents and dogs following ingestion of triclosan is mainly hepatic in nature, as demonstrated by hepatocellular necrosis, vacuolization, inflammation and other morphological changes in the liver, with the mouse being the most sensitive species. Triclosan produced hepatic effects and hepatic tumours in mice, but only limited hepatic effects and no tumours in rats. There is evidence that liver effects observed in mice were typical of a PPAR agonist.

A FIFRA Scientific Advisory Panel convened in 2003 reviewed the issue of PPARα agonist–mediated hepatocarcinogenesis in rodents and its relevance to human health risk assessment (SAP 2004). Overall, the majority of the Panel felt that there was adequate evidence in support of the proposed MOA for PPARα agonist–induced rodent hepatocarcinogenesis and that there are relevant data indicating that humans are less sensitive than rodents to the hepatic effects of PPARα agonists, although the opinions of the experts ranged from full agreement to complete disagreement. The basis for the disagreement was the lack of human data and the evidence that would be necessary to fully support the proposed MOA and its relevance to humans.

More recently, two different transgenic PPARα-humanized mouse models have been generated, demonstrating that while peroxisome proliferators can activate human PPARα expression, the mitogenic and hepatocarcinogenic effects do not occur (Cheung et al. 2004; Morimura et al. 2006). It was suggested that the difference in species response may be due to species-specific regulation of a micro-ribonucleic acid (RNA) (Shah et al. 2007; Peters 2008).

Although it is generally accepted that hepatocarcinogenesis in rodents by a PPAR agonist is irrelevant to humans, the same cannot be concluded for activation of PPARα, which alters the expression of genes involved in lipid metabolism that induce hypolipidemia (SAP 2004). Further, it cannot be excluded that non-cancer liver effects observed in rodent studies may also be a result of other modes of triclosan toxicity, such as CAR and PXR activation.

Toxicity in hamsters and baboons was different from that observed in rodents and dogs. Hamsters showed no increased liver toxicity and no tumours following chronic exposure (US EPA 2008b), which is consistent with the apparent differences in triclosan toxicokinetics metabolite profile in this species. Chronic toxicity was characterized by urinary and stomach lesions, which is consistent with the rapid conjugation and urinary

excretion of triclosan. Chronic oral administration of triclosan via capsule to baboons did not lead to systemic toxicity, with the exception of clinical signs of vomiting and diarrhea occurring 4–6 hours after dosing, consistent with stomach irritation (US EPA 2008b). Similar to hamsters, liver toxicity was absent. Limited subchronic studies in rabbits also showed no clinical signs of toxicity from triclosan exposure (SCCP 2009).

Minor changes in hematology were considered adaptive, and alterations in biochemical parameters observed following short-term (mice), subchronic and chronic oral exposures to triclosan in rats and mice were considered secondary to liver toxicity in these species.

The data from the reproductive study in rats provide evidence of reduced viability of the offspring in the early postnatal days and a reduced weaning index in both generations. In a developmental toxicity study in mice, an irregular ossification was reported in fetuses (US EPA 2008b). These effects in rodents were observed at doses that also caused maternal toxicity. Increased liver weights in adult mice and increased incidence of liver discoloration in adult rats were observed in these studies; however, no histopathological assessment was undertaken (US EPA 2008b). The data from studies examining triclosan effects on male reproduction parameters in rats and hamsters provide conflicting evidence with regards to the potential testicular toxicity following exposure to triclosan. No association between exposure to triclosan and infertility was found in rats.

Triclosan exposure results in a modest decrease in serum T4, but not T3 or TSH levels in rat. However, there is uncertainty as to whether the observed magnitude of triclosan-induced maternal or early neonatal hypothyroxinemia is sufficient to affect brain development in rats.

In summary, with respect to the observed effects of triclosan on thyroid hormone system in the rat and their relevance to humans, the following can be observed:

1) a decrease in T_4 levels in rats is caused by disruption in the target organ (liver), based on rodent-specific metabolism of triclosan;
2) a decrease in T_4 levels in rats is likely to occur via up-regulation of hepatic catabolism and elimination of T_4 following exposure to triclosan;
3) there are no indications of adverse effects on thyroid function in the animal database;
4) the available human data show no changes in thyroid hormone levels or liver function after chronic, low dose exposure from toothpaste use; and
5) humans have a much greater capacity to adapt to deviations in T_4 levels.
6)

Consequently, the overall database does not currently support effects of triclosan on thyroid function as a critical effect for risk characterization in humans.

Even though the level of concern for developmental neurotoxicity is low, an additional 3-fold uncertainty factor for database deficiency is being applied by Health Canada to all exposure scenarios to account for the lack of a confirmatory neurodevelopmental study in the rat.

3.2.2 PCPA hazard characterization

For assessing risks from exposure to chemicals in products used in or around homes or schools, the PCPA requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of and toxicity to infants and children and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate based on reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the database for triclosan contains the full complement of required studies, including developmental toxicity studies in rats, mice and rabbits and a two-generation reproductive toxicity study in rats. The lack of a developmental neurotoxicity study was accounted for through the use of an uncertainty factor for database deficiency.

With respect to identified concerns relevant to the assessment of risk to infants and children, in the developmental toxicity study in mice, a decrease in fetal weight was observed at a dose that also caused maternal toxicity. No treatment-related developmental effects were observed in developmental toxicity studies in rats and rabbits (US EPA 2008b). No evidence of increased susceptibility was observed in offspring in the available two-generation reproductive toxicity study conducted with rats. Effects in offspring, including reduced pup weight and viability in both generations, were observed following *in utero* and/or lactational exposure at a dose that was also associated with maternal toxicity (NOAEL of 50 mg/kg bw per day, LOAEL of 150 mg/kg bw per day; US EPA 2008b).

Reduced pup viability is considered a serious endpoint and, if selected for risk assessment purposes, would be subject to the application of the PCPA factor. As concern for this endpoint is tempered by the occurrence of maternal toxicity at the same dose level, the PCPA factor would be reduced from 10-fold to 3-fold for scenarios involving *in utero* and lactational exposure; however, when a point of departure less than or equal to the NOAEL of 50 mg/kg bw per day is utilized for risk assessment, the concerns identified under the PCPA 3-fold factor are considered to be subsumed by the 3-fold uncertainty factor for database deficiency, to temper compounding conservatism. Accordingly, the PCPA factor was reduced to 1-fold, since uncertainties with respect to the completeness of the data were accounted for through application of the database deficiency factor, and there was a low level of concern for prenatal and postnatal toxicity, given the endpoints and uncertainty factors selected for risk assessment.

It should be noted that the submission of a developmental neurotoxicity study could result in the potential removal of the uncertainty factor for database deficiency, pending the results of the study. However, reference doses would need to be reconsidered in totality to determine whether they remain protective of all vulnerable populations.

3.2.3 Acceptable daily intake (all populations)

A number of studies were considered in the selection of the acceptable daily intake (ADI), an estimate of a daily intake of a substance over a lifetime that is considered to be without appreciable health risk, for the general population. Subchronic oral studies in the dog were not considered suitable for endpoint selection due to a number of factors, including study deficiencies, limited reporting, the age of the studies and the inconsistent results obtained (i.e., capsule studies demonstrated a LOAEL of 25 mg/kg bw per day, whereas a dietary study demonstrated no effects at this same level; US EPA 2008b). The results of the 1-year baboon study (NOAEL of 30 mg/kg bw per day, LOAEL of 100 mg/kg bw per day) were similarly disregarded, as the effects observed (i.e., diarrhoea and vomiting) following administration by capsule were thought to reflect the irritant properties of triclosan rather than systemic toxicity (US EPA 2008b).

In the remaining species tested, the mouse exhibited a NOAEL of 25 mg/kg bw per day (LOAEL of 75 mg/kg bw per day) in the 90-day and developmental toxicity studies for non-cancer effects (liver effects and decreased fetal body weight), compared with NOAELs of approximately 50 mg/kg bw per day in the rat (reduced pup weights and reduced pup viability in a reproductive toxicity study and liver effects in a 2-year oral toxicity study) and 75 mg/kg bw per day in the hamster (kidney effects in a 90-week study) (US EPA 2008b). Liver effects observed at the NOAEL in the mouse studies (e.g., increased liver weights, hypertrophy) were typical of a PPAR agonist. However, it cannot be excluded that the observed liver effects may also be the result of other triclosan modes of toxicity, such as PXR and CAR activation. Additional effects on hematology (mild decreases in erythrocyte parameters in the 90-day study), clinical chemistry parameters (decreased cholesterol) and liver pathology (vacuolization) were observed at the NOAEL that progressed to adversity at higher dose levels. It is well recognized that humans are generally less sensitive to PPARα agonist–induced hepatocarcinogenesis, primarily due to a reduced quantity of functional receptors in the human liver (compared with the mouse). That said, humans are at least as sensitive to activation of PPARα, which alters the expression of genes involved in lipid metabolism that induce hypolipidemia (SAP 2004).

Considering the current available information on the adverse effects of triclosan, a database NOAEL of 25 mg/kg bw per day was identified from a 90 day oral toxicity study in mice and was conservatively selected to be protective of a number of effects observed in multiple species with LOAELs ranging from 50 to 75 mg/kg bw per day.

This NOAEL was considered protective for potential liver effects, if any, that could occur in humans as well as effects in other organs and systems. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional uncertainty factor of 3-fold has been applied to account for database deficiency (i.e., lack of a developmental neurotoxicity study). For the reasons outlined in Section 3.2.2, the PCPA factor was reduced to 1-fold for risk assessment purposes. This results in a composite assessment factor (CAF) (or target margin of exposure [MOE]) of 300.

The ADI for all populations is calculated according to the following formula:

AD1 = NOAEL/CAF = 25 mg/kg bw per day/ 300 = 0.08 mg/kg bw per day

This ADI provides a margin of greater than 600 to the NOAEL for reduced pup viability (50 mg/kg bw per day) and is considered protective for pregnant women and their fetuses as well as nursing infants.

3.2.4 Toxicological endpoints for residential and occupational risk assessment

3.2.4.1 Incidental oral exposure (directly exposed children)

For short-term incidental oral exposure (object-to-mouth and hand-to-mouth scenarios) of all children, the database NOAEL of 25 mg/kg bw per day was considered the most appropriate endpoint (as per the ADI). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional uncertainty factor of 3-fold has been applied to account for database deficiency (i.e., lack of a developmental neurotoxicity study). For the reasons outlined in Section 3.2.2, the PCPA factor was reduced to 1-fold for risk assessment purposes. This results in a target MOE (or CAF) of 300.

3.2.4.2 Dermal exposure

For dermal exposure of all durations for all populations, the NOAEL of 40 mg/kg bw per day from a 90-day dermal toxicity study in rats was considered the most appropriate endpoint. Treatment-related effects at the LOAEL of 80 mg/kg bw per day included minor hematological changes (males), reduced triglyceride (males) and cholesterol levels (males and females), occult blood in urine and a slight focal degeneration of cortical tubules (males) (US EPA 2008b). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional uncertainty factor of 3-fold has been applied to account for database deficiency (i.e., lack of a developmental neurotoxicity study). For the reasons outlined in Section 3.2.2, the PCPA factor was reduced to 1-fold for risk assessments pertaining to

residential scenarios. This results in a target MOE (or CAF) of 300 for the general population.

3.2.4.3 Inhalation exposure

For inhalation exposure assessments, the NOAEL of 3.21 mg/kg bw per day from a 21-day inhalation toxicity study in rats was considered the most appropriate endpoint for all populations. Effects at the LOAEL of 7.97 mg/kg bw per day included changes in body weight, hematology and clinical chemistry and a slight increase in respiratory irritation (US EPA 2008b). The selected NOAEL is considered protective of effects observed in other species. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional uncertainty factor of 3-fold has been applied to account for database deficiency (i.e., lack of a developmental neurotoxicity study). For the reasons outlined in Section 3.2.2, the PCPA factor was reduced to 1-fold for risk assessments pertaining to residential scenarios. This results in a target MOE of 300 for the general population. The target MOE (or CAF) for all inhalation scenarios and populations is therefore 300.

3.2.5 Aggregate exposure scenarios

Aggregate exposures of adults and children to triclosan in products used by consumers (e.g., treated clothing, cosmetics, toothpaste and toys) are expected in residential settings. Exposures are expected to occur via the oral and dermal routes; inhalation exposure to triclosan is expected to be a negligible contributor to the aggregate exposure due to its low volatility.

For assessing aggregate exposure of the general population, the assessment can be performed using the endpoints and assessment factors selected for the ADI for the general population. Both oral and dermal studies have shown minor, but consistent, effects on hematology parameters at the LOAEL, as well as effects on cholesterol. Consequently, the database NOAEL of 25 mg/kg bw per day, was considered the most appropriate endpoint for assessing aggregate risks for all populations (US EPA 2008b). Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. An additional uncertainty factor of 3-fold has been applied to account for database deficiency (i.e., lack of a developmental neurotoxicity study). For the reasons outlined in Section 3.2.2, the PCPA factor was reduced to 1-fold for risk assessments pertaining to residential scenarios. This results in a target MOE (or CAF) of 300 for the general population.

3.2.6 Cancer risk assessment

Hepatic adenomas and carcinomas were observed in both sexes of mice in an 18-month dietary study; however, there was no evidence of carcinogenicity in long-term dietary studies in rats or hamsters (US EPA 2008b). Based on the available data, triclosan was not considered genotoxic, suggesting that the mouse tumours occurred as a result of a non-genotoxic MOA. It was determined that the hepatic tumours in mice were the consequence of a species-specific response to the peroxisome-proliferating properties of triclosan. This specificity has been demonstrated both morphologically and biochemically. Notably, mouse livers have shown dose-dependent increases in the numbers of peroxisomes and sensitivity to biochemical indicators of peroxisome proliferation, such as peroxisomal fatty acid β-oxidation, 11- and 12-hydroxylation of lauric acid and levels of CYP4A proteins. In comparison, effects in rats and hamsters are less pronounced (i.e., no increases in numbers of peroxisomes and biochemical indicators either unaffected or affected at high doses only) (Klaunig et al. 2003). It is generally accepted in the scientific community that mouse liver tumours induced through the MOA of peroxisome proliferation are of little relevance to humans (Section 3.1.8). While PPAR can be activated in humans following exposure to known agonists with resulting hypolipidemia, there is little evidence to indicate that hepatocellular proliferation and clonal expansion of initiated hepatocytes (required for tumour development) occur in humans. Accordingly, no quantitative cancer risk assessment is warranted for triclosan.

Endpoints of toxicological concern selected for use in the human health risk assessment are summarized in Appendix A.

3.3 Human Health Exposure and Risk

The approach taken in the health portion of this assessment report is to examine various lines of technical information and develop conclusions based on a weight of evidence approach and applying precaution as required under CEPA.
The assessment of general population exposure to triclosan is based on several Canadian biomonitoring studies including the Canadian Health Measures Survey (CHMS), the Plastics and Personal-Care Product Use in Pregnancy (or P4) Study, and the Maternal-Infant Research on Environmental Chemicals (or MIREC) Study. These data encompass exposures to triclosan from all potential sources and routes, and are considered the most accurate estimates of total exposure of the general population in Canada to triclosan. Additional exposure characterization was undertaken as appropriate.

3.3.1 General population exposure and risk assessment

The potential sources of exposure to triclosan for Canadians include products used by consumers which are treated with or containing triclosan (including, but not limited to, drugs, cosmetics, and natural health products), drinking water, breast milk and

household dust. Triclosan has also been measured in biosolids/wastewater sludge in Canada (Lee et al. 2013; Lee and Peart 2002; Chu and Metcalfe 2007; CCME 2010a; Sabourin et al. 2012), and, in some cases, has been taken up by plants such as soybeans, carrots, lettuce and radishes (Wu et al. 2010a; Macherius et al. 2012; Pannu et al. 2012a). However the overall exposure to the general population via food is expected to be minimal. Domestic-class pest control products containing triclosan are not registered in Canada. The biomonitoring data for triclosan provide actual internal measures of exposure, not only because they include specific measurements of triclosan in urine, but also because they reflect the integrated exposure to triclosan from all sources and pathways including use of products used by consumers which contain triclosan.

In April 2013, Health Canada released the second cycle of biomonitoring data collected as part of the Canadian Health Measures Survey (CHMS), an ongoing nationally representative survey that collects important health and wellness data as well as biological samples from individuals across the country (Health Canada 2013). Total triclosan (conjugated and free forms) was measured in spot urine samples for approximately 2500 individuals aged 3 to 79 years at 18 sites across Canada from 2009 to 2011. According to Statistic Canada (2013a) and Health Canada (2013), triclosan was detected in urine in approximately 72% of the population indicating that the majority of the Canadian population was exposed to this chemical. The CHMS does not include individuals living on reserves or in other Aboriginal settlements in the provinces, residents of institutions, full-time members of the Canadian Forces, persons living in certain remote areas, and persons living in areas with a low population density (Health Canada 2013).

Another study initiated by Health Canada in 2008, the Plastics and Personal-Care Product Use in Pregnancy (referred to as the P4 Study), recruited 80 pregnant women from the Ottawa, Ontario, area from December 2009 to December 2010, in order to collect multiple maternal urine samples, detailed products used by consumers/food packaging diaries, infant urine and meconium samples, breast milk and infant formula. Total triclosan (conjugated and free forms) was detected in more than 80% of the maternal urine samples (Arbuckle et al. 2015b).

The Maternal-Infant Research on Environmental Chemicals (MIREC) Study also measured various substances in Canadian pregnant women. The MIREC Study recruited approximately 2000 women in their first trimester of pregnancy from 10 cities across Canada between 2008 and 2011 (Arbuckle et al. 2013). Health Canada in collaboration with the US National Institute of Child Health and Human Development and the National Children's Study analysed total urinary triclosan (conjugated and free forms) from stored urine samples from this study. Total triclosan was detected in over 99% of the maternal urine samples; however, a more sensitive method was employed than in the P4 Study (Arbuckle et al. 2015b). The median maternal urinary triclosan concentration in the P4 Study was 25.3 µg/L (based on 1247 urine samples from 80

women) and was 8.74 µg/L in the MIREC Study (based on one urine sample each from 1861 women).

A follow-up study was initiated, MIREC-Child Development Plus (MIREC-CD Plus), which measured urinary triclosan concentrations in children from the original MIREC Study on a subsample of 200 children aged 23 to 36 months (unpublished data, personal communication September 2014 from Environmental Health Science and Research Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

General population (3 to 79 years of age) daily dose estimates derived from the CHMS, P4 and MIREC studies will be used to assess risks to the Canadian population (3 to 79 years of age) in section 3.3.2. For children less than 3 years of age, daily dose estimates are derived using a combination of biomonitoring data from the P4 Study, preliminary results from MIREC CD Plus, as well as deterministic estimates to account for potential exposures via breast milk, household dust and mouthing of triclosan-treated plastic products (refer to section 3.3.4 for details).

3.3.2 Estimation of the daily exposure dose based on the urinary triclosan concentration

Given that the health effect levels are expressed in mass of the substance (e.g., in milligrams) per kilogram body weight per day, it is necessary to convert the triclosan concentration in spot urine samples to estimates of daily exposure.

In order to interpret urinary concentrations for any chemical, it is important to adjust the urine concentrations to account for hydration status (Haddow et al. 1994; Miller et al. 2004). There are various methods available to adjust for urine dilution including normalization of urine concentration by urinary creatinine concentration, osmolality, specific gravity, and/or estimation of total urine output using urine flow-rate. Selecting a particular method depends on availability of relevant data, and the substance being measured. Considering wide variations in urine dilution and creatinine excretion due to wide fluctuations in fluid intake and differences in physiology in the general population, the preferred option would be to use the 24-hour urine samples. However, these data are not available in the CHMS, P4 or MIREC Studies. The CHMS, P4 and MIREC Studies measured specific gravity and/or creatinine thus urinary triclosan concentrations have been adjusted using creatinine and/or specific gravity adjustments. Creatinine is commonly used to correct urine spot samples in occupational and environmental monitoring studies; however, it varies greatly with age, time of day, season, as well as exercise and consumption of red meat (Barr et al. 2005, Pearson et al. 2009), and therefore, may be problematic for populations experiencing rapid physiological changes such as pregnant women (Abduljalil et al. 2012), newborns and infants (Matos et al. 1999, Quigley 2012). For this reason, it was not used to adjust urinary triclosan

concentrations in the P4 and MIREC Studies. Although specific gravity is used less often in biomonitoring studies, it is considered less variable than creatinine (Pearson et al. 2009) and was considered to be slightly more correlated with the urinary excretion rate (often considered the "true" dilution status of the sample) in a recent study conducted by Koch et al. (2014). Given the potential issues related to creatinine adjustment for infants and pregnant women, and that specific gravity was considered slightly more correlated to true excretion, only the specific gravity adjusted concentrations and daily intake estimates will be presented in the assessment report. The unadjusted and creatinine adjusted methods are presented in the appendices.

The approach used to estimate daily intakes from the CHMS data included the use of individual adjusted body weight urinary concentrations (derived by Statistics Canada (2013a), see Appendix B) along with a range of typical urine volumes (L/day) reported in the literature (see Appendix C), as well as daily creatinine excretion derived from the Mage equations described in Huber et al. (2011) (Appendix D). A similar approach was used to estimate daily intakes from the unadjusted and specific gravity-adjusted urinary concentrations from the P4 and MIREC data; however, these values were derived by Health Canada (January 2014 personal communication from the Environmental Health Science and Research Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced) (see Appendix B).

In addition to adjusting for urine dilution, urinary triclosan concentrations were adjusted for incomplete excretion of triclosan in urine while computing exposure estimates. Based on pharmacokinetic studies (Table 3-1) investigating the absorption, metabolism and excretion of triclosan in humans with several different routes of administration, including oral exposure to triclosan-containing products (e.g., toothpaste), oral ingestion of capsules, aqueous solutions and dental slurries (i.e., following brushing with triclosan-containing toothpaste) and percutaneous exposure (*in vivo* and *in vitro*), the SCCP (2009) concluded that ingested triclosan is almost completely absorbed, whereas oral cavity and percutaneous exposure to triclosan-containing products (e.g., toothpaste, soap, cream) results in limited absorption. The SCCP (2009) also concluded that following all routes of administration, absorbed triclosan is nearly totally converted to glucuronic and sulfuric acid conjugates (varied relative proportions), with only trace amounts of the parent compound detected in the plasma, and the predominant route of excretion was the urine, with the majority of the compound appearing as the glucuronide conjugate.

Table 3-1. Summary of triclosan excretion data in humans

Type of administered dose	Dose excreted in urine (%)	Dose excreted in feces (%)	References
Single or multiple oral doses,	57–87	10–33	Stierlin 1972; Ciba-Geigy 1976b; Lucker et al. 1990

Type of administered dose	Dose excreted in urine (%)	Dose excreted in feces (%)	References
capsule			
Single oral dose, aqueous	24–83	Not measured	Sandborgh-Englund et al. 2006
Dermal dose	2–14	0.5–2	Stierlin 1972; Caudal et al. 1974; Thompson et al. 1975; Queckenberg et al. 2010
Intravenous dose	65	21	Maibach 1969

Following single and multiple oral doses of triclosan, 57–87% of the administered dose was excreted in urine, with much smaller amounts appearing in the feces (10–33% of the administered dose), based on studies by Lucker et al. (1990), Stierlin (1972) and Ciba-Geigy (1976b). In a study using single doses of aqueous solutions containing triclosan, the major fraction was excreted within 24 hours of exposure, with between 24% and 83% (median 54%) of the oral dose excreted within the first 4 days after dosing (Sandborgh-Englund et al. 2006). For dermal dosing, the excretion profile was similar, with the predominant route of excretion in the urine (2–14%) based on studies by Stierlin (1972), Caudal et al. (1974) and Thompson et al. (1975), with much smaller amounts appearing in the feces (0.5–2% of the applied dose) (SCCP 2009). The SCCP (2009) also concluded that excretion data obtained from an intravenous study were consistent with those obtained from the oral studies, with the majority of the dose (approximately 65%) excreted in the urine, while approximately 21% was excreted in the feces (Maibach 1969).

To account for variability in urinary excretion of triclosan between individuals, a conservative median urinary excretion of 54%, as reported in the Sandborgh-Englund et al. (2006) oral study, was assumed for all individuals (i.e., 54% of triclosan is excreted in the urine). This value is considered appropriate given the high absorption of triclosan via the oral route and limited absorption via the dermal route combined with similar excretion noted via intravenous administration (65%). Consequently, all exposure estimates were adjusted by a factor of 0.54 to account for incomplete urinary excretion following exposure via multiple routes. For children, although there are limited pharmacokinetic data, the SCCP (2009) concluded that the rate of elimination is comparable to that of adults; therefore, the same correction factor was applied to the assessment for children under the age of 3 years.

Estimated daily doses of triclosan for the general population of Canada were derived using urinary concentrations (adjusted and unadjusted) per kg body weight and the median urinary excretion fraction of 0.54 (see Appendix D). The estimated daily doses derived using the specific gravity-adjusted urinary triclosan concentrations resulted in the highest estimated doses and are presented below in Table 3-2. The estimated daily

doses derived using the unadjusted and creatinine-adjusted urinary triclosan concentrations are presented in Appendix D.

3.3.2.1 CHMS cycle 2

The second biomonitoring report published by Health Canada in 2013 contains summary statistics for the unadjusted and creatinine-adjusted urinary triclosan concentrations (Health Canada 2013). Statistics Canada (2013a) provided additional analyses of this data: specifically, urine concentrations were adjusted by specific gravity and all urinary concentrations were divided by each individual's body weight (µg/L/kg or µg/g/kg) for use in the estimation of daily doses. In order to perform these analyses, the CHMS Data Users Guide was used (Statistics Canada 2013b). Additional details on these analyses, including the methods used for specific gravity and creatinine adjustments, can be found in Appendices B-D.

The geometric mean and 95th percentile unadjusted urinary triclosan concentrations for males and females aged 3-79 year olds are 16 µg/L and 710 µg/L, respectively (Health Canada 2013). When the data were adjusted using specific gravity, the geometric mean and 95th percentile urinary triclosan concentrations are 22 µg/L and 990 µg/L, respectively (Statistics Canada 2013a). The geometric mean and 95th percentile creatinine adjusted urinary triclosan concentrations are 15 µg/g, and 620 µg/g, respectively (Statistics Canada 2013a). Based on the 95% confidence intervals, there is no apparent difference in triclosan urine concentrations (both unadjusted and specific gravity adjusted) between males and females; however, urinary triclosan concentrations were significantly lower in children 3 to 11 year olds compared to 12 to 59 year olds. Based on the 95% confidence intervals for the creatinine adjusted values, there appears to be no significant difference between males and females or between age groups. These unadjusted urinary concentrations are in similar range to recent levels reported in CHMS cycle 3 (Health Canada 2015) as well as those used in the preliminary assessment from NHANES 2007-2008 (geometric mean of 15.3 µg/L for 6 years of age and older) and to more recent data reported from 2009-2010 and 2011-2012 (geometric mean of 14.5 µg/L and 11.8 µg/L for 6 years of age and older, respectively) (CDC 2015). The Canadian urinary triclosan concentrations are somewhat higher than those reported in the Korean National Human Biomonitoring Survey (Kim et al. 2011) (geometric mean of 1.68 µg/L), as well as several other smaller studies from Belgium (Pirard et al. 2012; Den Hond et al. 2013), Denmark (Frederiksen et al. 2013a, 2013b), Greece (Asimakopoulos et al. 2014) and China (Li et al. 2013; Chen et al. 2012, 2013; Engel et al. 2014). Given the distribution of the dataset from the CHMS Cycle 2, the geometric means for different age groups were used for estimating the mean daily doses as described in Section 3.3.3.

3.3.2.2 Urinary triclosan concentrations from the P4 study

In the P4 Study, triclosan was detected in more than 80% of the maternal urine samples (multiple samples throughout pregnancy from each participant) (Arbuckle et al. 2015b). The unadjusted and specific gravity adjusted urinary triclosan concentrations for pregnant women are shown in Appendix E, Table E-4. The geometric means and 95th percentile unadjusted and specific gravity adjusted urinary concentrations are 21.61 µg/L and 833.4 µg/L, and 22.9 µg/L and 774.9 µg/L, respectively (Arbuckle et al. 2015b). Temporal variability of urinary triclosan concentrations has been reported in a recent publication of the P4 Study (Weiss et al. 2015). In addition, this publication showed that the ability of a single spot urine sample collected at any time during or post-pregnancy to predict an individual's geometric mean urinary triclosan levels corresponding to low, medium or high exposure was 86.7%.The authors noted that since the data reflect a small subset of the Canadian population, the study results may not be generalizable to other populations (Weiss et al. 2015). Information from this study on the presence of triclosan in infant urine, meconium, breast milk and infant formula will be examined in section 3.3.4.

3.3.2.3 Urinary triclosan concentrations from the MIREC study

Almost all of the women in the MIREC Study had detectable levels of triclosan in their urine (one sample from each participant) and the results are shown in Appendix E, Table D. The geometric mean and 95th percentile unadjusted and specific gravity adjusted urinary concentrations are 12.64 µg/L and 697.58 µg/L, and 14.36 µg/L and 571.10 µg/L, respectively (Arbuckle et al. 2015a).

The urinary triclosan concentrations from both the P4 and MIREC Studies are similar to those reported in CHMS including females of child-bearing age (13 to 49 years of age), and were similar or slightly lower than those identified from several other studies that measured triclosan in urine of pregnant women including the United States (Wolff et al. 2008; Biomonitoring California 2013; Philippat et al. 2013; Mortensen et al. 2014), Puerto Rico (Meeker et al. 2013), Denmark (Tefre de Ranzy-Martin et al. 2014) and Norway (Bertelsen et al. 2013).

3.3.2.4 Uncertainties associated with dose conversion

There are several uncertainties associated with using triclosan concentrations in spot urine samples to estimate human exposures to triclosan. Spot urine samples (Appendix E) were used as a surrogate for 24-hour urine samples. In order to estimate daily doses from these spot samples, a range of typical daily urine volumes specific to a given subpopulation were used (Appendix C). There is high variability with daily urine volumes both between and within individuals therefore the range of typical urine volumes identified from various sources was selected to account for this variability. The 95th percentile urinary triclosan concentration from a spot urine sample will likely overestimate the 95th percentile from a 24-hour urine sample (Summit Toxicology 2013); therefore, the 95th percentile urinary triclosan concentration adjusted for body weight

and the high end of the mean urine volumes were used to calculate an upper-bounding estimate of exposure for the general population of Canada. Since it has been shown that there is a statistically significant inverse relationship between body-weight adjusted urine triclosan concentrations and urinary flow rate in all age groups (Summit Toxicology 2013), the full range of urine volumes was not used as this would result in an overestimate of actual upper bound daily intakes given the use of 95th percentile body weight adjusted concentrations.

Another uncertainty in the dose conversion of spot urine samples for all age groups is the assumption that absorption, distribution, metabolism and elimination parameters are the same for all Canadians and remain constant within individuals over time. There is uncertainty associated with the use of the median value of 54% to account for urinary excretion of triclosan for all individuals, as the values were highly variable (24–83%) and were based on oral dosing (Sandborgh-Englund et al. 2006). However, according to Krishnan et al. (2010), the data from the Sandborgh-Englund et al. (2006) study were considered to be fairly robust. In addition, the SCCP (2009) concluded that, although there are limited pharmacokinetic data for children and no direct comparisons with adults were possible given differences in doses and dosing formulations in various studies, elimination was determined to be essentially the same for children and adults based on an oral dosing study with toothpaste and dental slurry. Given the number of potential sources of exposure via the dermal route, there is uncertainty in correcting spot urine samples for incomplete excretion using an oral dosing study. However, given the high absorption of triclosan via the oral route and limited absorption via the dermal route combined with similar excretion noted via intravenous administration (65%), correction using a median of 54% via oral dosing is considered appropriate.

There is also some uncertainty with converting spot urine samples to a daily dose, as the routes of exposure and timing of exposure in relation to the timing of sampling are unknown. However, given the short half-life of triclosan in urine of 11 hours (Sandborgh-Englund et al. 2006), and the widespread daily use of triclosan-containing products, the spot urine samples for triclosan represent a range of short- and long-term measurements of exposure. Since the dose estimation likely represents a range of exposure durations, the high percentage (72%) of individuals with detectable levels of triclosan in urine (Statistics Canada 2013), and that triclosan is found in a number of products used by consumers that could be used more than once a day, it is reasonable to assume that the elimination of triclosan in urine of individuals in the CHMS data is at steady state.

3.3.3 Aggregate risk assessment for the general population (3-79 years of age)

The CHMS data provide information on the total exposure to triclosan of individuals 3-79 years of age. As such, exposure and risk for children less than 3 years of age were

assessed separately (see section 3.3.4). The unadjusted and adjusted urinary concentrations from all Canadian biomonitoring studies used in this assessment are presented in Appendix E; however, only the concentrations, and estimated daily intakes, adjusted for specific gravity are shown in the text. The risk for the Canadian population (≥ 3 years of age) was characterized by comparing the estimated daily dose for each population subgroup with the relevant health effect endpoint identified by Health Canada (Appendices A, D).

The methods used to estimate daily doses from the spot urinary triclosan concentrations are described in Appendix D. The mean daily dose estimates were derived based on the geometric means of data from the CHMS Cycle 2 (2009–2011) (Health Canada 2013, Statistics Canada 2013a), the P4 (Arbuckle 2015b) and the MIREC Studies (Arbuckle 2015a), as summarized in Table 3-2.

Table 3-2. General population risk based daily dose estimates derived from geometric mean and 95th percentile specific gravity adjusted urinary concentrations and a range of typical urine volumes

Study[a]	Group	Mean estimated daily dose[b] (µg/kg bw per day)	MOE range[c] (means)	95th percentile estimated daily dose[d] (µg/kg bw per day)	MOE range[c] (95th percentile)
CHMS Cycle 2	Children 3–5 years of age	0.47–0.74	33 784–53 191	5.99–9.33	2680–4174
CHMS Cycle 2	Children 6–11 years of age	0.15–0.61	40 983–166 667	4.87–20.27	1233–5133
CHMS Cycle 2	Adolescents 12–19 years of age	0.31–0.99	25 252–80 645	9.80–31.11	803–2551
CHMS Cycle 2	Adults 20–59 years of age	0.41–1.39	17 986–60 976	16.67–56.39	443–1500
CHMS Cycle 2	Adults greater than or equal to 60 years of age	Not shown–>40% (less than LOD)	NA	4.63–44.44	563–5400
CHMS Cycle 2	Females: 13–49 years of age	0.48–1.62	15 432–52 083	17.78–60.15	416–1406
P4 and MIREC	Females: pregnant	0.31–1.60	15 625–80 645	12.59–57.10	438–1986

Abbreviations: NA, not applicable.

[a]CHMS Cycle 2 (2009-2011), P4 (2008-2011), MIREC (2008-2011)
[b]Estimated daily dose using the geometric mean urinary concentrations per kg body weight (Appendix 4) and a range of mean urine volumes (Appendix 5).
[c]MOE (Margin of Exposure) = NOAEL (µg/kg bw per day) / exposure dose (µg/kg bw per day), where the NOAEL of 25 000 µg/kg bw per day, with a target MOE of 300, was selected for all populations.
[d]Estimated daily dose using the 95th percentile urinary concentrations per kg body weight (Appendix 4) and a range of typical urine volumes (Appendix 5).

To account for uncertainties with respect to the dose estimation (e.g., high variability between individuals' pharmacokinetic data for triclosan) and potentially higher exposure of some individuals due to high use of products used by consumers which contain triclosan or a single event such as swallowing toothpaste prior to sampling, exposure estimates were also determined based on the 95th percentile urine concentrations and a range of typical urine volumes (Table 3-2).

Based on an analysis on the relationship between spot urine concentrations, 24-hour composite average, and longer-term averages it was found that single spot urine samples of triclosan are reliable for measuring individual's longer-term exposures (Summit Toxicology 2013). The 95th percentile spot urine samples were also found to overestimate the 95th percentile of the 24-hour composite urine samples (for substances with shorter half-lives); however, there is some uncertainty in the percentile estimates for the 24-hour composite samples due to the small number of data points (n=8) (Summit Toxicology 2013).

Based on the results of the aggregate risk assessment, it can be concluded that exposure of adults (including pregnant females) and children over the age of 3 years to triclosan residues is below the level of concern.

3.3.4 Aggregate risk assessment for children younger than 3 years of age

Although CHMS did not sample children younger than 3 years of age, triclosan has been measured in the urine of infants and children younger than 3 years of age, as reported in other Canadian studies. Results of the spot urine triclosan concentration are available from the Canadian P4 Study for infants under 1 month of age and 2–3 months of age (or 0 to 3 months old). Triclosan was measured in 61% of the urine samples from infants aged 0 to 3 months old (some infants were measured at both <1 month and at 2-3 months of age) (Arbuckle et al. 2015b). The MIREC-CD Plus Study also measured urinary triclosan concentrations in children aged 23 to 36 months. Triclosan was detected in 58% of the 200 urine samples (Personal communication Sept 2014 from Environmental Health Science and Research Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Other biomonitoring data for children in the under 3 years of age group were identified, including a study that collected urine from 42 premature infants in Boston,

Massachusetts (Calafat et al. 2009), a study from Belgium that included urine data for children 0-6 years old (Pirard et al. 2012), and urine samples from 56 children 3–6 years of age collected in Guangzhou, China (Li et al. 2013). The results of these three studies are shown in Table 3-3.

Table 3-3. Unadjusted concentrations of total triclosan in urine of children less than 6 years of age

Location	Age	Number of Samples	Triclosan concentration (µg/L)	Limit of detection (µg/L)	Reference
Canada	Infants (0–3 months)[b]	100[c]	2.8[d] (GM) (95P = 52.0)	3.0	Arbuckle et al. 2015b
Canada[a]	23–36 months	200	3.64 (GM) (95P = 140.65)	3.0	Personal Communication (Health Canada 2014)
Boston, MA	Premature infants	42	>2.3–16.7	2.3	Calafat et al. 2009
Belgium	0–6 years	21	1.70 (GM)	0.33	Pirard et al. 2012
China	3–6 years	56	3.77 (GM)	0.0009	Li et al. 2013

Abbreviations: GM, geometric mean; 95P, 95th percentile
[a]Preliminary data from MIREC-CD Plus Study
[b]Formula-fed Infants (n=6) were noted to have higher triclosan concentrations compared to nursing or combination of the two (breast fed and formula) (n=47) (Arbuckle et al. 2015b)
[c]For P4 Study, it refers to number of urine samples.
[d]Authors used results that were less than the limits of detection in their calculations.

Among young children, infants 6–12 months of age are likely to have the highest exposure to triclosan, given that children in this age group display a number of additional behavioural activities that may not be captured by the 3-5 year age category. These behaviours include nursing, “object-to-mouth” (e.g., mouthing plastic toy), “hand-to-mouth” (e.g., touching triclosan-impregnated products or crawling) and inhalation of contaminated dust (created as a result of children’s activities on the floor/carpet). Younger age groups (i.e., birth to < 1 month, 1 to < 3 months and 3 to < 6 months) are considered to have lower exposures relative to body weight due to less frequent contact with treated objects (i.e., hand-to-mouth and object-to-mouth activities). Older age groups (i.e., 1 to < 2 years, 2 to < 3 years, 3 to < 6 years of age) are expected to have lower exposures than infants due to the cessation of nursing and a reduction in hand-to-mouth activities (US EPA 2011b).

Using the same method as was used for individuals 3 years of age and older to convert spot urine samples to dose, the estimated daily dose for infants ranged from 0.018 to

13.07 µg/kg bw per day based on the mean and 95th percentile specific gravity adjusted urinary concentrations from the P4 Study (Arbuckle et al. 2015b), range of typical urine volumes (Appendix C), and a factor of 54% to account for urinary excretion. The estimated daily dose for children aged 23 to 36 months ranged from 0.22 to 10.67 µg/kg bw per day based on the mean and 95th percentile specific gravity adjusted urinary concentrations from the MIREC-CD Plus Study (Personal communication Sept 2014 from Environmental Health Science and Research Bureau, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). Although there are limited pharmacokinetic data for children and no direct comparisons with adults, elimination of triclosan was determined to be essentially the same for children and adults based on an oral dosing study with toothpaste and dental slurry (SCCP 2009). Using the database NOAEL of 25 mg/kg bw per day and estimated daily doses, the resulting MOEs are greater than 2300 (target MOE of 300).

3.3.4.1 Meconium and amniotic fluid

The presence of triclosan in both meconium and amniotic fluid provides some evidence of transplacental exposure *in utero* (over a period of time during gestation). Meconium is the fecal material that is passed during the first few days of birth (Abudu 2011). It is considered to be a repository for substances that the fetus has been exposed to throughout pregnancy from approximately the 12th week of pregnancy (Ostrea et al. 2006). Amniotic fluid is the liquid that surrounds an unborn baby during pregnancy and is considered to be a potential matrix for measuring fetal exposure (NLM 2014, Cooke 2014).

One of the components of the P4 Study was to measure triclosan in meconium as a potential matrix for measuring in utero exposure. Triclosan was detected in approximately 81% of the meconium samples ranging from below the limit of detection (0.49 ng/g) to 77.0 ng/g with a geometric mean of 2.24 ng/g and a 95th percentile of 68.8 ng/g (Arbuckle et al. 2015b). According to the authors, triclosan concentrations in meconium were significantly correlated with both maternal (during pregnancy) and infant urinary concentrations shortly after birth. The authors also reported that triclosan concentrations in meconium from female infants were significantly higher than those measured in males (Arbuckle 2015b).

Philippat et al. (2013) assessed the relationship between maternal urine and amniotic fluid concentrations of nine environmental phenols, including triclosan, among pregnant women. Triclosan was measured in 69 samples of amniotic fluid but was only detected in 6% of the samples (limit of detection = 2.3 µg/L) with a median of less than the LOD and a 95th percentile of 19.4 µg/L (Philippat et al. 2013). The authors concluded that amniotic fluid may not be a suitable matrix for assessing fetal exposure to certain phenols given the infrequent detection and the lower concentrations measured in amniotic fluid compared to maternal urine.

Based on the presence of triclosan in meconium measured by Arbuckle et al. 2015b, there is evidence of potential foetal exposure to triclosan *in utero*; however, there is uncertainty in deriving daily exposure estimates and characterizing risk from this matrix for instance, the potential contamination from infant urine could not be ruled out.

3.3.4.2 Infant-specific exposure scenarios

3.3.4.2.1 Nursing

Triclosan has been measured in human breast milk in Canada, the United States, Australia, Europe and China (Arbuckle et al. 2015b; Adolfsson-Erici et al. 2002; Allmyr et al. 2006; Dayan 2007; Ye et al. 2008; Toms et al. 2011; Azzouz et al. 2011; Wang et al. 2011). A summary of the results of these studies is shown in Table 3-4.

Table 3-4. Concentration of total triclosan in human breast milk

Location	Number of Samples	Mean (µg/kg lipid)	Minimum (µg/kg lipid)	Maximum (µg/kg lipid)	LOD (µg/kg lipid)	Reference
Canada	52	2.50[a] (geomean)	>LOD	2287.0	14.1[b] (0.58 µg/L)	Arbuckle et al. 2015b
United States	62	Not specified	>LOD	2100	0.150	Dayan 2007
United States	4	Not specified	>LOD	353	24.3	Ye et al. 2008
Sweden	36	8.3–13.5 (median)	>LOQ	23.8	0.45	Allmyr et al. 2006
Sweden	5	Not specified	>20	300	Not specified	Adolfsson-Erici et al. 2002
Spain and Morocco	3	Not specified	>LOD	6.3	0.015	Azzouz et al. 2011
China	10	Not specified	>MQL	309	3.5	Wang et al. 2011
Australia	151	32.5	>LOQ	475	0.39–0.46	Toms et al. 2011

Abbreviations: LOD, limit of detection; LOQ, limit of quantification; MQL, method quantification limit

[a] Authors used results that were less than the limits of detection in their calculations.

[b] The LOD was calculated using the following assumptions: density of human breast milk of 1.03 g/mL and fat content in human breast milk of 4% (US EPA 2011c). To convert µg/kg lipid concentration to µg/kg whole milk concentration simply multiply the µg/kg lipid x 4% lipid content in milk (or used measured lipid content from each sample). To convert ng/mL milk to µg/kg lipid: ng/mL milk / density of milk g/mL / 4%.

Daily exposure of infants to triclosan in breast milk was estimated by Health Canada (Table 3-5), assuming the geometric mean and maximum concentration of triclosan in breast milk of 0.051 µg/kg fresh weight and 73.18 µg/kg fresh weight, respectively (Arbuckle et al. 2015b) from Canadian mothers. Additional assumptions included mean breast milk intakes of 770 mL/day and 620 mL/day for infants under 6 months and 6–12 months of age, respectively, the density of human milk of 1.03 g/mL, and the body weights of 6 kg and 9.2 kg for infants less than 6 months of age and 6–12 months of age, respectively (US EPA 2011c).

Table 3-5. Exposure of infants to triclosan in breast milk

Exposure scenario	Triclosan concentration in milk (mg/kg)	Daily milk intake (mL/day)	Milk density (g/mL)	Body weight (kg)	Mean Estimated daily dose[a] (mg/kg bw per day)	Maximum Estimated daily dose[a] (mg/kg bw per day)
Birth to 6 months	0.000051–0.073	770	1.03	6	6.7×10^{-6}	0.010
6–12 months	0.000051–0.073	620	1.03	9.2	3.5×10^{-6}	0.005

[a]Estimated daily dose (mg/kg bw per day) = triclosan concentration in milk (mg/kg) × daily intake (mL/day) × milk density (g/mL) × conversion factor (0.001 kg/g) / body weight (kg).

For infants under 6 months of age and 6–12 months of age, maximum daily exposures to triclosan in breast milk were estimated to be 0.010 mg/kg bw per day and 0.005 mg/kg bw per day, respectively. Using these maximum estimated daily exposures and the database NOAEL of 25 mg/kg bw per day, the resulting MOEs are 2500 and 5000 (target MOE of 300) for infants under 6 months and 6–12 month of age, respectively.

3.3.4.2.2 Object-to-mouth activity

Incidental oral exposure of children to triclosan resulting from object-to-mouth behaviours was assessed for 6- to 12-month-old infants mouthing a plastic toy. The following assumptions were used in the assessment of a plastic toy being mouthed: maximum surface area of 50 cm^2 that can be mouthed, plastic weight of 5 g, application rate of 0.5% a.i., 0.5% a.i. available on the surface of the toy, a saliva extraction efficiency of 50% (US EPA 2011b) and an average infant body weight of 9.2 kg (US EPA 2011c). The exposure dose for children mouthing a plastic toy was estimated to be 0.0068 mg/kg bw per day (Table 3-6).

Table 3-6. Incidental oral exposure of a 6- to 12-month-old infant mouthing a toy made from plastic treated with triclosan

Scenario	Surface area mouthed (cm^2)	Plastic weight (g)	Amount available on plastic surface (% a.i.)	Maximum application rate (% a.i.)	Surface residue[a] (mg a.i./cm^2)	Saliva extraction efficiency (%)	Estimated daily dose[b] (mg/kg bw per day)
Child mouthing a plastic toy	50	5	0.5	0.5	0.0025	50	0.0068

[a]Surface residue (mg a.i./cm^2) = toy weight/toy surface (g/cm^2) × % a.i./100 × % a.i. available on surface/100 x conversion factor (1000 mg/g) = 0.0025.
[b]Estimated daily dose (mg/kg bw per day) = surface residue (mg a.i./cm^2) × saliva extraction efficiency (%)/100 x surface area (cm^2) / body weight (kg).

Using this estimated daily exposure and the database NOAEL of 25 mg/kg bw per day, the resulting MOE is 3676 (target MOE of 300).

3.3.4.2.3 Dust ingestion

Triclosan has been measured in indoor dust in Canada, Belgium and Spain (Canosa et al. 2007a, 2007b; Geens et al. 2009; Fan et al. 2010). A summary of the results of each study is shown in Table 3-7.

Table 3-7. Triclosan in household dust

Location	Number of Samples	Mean (ng/g)	Minimum (ng/g)	Maximum (ng/g)	Limit of detection (ng/g)	Reference
Canada	63 homes	Median = 571 (fresh sample)	87	3040	8.7	Fan et al. 2010
Canada	63 homes	Median = 378 (composite sample)	82	4090	8.7	Fan et al. 2010
Canada	261 homes	733 (Median = 415)	32	7849	8.7	Unpublished data[a]
Belgium	18 homes	484	25	1828	0.5	Geens et al. 2009

Location	Number of Samples	Mean (ng/g)	Minimum (ng/g)	Maximum (ng/g)	Limit of detection (ng/g)	Reference
Spain	10 homes	702	240	2200	Not specified	Canosa et al. 2007a
Spain	8 homes	1134	90	2444	1.2	Canosa et al. 2007b

[a]Unpublished Canadian House Dust Study data: 2011 e-mail from Environmental Health Science and Research Bureau, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced.

Incidental oral exposure of children resulting from hand-to-mouth activities was assessed based on a representative scenario of a 6- to 12-month-old infant crawling on a floor or carpet and ingesting triclosan-contaminated dust stuck to his or her hands. The assessment of potential oral exposure of children from hand-to-mouth activities was based on modelled estimates using a range (20 to 74 mg/day) of dust ingestion rates reported by Özkaynak et al. (2011) and Wilson et al. (2013), and the mean and maximum dust concentrations from the unpublished Canadian study. Estimated daily doses for 6- to 12-month-old infants with a body weight of 9.2 kg ranged from 1.59×10^{-6} mg/kg bw per day to 6.31×10^{-5} mg/kg bw per day.

For 6- to 12-month-old infants, the daily exposure resulting from ingestion of triclosan-contaminated dust was estimated to be 3.27×10^{-6} mg/kg bw per day (mean dust concentration from the unpublished study and mean dust ingestion rate for toddlers from Wilson et al. 2013). Using this estimated daily exposure and the NOAEL of 25 mg/kg bw per day, the resulting MOE is greater than 7 000 000 (target MOE of 300).

3.3.4.2.4 Inhalation of triclosan-contaminated dust

Inhalation exposure of infants to triclosan in household dust was estimated using available dust standards (US EPA 2008d) and a maximum triclosan concentration in dust of 7849 ng/g from the unpublished Canadian House Dust study (see Table 3-7). Additional assumptions included an inhalation rate for a child < 1 year of age of 5.4 m^3/day (US EPA 2011c) and the average body weight of a 6- to 12-month-old infant of 9.2 kg. The estimated daily doses ranged from 6.45×10^{-8} to 6.45×10^{-6} mg/kg bw per day.

For 6- to 12-month-old infants, the maximum daily exposure resulting from inhalation of triclosan-contaminated dust was estimated to be 6.91×10^{-5} mg/kg bw per day. Using this estimated daily exposure and the NOAEL of 3.21 mg/kg bw per day from the inhalation study in rats, the resulting MOE is greater than 46 450 (target MOE of 300). This is considered a conservative estimate and is based on the assumption that all triclosan-contaminated dust is bioaccessible and thus readily absorbed.

3.3.4.2 Aggregate exposure of children less than 3 years of age

The Canadian biomonitoring data available for children less than 3 years of age are limited to infants 0 to 3 months old and children aged 23 up to 36 months of age. No Canadian biomonitoring data are available for 4- to <23 months.

The aggregate risk for children was estimated by combining estimated daily doses from infant-specific scenarios with estimated daily doses derived from biomonitoring data for either children 23 to 36 months (MIREC-CD Plus; unpublished) or infants (0-3 months old) (Arbuckle et al. 2015b) (Table 3-8). A combined MOE approach is used to aggregate estimated daily exposures from scenarios with the same target MOE. According to information obtained for infants in the P4 Study, the majority of the urine concentrations are from breast fed or breastfed and formula-fed infants (Arbuckle et al. 2015b); therefore, inclusion of exposure (and MOE) for 0- to 3-month old infants is expected to account for all potential routes of exposure, including nursing. The following aggregation equation was used to aggregate "unitless" MOEs into a total MOE (MOE_T):

$$MOE_T = 1 / [1/MOE_1 + 1/MOE_2 + \ldots + 1/MOE_n]$$

where MOE_1, MOE_2, …, MOE_n represent route-specific scenarios (i.e., object-to-mouth, hand-to-mouth and P4 biomonitoring data for a 0- to 3-month-old infants or MIREC-CD Plus biomonitoring data for children 23 to 36 months. A total MOE greater than the target MOE of 300 indicates that risk is not of concern.

Table 3-8. Aggregate risk estimates for children less than 3 years of age

Scenario	Estimated daily dose (mg/kg bw per day)	MOE	Details
Urine data (MIREC-CD Plus)	3.37×10^{-4}	74250	Preliminary MIREC-CD Plus urine data for children 23–36 months (mean concentration and high end mean urine volume)
Urine data (P4 Study)	6.90×10^{-4}	36 232	P4 urine data for infants 0–3 months of age (mean exposure dose)
Nursing	3.50×10^{-6}	7 142 857	Infants 6–12 months of age (geomean concentration)
Dust ingestion	3.27×10^{-6}	7 645 260	Infants 6–12 months of age (mean concentration and mean ingestion rate from Wilson et al. 2013)

Scenario	Estimated daily dose (mg/kg bw per day)	MOE	Details
Object-to-mouth	6.8×10^{-3}	3676	Infants 6–12 months of age
Combined MOE approach[a]	NA	3500	Preliminary MIREC-CD Plus (children 23–36 months) + dust ingestion + object-to-mouth + nursing
Combined MOE approach[a]	NA	3336	P4 (infants 0–3 months old) + dust ingestion + object-to-mouth

Abbreviations: NA, not applicable.
[a]Combined MOE = $1 /(1/MOE_1 + 1/MOE_2 + \ldots + 1/MOE_n)$, where MOE_1, MOE_2, …, MOE_n represent route-specific scenarios.

The inhalation estimate was not included in the aggregate exposure assessment, since the contribution of inhalation exposure was considered negligible when compared with other potential routes of exposure (see above).

Using the combined MOE approach, aggregate exposure of 6- to 12-month-old infants resulted in combined MOEs ranging from 3336 to 3500 (target MOE of 300). The results of this highly conservative risk assessment indicate that the aggregate risk for children less than 3 years of age, including breastfed infants, is below the level of concern.

3.3.4.3 Uncertainties associated with aggregate risk assessment for children

There are uncertainties and conservative assumptions in conducting an aggregate exposure and risk assessment for children, due to a lack of adequate data to fully characterize the exposure of young children to triclosan. These uncertainties are highlighted below.

Similar to the uncertainties identified in section 3.3.2.5 for individuals aged 3 and older, there are generally recognized uncertainties associated with using spot urine samples to estimate human exposures to triclosan. To account for this uncertainty, a range of mean infant daily urine volumes were used (Appendix C). Another uncertainty in the dose conversion of infant spot urine samples is the use of the median value of 54% to account for urinary excretion of triclosan in infants and therefore assuming that absorption, distribution, metabolism and elimination parameters are the same for all individuals and remain constant within individuals over time. The SCCP (2009) concluded that, although there are limited pharmacokinetic data for children and no direct comparisons with adults were possible given differences in doses and dosing formulations in various studies, elimination was determined to be essentially the same for children and adults, rapid, based on an oral dosing study with toothpaste and dental slurry. No pharmacokinetic data related to triclosan for infants was identified. However,

it is known that infants in their first year of life do not have the fully mature metabolic capacity that adults do, and that certain renal clearance mechanisms are also not fully developed in infants up to 6 months of age (Alcorn and McNamara 2002).

There is an uncertainty with respect to the dose estimation for breastfed infants due to the high variability of triclosan measurements in breast milk, possibly related to its short half-life. It is unknown if high levels of triclosan in some breast milk samples were the result of abundant use of products used by consumers or the result of an isolated contamination of sample. For that reason, an assumption of the maximum triclosan concentration detected in breast milk for the nursing exposure scenario is considered highly conservative.

There is uncertainty regarding the potential co-occurrence of all identified scenarios in practice. An assumption that a child will be exposed daily to high triclosan residues as identified for each scenario is considered conservative. The assumption that all potential exposure scenarios will co-occur also represents conservatism in the aggregate assessment for infants 6–12 months of age. Further, assumptions used in incidental oral exposure assessments (i.e., hand-to-mouth and object-to-mouth) are considered conservative, since it is unlikely that all plastic toys will be made with material treated with triclosan.

There is also uncertainty regarding the inclusion of the MIREC-CD Plus estimate for children 23 to 36 months in the aggregate risk assessment for 6- to 12-month-old infants. The inclusion of the MIREC CD Plus estimate is expected to err on the side of overestimating the potential aggregate dose, since additional sources of exposure that are not relevant to the infant scenario are also captured (e.g., washing hand with antimicrobial soap).

3.3.5 Human health risk assessment for workers exposed to pest control products containing triclosan

Workers can be exposed to triclosan via inhalation and dermal contact with this active ingredient while handling the chemical during the manufacturing process or when handling the manufactured goods.

3.3.5.1 Handler exposure and risk

There were no chemical-specific exposure studies available for triclosan. Health Canada's PMRA assessed occupational exposure in industrial settings using exposure data from the Chemical Manufacturers' Association (CMA) Antimicrobial Exposure Assessment Study (CMA 1990). The objective of the CMA Study was to measure occupational exposure of industrial workers during mixing or transfer of antimicrobials to industrial systems. The study monitored workers' exposure to chemicals used as

preservatives in metal working fluids, paints and coatings, in wood, pulp and paper facilities and in cooling towers. Worker exposure was measured for different application methods, including a liquid pour (open mixing/transfer) and liquid pump (closed mixing/transfer).

Dermal and inhalation exposures of individuals involved in the transfer of the antimicrobial (as many transfers as are normally conducted in a workday) from the container to the production batch were monitored in the study. Dermal exposure was assessed by inside and outside gauze patch dosimeters through one layer of clothing. Exposure of the hands was measured using cotton fabric gloves. Inhalation exposure was measured by using a personal sampling pump. Due to the diversity of the products used, there was significant variability in the types of protective clothing worn. Most individuals wore long-sleeved shirts and long pants. Each replicate was representative of the time spent performing the antimicrobial-related task in 1 day; therefore, the data were not normalized. Laboratory and field recoveries were measured; however, recoveries were highly variable due to an insufficient number of spiked samples, poor collection efficiency of sample media, difficulty in the analysis for the active ingredient and poor storage stability. These are considered limitations of the CMA exposure study.

Monitoring times and the amount of active ingredient handled daily in plants manufacturing paints and coatings, in plants using metal working fluids and in cooling towers ranged from 2 to 285 minutes and from 0.006 to 265 kg, respectively. In all scenarios, exposure was primarily dermal. Total exposure for each replicate was calculated by summing the total dermal and inhalation doses for each replicate. Since applications of biocides in industrial processes are similar regardless of the use site (e.g., cooling towers, pulp and paper), it was considered appropriate to combine replicates based on the application method. Thus, the replicates with liquid pour and pump application in material preservatives, cooling towers and pulp and paper scenarios were combined to generate exposure estimates. Given the limitations of the exposure study (low and variable laboratory and field recoveries), the 90th percentiles generated from the input CMA data were used by Health Canada's PMRA to estimate potential risks to operators handling industrial products containing triclosan. Dermal and inhalation exposure estimates represent the 90th percentile of exposure dose normalized to a 70 kg body weight (Table 3-9). Since most individuals in the CMA Study wore long sleeves, long pants and cotton gloves, these data are considered representative of an individual wearing a single layer and gloves.

Table 3-9. Occupational risk assessment for industrial handler

Application method	Dermal exposure[a] (mg/kg bw per day)	Inhalation exposure[a] (mg/kg bw per day)	MOE[b] Dermal	MOE[b] Inhalation
Liquid, pour	0.1034	0.0010	387	3210

Liquid, pump	0.0268	0.0032	1493	1003

[a]90th percentile of the exposure dose normalized to a 70 kg body weight (CMA 1990).
[b]MOE = NOAEL (mg/kg bw per day) /daily exposure dose (mg/kg bw per day), where the NOAEL of 40 mg/kg bw per day with a target MOE of 300 was selected for the dermal scenarios, while the NOAEL of 3.21 mg/kg bw per day with a target MOE of 300 was selected for the inhalation scenarios.

The results of the occupational risk assessment for workers applying triclosan in industrial settings via the closed delivery system or an open pour method indicate that risks are below the level of concern.

3.3.5.2 Occupational post-application exposure and risk

Occupational post-application exposure of workers handling manufactured products is not expected to be of concern based on the registered use pattern, since triclosan is applied at low application rates during the manufacturing process and is expected to be embedded in the finished product.

3.3.5.3 Uncertainties in worker exposure estimation

There are uncertainties and conservatisms in conducting occupational risk assessments due to a lack of adequate tools and data to fully characterize exposure from all possible routes. Some of these uncertainties are highlighted below.

Occupational exposure estimates are based on data from the CMA Antimicrobial Exposure Assessment Study. Even though there are a number of limitations associated with the study, it is currently the only occupational study available with which to assess potential exposure from antimicrobial uses of pest control products. Low and variable laboratory and field recoveries were obtained in this study, which may affect the validity of the reported exposure estimates. However, since the 90th percentile estimates from this study were used for risk assessment purposes, exposure estimates are not expected to be underestimated.

Because of the limitations described above, the exposure estimates from the CMA Antimicrobial Exposure Assessment Study were not normalized to the amount of active ingredient handled per day. The activities monitored in the study were considered representative of a typical workday; thus, no normalization was conducted. In addition, many of the activities do not involve direct handling of the biocide, but rather a change in coupling or hose from the biocide container. It is uncertain whether the amount of triclosan handled per day by workers is within the range of kilograms of active ingredient handled in the CMA Antimicrobial Exposure Assessment Study.

3.4 Cumulative Effects

Health Canada's Science Policy Notice SPN2001-01, *Guidance for Identifying Pesticides that have a Common Mechanism of Toxicity for Human Health Risk Assessment,* describes the steps for identifying mechanisms of toxicity of pesticides that cause a common toxic effect, the types of data needed and their sources, how these data are to be used in reaching conclusions regarding commonality of mechanisms of toxicity, and the criteria Health Canada applies for categorizing pesticides for the purpose of cumulative risk assessments. No relevant evidence indicating that triclosan shares a common mechanism of toxicity with other pesticides or shares a toxic metabolite produces by other pesticides has been identified (US EPA 2008a, US EPA 2014).

3.5 Transformation Products

There are a number of potential environmental transformation products of triclosan to which the general population may be exposed, including methyl-triclosan, 2,4-dichlorophenol (2,4-DCP) and PCDDs (Section 4.2).

Methyl-triclosan is a major environmental transformation product formed as a result of biomethylation in soil and water systems (see Sections 4.1.2.2 and 4.2.5.2). It is also formed during the aerobic treatment of wastewater and is discharged in effluents from WWTPs with triclosan. While there is limited monitoring information for methyl-triclosan in the environment and there is uncertainty regarding the observed half-lives and bioaccumulation estimates for this compound, the available laboratory and aquatic field evidence indicates that methyl-triclosan is likely to be both more persistent and more bioaccumulative than triclosan.

2,4-DCP and the lower chlorinated dioxins 2,7/2,8-DCDD are major photoproducts of triclosan (see Section 4.2.3). In addition, 2,4-DCP as well as PCDDs (1,2,8-trichlorodibenzo-*p*-dioxin [1,2,8-TriCDD], 2,3,7-TriCDD and 1,2,3,8-TCDD) can form in natural water as a result of further phototransformation of chlorinated triclosan derivatives (formed during the disinfection of wastewater). A SIDS Initial Report for 2,4-DCP (under the OECD High Production Volume [HPV] Chemicals Programme) indicated that human exposure to this chemical from the use of products containing 2,4-DCP and from the environment is expected to be low (OECD 2007). Dioxins usually enter and are present in the environment as complex mixtures. The toxicity of different dioxins is expressed on a common basis using the international toxicity equivalency factors that recognize and compare the similarities and differences between the toxic actions of the dioxins. The lower chlorinated dibenzodioxins (2,7/2,8-DCDD, 1,2,8-TriCDD, 2,3,7-TriCDD and 1,2,3,8-TCDD) are not listed on the list of 17 dioxins and furans that are of the greatest concern to human health based on international toxicity equivalency factors (NATO 1988), which means that they will be expected to contribute comparatively little to the toxicity of a complex mixture. On this basis, the potential for general population risk from these dioxins is expected to be low.

Triclosan was also shown to react with chlorine ion in tap water to form chloroform (Rule et al. 2005). The 2001 Government of Canada Priority Substances List Assessment Report for Chloroform (Canada 2001) indicated that human exposure to chloroform from all potential routes and sources of exposure is expected to be considerably less than the level to which a person may be exposed daily over a lifetime without harmful effect.

3.6 Antimicrobial Resistance

The potential of triclosan to induce antimicrobial resistance (AMR) was reviewed in assessments published by the Australian Department of Health and Ageing (NICNAS 2009) and the European Commission (SCENIHR 2009, 2010; SCCS 2010).

In 2009, NICNAS concluded, based on a comprehensive review of literature published in scientific journals between 2002 and 2005 and the 2002 European Commission Scientific Steering Committee review of triclosan AMR (European Commission 2002), that there was “no evidence that the use of triclosan is leading to an increase in triclosan-resistant bacterial populations or that there is any increased risk to humans regarding antibiotic resistance” (EU 2002; NICNAS 2009).

In 2009 and 2010, the European Commission also published comprehensive reviews of available scientific data on the antibiotic resistance effects of triclosan. The studies reviewed by the EU’s Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) indicated that triclosan-resistant bacteria can be found in health care settings and in products used by consumers. Although laboratory studies showed that it is possible to develop bacterial mutants with reduced susceptibility to both triclosan and antibiotics, no notable selection of antibiotic resistance in bacteria exposed to triclosan was observed in the environmental studies. In addition, the lack of data on other biocide compounds prevented the SCENIHR from reaching a conclusion regarding the potential for triclosan to induce bacterial antibiotic resistance under field use conditions (SCENIHR 2009). The EU’s Scientific Committee on Consumer Safety (SCCS) concluded that, based on the available scientific information, it was not possible to quantify the risk of development of AMR induced by triclosan applications, including its use in cosmetics (SCCS 2010). This position was confirmed in a parliamentary response in May 2013 (European Parliament 2014).

A more recent review of all available information on the potential for triclosan to induce AMR was conducted on behalf of Health Canada via an external expert review (Tetra Tech 2014). This review, spanning publicly-available literature between 2009 to 2013 with judicious review of the older literature, addressed the following: development of triclosan resistance, bacterial cross resistance arising from triclosan exposure, uses of triclosan as it relates to clinical versus environmental and household settings, as well as fate and environmental occurrence of triclosan.

Consistent with the previous conclusions stated by SCENIHR (2009), this review identified studies that indicated that there is the potential for triclosan-resistant bacteria to exist in clinical settings (environments not representative of general population exposure), but this has not been documented outside of clinical use (e.g. household settings) (Larson et al. 2003; Lanini et al. 2011; Skovgaard et al. 2013; Guiliano et al. 2015).

More recently, a large-scale study examining 3319 clinical isolates from three different locations (research lab, hospital, and university) did not find any significant evidence of triclosan resistance[2] (Morrissey et al. 2014). It should also be noted that uses of triclosan-containing soaps in clinical settings differ from consumer (household) settings in: the formulations used, the concentration of triclosan in the soap, the duration of scrubbing and the frequency of scrubbing and these factors are important in interpretation of relevance for the general population.

There were no studies demonstrating the development of AMR after repeated sublethal exposures of triclosan to bacteria found in household settings through use of antimicrobial soaps compared to plain soaps (Cole et al. 2003), triclosan-containing flooring (Møretrø et al. 2011), dental samples (McBain et al. 2004), triclosan-containing boxes (Braid and Wale 2002), or in sinks and drains of users and non-users of biocidal cleaning agents, including triclosan (McBain et al. 2003; Marshall et al. 2012).

A more recent study by Cullinan et al. (2013) investigated whether long-term continuous use of triclosan-containing toothpaste (0.3% w/w) selected for triclosan-resistant bacteria commonly found in the mouth. Common species between both the placebo and triclosan user dental plaque isolates showed similar Minimum Inhibitory Concentrations (MICs) for a range of concentrations (125-1000 µg/ml) of triclosan leading the authors to conclude that continuous use of triclosan-containing toothpaste over 5 years did not result in the development of triclosan-resistant bacteria in the mouth. This is further supported by annual results from a 19-year-long evaluation (1991-2010) of dental plaques of 58 subjects who used triclosan dentifrice for at least 5 years and showed no changes in oral microbial susceptibility to triclosan over this long period of time (Haraszthy et al. 2014).

Previous studies have reported the potential for the generation of triclosan-resistant bacterial strains in the laboratory (Heath et al. 1998; Heath et al. 1999; McMurray 1999). However, in the few cases where resistant organisms have been isolated, there is little data to suggest that this resistance was the result of triclosan. There have been cases where cross-resistance was claimed in laboratory and clinical triclosan resistant strains *in vitro* (Aiello et al. 2007), but there have also been several papers that were unable to

[2]One exception was the case of *S. aureus* which appeared resistant to triclosan which authors concluded was due to heterologous duplication of the fabI gene and this duplication did not affect the susceptibility to antibiotics currently in use at clinics, thereby not contributing to an increase in AMR (Morrissey et al., 2014).

find evidence of cross-resistance (Suller and Russell 2000; Wingnal et al. 2008; Cottell et al. 2009; Saleh et al. 2010; Skovgaard et al. 2013). Furthermore, differences in formulations of triclosan used in clinical and laboratory settings compared to commercial applications are unknown.

Concentrations of triclosan observed in Canadian surface waters and wastewaters are well below those required to inhibit bacterial growth (Koburger et al. 2010; Latimer et al. 2012; Blair et al. 2013). Resistant phenotypes develop over a wide range of concentrations, depending on the organism, but even the lowest triclosan concentration (0.23 µg/mL; Latimer et al. 2012) at which resistant phenotypes have been observed is at least an order of magnitude above the highest observed surface water concentration (Table 4-3). In addition, correlation between the presence of triclosan in surface water or waste water and the presence of bacteria resistant to other antimicrobials and antibiotics is not consistently observed (Novo et al. 2013; Carey and McNamara 2015*)*.

Overall, although there is the potential for triclosan-resistant bacteria to exist in clinical and laboratory settings, this has not been well documented outside of clinical use (e.g. households, toothpaste use, and environmental waters), and, due to the unavoidable limitations in clinical and laboratory studies as they relate to the potential for triclosan to induce AMR outside of these settings, interpretation for relevance to the general population is also limited. Therefore, based on available information, induction of AMR from current levels of triclosan has not been identified as a concern for human health.

4. Environment

4.1 Releases and Presence of Triclosan in the Environment

There are no known natural sources of triclosan; its presence in the environment is due solely to human activity. The possible pathways for releases of triclosan to the environment are presented in Figure 4-1; they are based on a conceptual diagram proposed by Bound and Voulvoulis (2005) for pharmaceuticals in the environment.

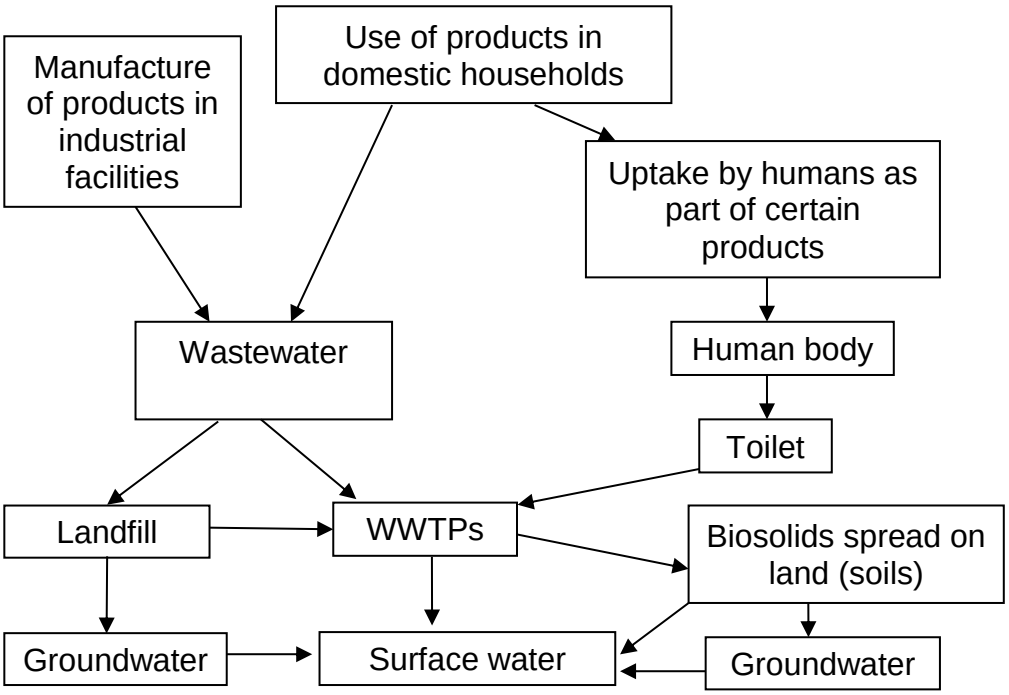


Figure 4-1. Possible pathways for releases of triclosan to the environment (modified from Bound and Voulvoulis 2005)

Triclosan can be released to the environment as a result of its use in many products used by consumers, or as a result of the industrial manufacture or formulation of products containing triclosan. Use in products is considered to be the major contributor to releases of triclosan down the drain. Triclosan released into wastewater reaches WWTPs, where it is partly removed from wastewater, depending on the type of treatment. Triclosan is released to surface water as part of WWTP effluents. Some triclosan partitions to sludge during the wastewater treatment process. As a result, triclosan also reaches soils by way of biosolids amendment to agricultural land. Other possible pathways included in Figure 4-1 are expected to be less important in terms of environmental releases of triclosan (see sections below).

Additional details on potential sources of triclosan for the aquatic and soil compartments are provided in the following sections. Releases of triclosan to water and soil are

described in sections 4.1.1 and 4.1.2. Presence of triclosan in surface waters, sediments and soil in Canada and in other countries is described in section 4.1.3. Metabolites of triclosan, methyl-triclosan and lower-chlorinated dioxins, are also described and considered in the following sections as appropriate.

Triclosan is not expected to be released to air based on the documented uses of triclosan in Canada and on its physical/chemical properties (e.g., low volatility). Air monitoring data for triclosan and its metabolite methyl-triclosan were not identified. Therefore, exposure to triclosan in air is not considered further in this assessment, and additional information is limited to the prediction of the environmental fate that included the air compartment, and estimation the half-life in air (see section 4.2.2).

4.1.1 Releases to water

4.1.1.1 Releases from industry/household to wastewater treatment plants

Triclosan is used in a variety of products used by consumers, mainly soaps and skin cleansers. These products are for the most part released down the drain, discharged into sewers and carried to WWTPs. Triclosan is not manufactured in Canada; however, it is imported by a number of companies to manufacture products that contain triclosan. Industrial activities associated with manufacturing of these products may also release some triclosan into sewers. Based on an analysis of the results obtained through the survey conducted under section 71 of CEPA (Environment Canada 2013), the overall relative contribution from manufacturing facilities compared to households in terms of releases of triclosan to WWTPs is expected to be minor.

Also, triclosan that is present in products such as drugs, cleansers and toothpaste can be absorbed orally by humans and then excreted (up to 83% of the oral dose; Sandborgh-Englund et al. 2006) or directly released into the sink. The excreted triclosan is then carried to WWTPs through sewers. Triclosan is also applied on textiles such as T-shirts to prevent emissions of undesirable odours. Based on published studies, it is estimated that the washing of these T-shirts during their use life can release 1.5% of the mass of triclosan that they contain (22 mg per shirt) to sewers (Walser et al. 2011). Junker and Hay (2004) showed that only trace amounts of triclosan are desorbed from plastic when exposed to water in a laboratory setting. Considering that as of December 31, 2014, triclosan is no longer registered in Canada as a pest control product (i.e., can no longer be used to treat textiles, leather, paper, plastics or rubber materials manufactured in Canada), any potential environmental contribution from triclosan-treated articles is expected to be reduced.

Measured concentrations of triclosan in the influent (i.e., in wastewater at point of entry into WWTP) or effluent of several WWTPs located across Canada are shown in Table 4-1. Most of the wastewater systems listed in Table 4-1 use a secondary level of

treatment to treat wastewater while two of these systems use a primary level of treatment, and five of the systems are lagoons. The Capital Regional District of Victoria has no wastewater treatment. It can be noted that the WWTP that has a concentration of 20 750 ng/L of triclosan in its influent receives wastewater from a soap manufacturer that reported using triclosan (Environment Canada 2013). The concentration of triclosan in the effluent of this WWTP is however very low due to a high removal efficiency of the wastewater treatment.

Table 4-1. Concentration of triclosan in the influent and effluent of certain WWTPs in Canada

Table 4-1a. Concentration of triclosan in the influent and effluent of certain WWTPs in Quebec

Location of WWTPs	Sampling year	Conc. in influent (min.–max. or average, ng/L)	Conc. in effluent (min.–max. or average, ng/L)	Reference
Montreal (population served 1 620 693)	2005–2006	102–811	55–662	Lajeunesse and Gagnon 2007
1 WWTP[a] in Quebec	2010–2012	500	360	Pers. comm.[b,c]
1 WWTP[a] in Quebec	2011–2013	2050	525	Pers. comm.[c]

Note: For table abbreviations and footnotes, see Table 4-1c.

Table 4-1b. Concentration of triclosan in the influent and effluent of certain WWTPs in Ontario

Location of WWTPs	Sampling year	Conc. in influent (min.–max. or average, ng/L)	Conc. in effluent (min.–max., or average, ng/L)	Reference
Hamilton (population served 352 000)	2002	1150	520–740	Lee et al. 2003
Toronto (4 WWTPs; (population served 75 000–1 750 000)	2002	380–1320	140–210	Lee et al. 2003

Location of WWTPs	**Sampling year**	**Conc. in influent (min.–max. or average, ng/L)**	**Conc. in effluent (min.–max., or average, ng/L)**	**Reference**
Burlington (population served 144 130)	2002	790	130	Lee et al. 2003
Guelph (population served 100 000)	2002	740	110–130	Lee et al. 2003
Dundas (population served 27 800)	2002	2910	30–50	Lee et al. 2003
Waterdown (population served is NA)	2002	2260	120–150	Lee et al. 2003
Windsor (population served 78 500)	2003–2004	4530	Mean prior to UV disinfection: 80–330 Mean after UV disinfection: 63	Hua et al. 2005; McPhedran et al. 2013

Location of WWTPs	Sampling year	Conc. in influent (min.–max. or average, ng/L)	Conc. in effluent (min.–max., or average, ng/L)	Reference
12 WWTPs[a] along the Thames River (receiving a mix of residential and industrial wastewater) (population served 2475–182 000)	2002	410–3640	Mean: 108 Max.: 324	Lishman et al. 2006
8 WWTPs[a] in southern Ontario (population served 77 225–1 750 000)	2004	870–1830	50–360	Lee et al. 2005
1 WWTP[a] in Ontario	2010–2013	1073	109	Pers. comm.[b,c]
1 WWTP[a] in Ontario	2010–2011	1908	90	Pers. comm.[b]
1 WWTP[a] in Ontario	2011–2012	2440	40	Pers. comm.[c]
1 WWTP[a] in Ontario	2011–2012	2600	20	Pers. comm.[c]
1 WWTP[a] in Ontario	2011–2013	20 750	12	Pers. comm.[c]
1 WWTP[a] in Ontario	2011–2013	865	40	Pers. comm.[c]

Note: For table abbreviations and footnotes, see Table 4-1c.

Table 4-1c. Concentration of triclosan in the influent and effluent of certain WWTPs in British Columbia

Location of WWTPs	Sampling year	Conc. in influent (min.–max. or average, ng/L)	Conc. in effluent (min.–max., or average ng/L)	Reference
1 WWTP[a] in British Columbia	2010–2013	1673	167	Pers. comm.[b,c]
1 WWTP[a] in British Columbia	2011–2013	1350	865	Pers. comm.[c]
Capital Regional District Victoria outfall (population served is NA)	2006	NA	2200–4160	Pers. comm.[d]

Abbreviations: conc., concentration; max., maximum; min., minimum; NA, not available; pers. comm., personal communication; UV, ultraviolet; WWTP, wastewater treatment plant.
[a]Identity cannot be divulged. Certain WWTPs are the same across studies.
[b]2011 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[c]2013 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[d]2008 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.

Some of the concentrations measured in influent and effluent cited in Table 4-1 as personal communication have been summarized by Guerra et al. (2014).

4.1.1.2 Removal by WWTPs

The fate of triclosan within WWTPs is somewhat complex and has been the subject of several investigations (Bester 2003, 2005; Sabaliunas et al. 2003; Thomas and Foster 2005; Waltman et al. 2006). Studies show that WWTPs are quite efficient in removing triclosan from wastewater, if they have secondary wastewater treatment system. Thomas and Foster (2005) reported that the majority of triclosan removal occurs during secondary treatment (55–88%) and that a smaller proportion (10–44%) is removed during the primary treatment.

In Canada, Lishman et al. (2006) reported 74–98% removal of triclosan in WWTPs located along the Thames River in Ontario. Most of these plants have at least secondary treatment with activated sludge as part of their process. Lee et al. (2003) also reported a median removal efficiency of 81% (range: 49–94%) in WWTPs located in southern Ontario, where most of the plants surveyed employed at least a secondary treatment. It is noted that, based on data from 2004, 26% of the 22 million Canadians serviced by sewer systems were provided with primary wastewater treatment or less

(Environment Canada 2007). In 2012, federal *Wastewater Systems Effluent Regulations* were put in place. These Regulations set national baseline effluent quality standards achievable through secondary wastewater treatment and require wastewater systems with no or little wastewater treatment to be upgraded (Canada 2012).

Canadian removal efficiencies compare with those measured in other countries. In the United States, triclosan removal of 95–96% (McAvoy et al. 2002), and up to 99% (Thomas and Foster 2005), was reported at WWTPs that use secondary treatment. In Europe, WWTP removal efficiencies for triclosan in the range of 87–96% were reported for Germany (Bester 2003, 2005), 94 % for Switzerland (Singer et al. 2002), and 95% for the United Kingdom (Sabaliunas et al. 2003), also for plants that have secondary treatment. These numbers show that efficient removal of triclosan is attributed to secondary treatment.

The removal mechanisms of triclosan from wastewater were investigated in a few studies. Thomas and Foster (2005) showed that adsorption to particulate matter is a likely removal mechanism for triclosan. Bester (2003) reported that 96% of triclosan was removed from wastewater, of which 22–43% was adsorbed to the sludge. This is in line with the moderately sorptive nature of this compound (log K_{oc} up to 4.67; see Table 2-2). Federle et al. (2002) conducted a continuous activated sludge test aimed at examining the degradation of triclosan. In this test, ^{14}C-labelled triclosan was used to establish a material balance. The authors reported that, at steady state, between 1.5% and 4.5% of triclosan was sorbed to solids, whereas 81–92% was mineralized to carbon dioxide or incorporated into microbial biomass. The ^{14}C present in the effluent consisted of extractable (in ethyl acetate) and non-extractable polar intermediates (0.4–7.2% and 2.3–10.5%, respectively). Overall, removal of the parent compound exceeded 98.5%. A second set of experiments was conducted by Federle et al. (2002) and showed that shock loading with triclosan, representative of a situation in which a WWTP receives a consistent low level of triclosan (e.g., from down-the-drain disposal of products used by consumers) with periodical pulses of higher levels (e.g., from a manufacturing facility), did not significantly change the removal pattern. Finally, in a batch activated sludge mineralization test, Federle et al. (2002) observed that 31–52% of triclosan had degraded to $^{14}CO_2$ in 71 days after its addition to the sludge. Following a lag period of 3–10 days, triclosan was spiked again in the test system, resulting in 79–81% of this second dose being recovered as $^{14}CO_2$ after 52 days.

Even though triclosan is removed efficiently by WWTPs, it may also be methylated to methyl-triclosan during the treatment process, likely during secondary treatment. The contribution of this reaction to the overall removal of triclosan from wastewater has not been quantified, but a decrease in triclosan levels has been associated with an increase in methyl-triclosan levels during secondary treatment (Lozano et al. 2013). Generally, the levels of methyl-triclosan in effluent from WWTPs are very low (Lindström et al. 2002; McAvoy et al. 2002), partly because this substance partitions to wastewater sludge (Lozano et al. 2013).

In addition, triclosan can react with chloramines which are used either as an alternative disinfectant to free chlorine in drinking water treatment or formed during the chlorination of non-nitrified wastewater effluent. Greyshock and Vikesland (2006) examined triclosan reactivity in chloraminated waters over a pH range of 6.5–10.5. The reactivity of triclosan in the presence of chloramines is low. The products of these reactions included three chlorinated forms of triclosan as well as 2,4-dichlorophenol and 2,4,6-trichlorophenol.

Impacts of triclosan exposure on bacterial communities in municipal digesters have not been extensively studied; however the few laboratory studies to date indicate that triclosan can alter bacterial community structure and proliferate antimicrobial resistance. It is noted that conditions and concentrations used in the laboratory studies differ from the actual environmental conditions, and exposure concentrations used are generally higher than those measured in the environment. Therefore, the extent of antimicrobial resistance and impacts on bacterial community structures in WWTP from present levels of triclosan are not clear. It has been shown that triclosan can decrease oxygen uptake and inhibit nitrification in activated sludge biomass (Stasinakis et al. 2008a). In a study using lab-scale anaerobic digesters, exposure to triclosan at 5, 50 and 500 mg/kg affected bacterial community structures and digester function, and resulted in proliferation of antimicrobial resistance genes (McNamara et al. 2014). Both the *Bacteria* and *Archaea* communities used in the McNamara (2014) study were observed to diverge from the control communities, overall digester function, assessed by means of methane production, diminished, with 50 mg/kg exposure concentration observed to be the point at which function began to fail in some communities, and the proliferation of triclosan resistance gene (*mexB*) increased at the exposure concentration of 500 mg/kg in previously unexposed communities (McNamara et al. 2014). In aerobic bacteria, alteration of community structure and selection for resistant bacteria in aerobic sediments and in aerobic activated sludge were also observed (Drury et al. 2013; Son et al. 2010).

4.1.1.3 Releases from WWTPs to surface water

4.1.1.3.1 In Canada

Results of several surveys have indicated that triclosan is released from Canadian WWTPs in the effluent (12–4160 ng/L; see Table 4-1). The wide range of concentrations measured in effluent reflects mainly the differences in the population served by the WWTPs as well as the various treatment levels used by the plants (from no treatment to secondary wastewater treatment). Given the multiple products containing triclosan and their ubiquity, a fairly consistent use pattern is expected across Canada.

4.1.1.3.2 In other countries

Concentrations of triclosan in WWTP influent and effluent were measured internationally, in the United States, Switzerland, Scandinavian countries, Spain, and Germany, and generally reflect the levels found in Canada. Monitoring of methyl-triclosan was also undertaken in the United States and Switzerland.

In the United States, samples of influent, primary effluent and final effluent were collected from five WWTPs and analyzed for triclosan and methyl-triclosan in a monitoring study (McAvoy et al. 2002). The plants sampled served populations of 2 445–398 000. The concentrations of triclosan in the final effluent sample ranged between 240 and 410 ng/L, and 1610 and 2700 ng/L for plants using activated sludge or trickling filter treatments, respectively. Methyl-triclosan, a transformation product, was qualitatively detectable in all samples and was estimated to be present in the range of 2–50 ng/L.

The trickling filter treatment involves the use of a bed of crushed rock or synthetic media to support a film of aerobic microorganisms. This method is recognized as being less effective than the activated sludge treatment. Less than 2% of WWTPs in Canada use this process.

In Switzerland, samples of primary and final effluent from WWTPs were collected in 1997 and 2001 from WWTPs that employed a biological treatment process (secondary treatment, but exact method not specified). The sampled WWTPs served populations of 4500–36 000 persons. Triclosan in the primary effluent was found at concentrations of 600–1300 ng/L, whereas methyl-triclosan was detected in much lower concentrations, from less than 1 to 4 ng/L. The corresponding final effluent concentrations were between 70 and 650 ng/L for triclosan and between less than 2 and 11 ng/L for methyl-triclosan. The higher concentrations of methyl-triclosan in the final effluent compared with the primary effluent indicate that this transformation product is formed during biological treatment.

A monitoring program in Denmark examined triclosan concentrations in the final effluent of a WWTP serving both a population of 750 000 and with industrial input. This WWTP included a biological treatment as part of its wastewater treatment process. The average triclosan concentration measured in the effluent was below the detection limit of 1000 ng/L (Pedersen and Nielsen 2003). In Sweden, the final effluent from the three largest WWTPs in the country were sampled and analyzed for several organic pollutants, including triclosan (Paxéus 1996). In two of the plants, triclosan was measured at a concentration of 500 ng/L; it was not detected in the effluent of the third plant (method detection limit [MDL] not specified).

International and domestic monitoring data for WWTP effluent was also summarized by the US EPA (US EPA 2008e). According to US EPA (2008e), triclosan concentrations in

WWTP effluent ranged from 10 to 2700 ng/L in the United States, from 80 to 269 000 ng/L in Spain, and from 10 to 600 ng/L in Germany.

4.1.2 Releases to soil

Some of the reported uses for triclosan in Canada may lead to this substance reaching landfills as part of solid wastes (e.g., products made of textile or rubber). Landfills that do not collect and treat their leachate may potentially release substances to soil, eventually reaching ground or surface water via leaching. However, no data on the quantity of triclosan following this disposal pathway are available.

The application of biosolids from wastewater treatment plants to agricultural lands can result in the presence of triclosan in soil. Considering this route of exposure, the presence of triclosan in sludge and biosolids was investigated.

4.1.2.1 Concentrations in wastewater treatment sludge and biosolids in Canada

Triclosan was readily found in sludge and biosolids collected from WWTPs across Canada as described in numerous studies and monitoring initiatives (Table 4-2).

Between 2011 and 2013, sludge from six Canadian WWTPs was sampled by Environment Canada; average triclosan concentrations ranged between 3.5 and 26.0 µg/g dw (median: 8.9 µg/g dw) (2013 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced). In a study conducted for the Canadian Council of Ministers of the Environment to document the occurrence of emerging substances of concern in biosolids, samples were collected in 2009 at 11 WWTPs located across Canada (CCME 2010a; Table 4-2). Overall, triclosan was found in 97% of the samples collected; the median concentration for all samples was 6.1 µg/g dw (range: < 0.1–46.4 µg/g dw), the highest median value among all of the 82 substances analyzed in this study. According to the study, aerobic treatment processes appeared successful in reducing the input mass of triclosan in the feed sludges (residual wastewater solids delivered to the treatment processes studied). This substance was not well reduced by anaerobic digestion. Chu and Metcalfe (2007) measured similar levels of triclosan, in the range of 0.68–11.55 µg/g dw, in treated biosolids collected in 2006 from four WWTPs located in southern Ontario. Concentrations of triclosan in wastewater sludge sampled in 25 WWTPs across Canada, from Vancouver to Moncton, were reported by Lee and Peart (2002). Most of the samples collected were from digested sludge (i.e., following secondary wastewater treatment). Triclosan was detected in all sludge samples in the range of 0.90–28.2 µg/g dry weight (dw) (median: 12.5 µg/g dw). According to Lee and Peart (2002), triclosan is

likely to be the most abundant polychlorinated phenol found in wastewater sludge, since only 3 out of 35 samples taken contained less than 5 µg/g dw of triclosan.

No monitoring data could be found for concentrations of methyl-triclosan in wastewater sludge from WWTPs in Canada.

Table 4-2. Concentrations of triclosan in wastewater sludge or biosolids in Canada (digested sludge unless specified otherwise)

WWTP location	Sampling period	Concentration (min.–max. or average, µg/g dw)	Reference
Vancouver (BC)	1994 and 1999	8.41–24.7	Lee and Peart 2002
Calgary (Bonny Brook) (AB)	1999	12.8	Lee and Peart 2002
Calgary (Fish Creek) (AB)	1999	19.5	Lee and Peart 2002
Edmonton (AB)	2000	22.0	Lee and Peart 2002
Regina (SK)	2000	18.9	Lee and Peart 2002
Saskatoon (SK)	2000	9.9	Lee and Peart 2002
Adelaide[a] (ON)	1998	8.9	Lee and Peart 2002
Burlington (ON)	2001	19.4	Lee and Peart 2002
Galt (ON)	1996	7.48	Lee and Peart 2002
Guelph (ON)	1999	28.2	Lee and Peart 2002
Hamilton (ON)	1997	16.2	Lee and Peart 2002
Ingersoll (ON)	1998	11.5	Lee and Peart 2002
Kitchener (ON)	1997	16.1	Lee and Peart 2002
Ottawa (ON)	2000	18.6	Lee and Peart 2002
Waterloo (ON)	1996	11.7	Lee and Peart 2002
Windsor (ON)	1997	8.84	Lee and Peart 2002
Toronto (Ashbridges Bay) (ON)	2000	20.3	Lee and Peart 2002
Toronto (Highland Creek)[a] (ON)	2000	16.5	Lee and Peart 2002
Toronto (Humber) (ON)	2000	16.6	Lee and Peart 2002
Toronto (North) (ON)	2000	5.4	Lee and Peart 2002
Montreal[a] (QC)	1999	6.1	Lee and Peart 2002
Granby (QC)	1996	0.90	Lee and Peart 2002
Quebec[a] (QC)	2000	5.5–9.8	Lee and Peart 2002
Moncton (NB)	1997	1.92	Lee and Peart 2002
Truro (NS)	1996	7.53	Lee and Peart 2002
Windsor (ON)	2004	5.29	McPhedran et al. 2013

WWTP location	Sampling period	Concentration (min.–max. or average, µg/g dw)	Reference
4 WWTPs in southern Ontario (ON)	2006	0.68–11.55	Chu and Metcalfe 2007
Salmon Arm (BC)	2009	Min.–max.: 21.3–24.0 Median: 21.5	CCME 2010a
Red Deer (AB)	2009	Min.–max.: 11.7–13.9 Median: 12.7	CCME 2010a
Saskatoon (SK)	2009	Min.–max.: 5.6–6.3 Median: 6.1	CCME 2010a
Prince Albert (SK)	2009	Min.–max.: 2.3–5.6 Median: 4.0	CCME 2010a
Eganville (ON)[b]	2009	Min.–max.: 0.6–30.6 Median: 3.1	CCME 2010a
Smiths Falls (ON)[b]	2009	Min.–max.: 11.8–11.9 Median: 11.8	CCME 2010a
Gatineau Valley (QC)[b]	2009	Min.–max.: 27.6–46.4 Median: 38.6	CCME 2010a
Gatineau Valley (QC)[c]	2009	Min.–max.: <0.1–0.92 Median: 0.78	CCME 2010a
Saguenay (QC)[b]	2009	Min.–max.: 0.9–2.8 Median: 1.3	CCME 2010a
Moncton (NB)[d]	2009	Min.–max.: 5.9–7.3 Median: 7.0	CCME 2010a
Moncton (NB)[c]	2009	Min.–max.: 0.60–0.96 Median: 0.63	CCME 2010a
Halifax (NS)[e]	2009	Min.–max.: 4.8–6.5 Median: 6.1	CCME 2010a
Gander (NL)	2009	Min.–max.: 9.2–20.3 Median: 9.6	CCME 2010a
3 WWTPs[f] in Ontario	2011–2013	3.5–14.5	Pers. comm.[g]
2 WWTPs[f] in British Columbia	2011–2013	6.5[b]–26.0	Pers. comm.[g]
1 WWTP[f] in Quebec[b]	2011–2012	7.7	Pers. comm.[g]

Abbreviations: dw, dry weight; pers. comm., personal communication; max., maximum; min., minimum; WWTP, wastewater treatment plant.
[a]In raw sludge.
[b]In dewatered biosolids cake.
[c]Composted biosolids.
[d]Lime-stabilized biosolids.
[e]This plant also treats sludge from Herring Cove, Bedford, Dartmouth and Aerotech.
[f]Identity cannot be divulged. Certain WWTPs are the same across studies.
[g]2013 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.

Some of the concentrations measured in biosolids cited in Table 4-2 as personal communication have been summarized by Guerra et al. (2014).

4.1.2.2 Concentrations in wastewater treatment sludge in other countries

Data on triclosan occurrence in sludge were available for the United States, Sweden, and Australia. Methyl-triclosan and chlorinated derivates of triclosan were also measured in samples from the United States. Triclosan sludge concentrations found in samples from both the United States and Sweden were within the range found in Canadian samples (presented in Table 4-2).

Triclosan and methyl-triclosan were measured in sludge samples taken from WWTPs in the United States (McAvoy et al. 2002). It was found that triclosan was rapidly removed during the aerobic sludge digestion process, whereas samples from a trickling filter treatment plant showed little or no removal of triclosan during anaerobic sludge digestion. Triclosan concentrations ranged from 0.5 to 15.6 µg/g dw, whereas those for methyl-triclosan ranged from below the limit of quantification (LOQ) to 1.03 µg/g dw, and concentrations of chlorinated derivatives were up to 0.42 µg/g dw (McAvoy et al. 2002). McClellan and Halden (2010) measured an average triclosan concentration of 12.6 µg/g dw and a maximum concentration of 19.7 µg/g dw in archived biosolids collected in 2001 from 94 WWTPs in the United States as part of a national survey. Among the 38 compounds that were detected in the sludge samples, triclosan was found at the second highest mean concentration after triclocarban, which is another antimicrobial agent.

In Sweden, Svensson (2002) sampled sludge from 19 WWTPs in 2001–2002. Concentrations of triclosan in the sludge samples ranged from 0.028 to 6.4 µg/g dw. Another investigation of sludge samples from four Swedish WWTPs in 2001 revealed similar triclosan levels in the range of 2.8–4.4 µg/g dw in anaerobically digested sludge (Remberger et al. 2002). For one of the plants surveyed, both a primary sludge and an anaerobically digested sludge sample were analyzed. The results of these analyses supported the findings of McAvoy et al. (2002) that little or no removal of triclosan occurs during anaerobic digestion.

In Australia, Langdon et al. (2011) sampled biosolids from 13 WWTPs and found triclosan concentrations ranging from 0.22 to 9.89 µg/g dw, with an average of 3.77 µg/g dw.

4.1.3 Environmental concentrations

Continuous releases of triclosan from products that contain it, most notably through wastewater, result in the ubiquitous presence of this chemical in the environment. Concentrations of triclosan have been found in surface waters, sediments, and soil in

the range of ppt to ppb. Monitoring of triclosan in the Canadian surface waters between early 2000 and until the latest available data for 2014 indicate that triclosan continues to be present at constant levels.

Available monitoring and surveillance data for water, sediments, and soil for Canada and other countries are summarized below.

4.1.3.1 Measured concentrations in surface waters

4.1.3.1.1 In Canada

Table 4-3 presents the range of triclosan concentrations measured in surface waters in Canada. The large portion of this data was generated by the Water Science and Technology Directorate, Environment Canada (personal communication, Table 4-3[b-h]; unreferenced). Data were available for all provinces and territories, except Prince Edward Island, from 2002 to 2013. Certain locations across Canada continued to be sampled in 2014. Levels reported spanned almost four orders of magnitude, from below the method detection limit (MDL) to 874 ng/L (reported method detection limits ranged from 4 to 42 ng/L); the highest median concentration was calculated as 139 ng/L. Since surface water in both heavily and lightly populated areas was sampled, this range is expected to be representative of the Canadian inland waters. The data for locations sampled over 8-10 years generally indicate that triclosan continues to be present at constant levels.

Table 4-3. Concentrations of triclosan in surface water in Canada

Table 4-3a. Concentrations of triclosan in surface water in Ontario.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
Detroit River, 600 m downstream of Little River WWTP (City of Windsor)	2003	3	NA	8 (mean)	NA	Hua et al. 2005
Mouth of Niagara River (Niagara-on-the-Lake)	2004–2005	10	0.34	0.69	3.20	Pers. comm.[b]
Head of Niagara River (Fort Erie)	2004–2005	11	<MDL	<MDL	0.43	Pers. comm.[b]
St. Lawrence	2004–2005	11	<MDL	0.11	0.25	Pers.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
River (south channel) at outlet of Lake Ontario (Wolfe Island)						comm.[b]
Thames River	2002	86	<MDL	<MDL	691	Pers. comm.[c]
Hamilton Harbour	2003–2004	59	<MDL	12	626	Pers. comm.[c]
Grand River	2003–2004	72	<MDL	11	260	Pers. comm.[c]
Andrews Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Blyth Brook	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Egbert Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Indian Creek	2005	4	<MDL	<MDL	599	Pers. comm.[c]
Kerrys Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Laurel Creek	2005	5	<MDL	<MDL	65	Pers. comm.[c]
Little Ausable River	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Middle Maitland River	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Mill Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Nineteen Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Nissouri Creek	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
North Maitland River	2005	6	<MDL	<MDL	<MDL	Pers. comm.[c]
Nottawasaga River	2005	6	<MDL	<MDL	22	Pers. comm.[c]
Spring Creek	2005	6	<MDL	<MDL	93	Pers. comm.[c]
Stokes River	2005	6	<MDL	<MDL	43	Pers.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
						comm.[c]
Twenty Mile Creek	2005	15	<MDL	<MDL	433	Pers. comm.[c]
Vineland Creek	2005	5	<MDL	34	66	Pers. comm.[c]
West Don River	2005	6	<MDL	23	64	Pers. comm.[c]
6 rivers and 3 lakes in Ontario	2009–2010	22	<MDL	<MDL	74	Pers. comm.[d]
Niagara River (at Niagara-on-the-Lake)	2012–2013	5	<MDL	<MDL	7.53	Pers. comm.[e]
Wolfe Island	2012–2013	5	<MDL	<MDL	<MDL	Pers. comm.[e]
Mimico Creek	2012–2014	19	<MDL	<MDL	80.4	Pers. comm.[e]
Highland Creek	2012–2014	18	<MDL	5.38	22.6	Pers. comm.[e]
Grand River (upstream of Kitchener WWTP)	2012–2014	16	<MDL	<MDL	6.7	Pers. comm.[e]
Grand River (downstream of Kitchener WWTP)	2012–2014	19	<MDL	12.5	44.2	Pers. comm.[e]
Thames River (upstream of London Greenway WWTP)	2012–2014	17	<MDL	<MDL	19.1	Pers. comm.[e]
Thames River (downstream of London Greenway WWTP)	2012–2014	17	<MDL	8.18	16.9	Pers. comm.[e]
4 sites in Hamilton Harbour	2012–2014	60	<MDL	5.92	268	Pers. comm.[e]
Taylor Creek	2012–2014	19	<MDL	20.8	58.8	Pers.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
						comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3b. Concentrations of triclosan in surface water in Québec.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
Ottawa River (Carillon)	2006–2008	10	<MDL	<MDL	9	Pers. comm.[f]
St. Maurice River (at Trois-Rivières)	2007–2008	4	<MDL	<MDL	<MDL	Pers. comm.[f]
St. Lawrence River (at Lavaltrie)	2006–2009	11	<MDL	16	29	Pers. comm.[f]
St. Lawrence River (at Bécancour)	2006–2009	10	<MDL	5	25	Pers. comm.[f]
Richelieu River (at Sorel)	2006–2009	11	<MDL	<MDL	11	Pers. comm.[f]
St. Lawrence River (at Lévis)	2006–2009	11	<MDL	6.9	34	Pers. comm.[f]
3 rivers and 1 lake in Québec	2009–2010	11	<MDL	41	146	Pers. comm.[d]
St. Lawrence River (at Lévis)	2012–2014	10	<MDL	<MDL	7.65	Pers. comm.[e]
St. Lawrence River (Lavaltrie)	2012–2014	17	<MDL	7.52	15.8	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3c. Concentrations of triclosan in surface water in Manitoba.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
2 rivers and 2 lakes in Manitoba	2009–2010	8	<MDL	<MDL	<MDL	Pers. comm.[d]
Red River (at Highway 4)	2013	2	<MDL	NA	5.73	Pers. comm.[e]
Red River (Selkirk)	2013-2014	5	<MDL	<MDL	14	Pers. comm.[e]
Red River	2013	2	<MDL	NA	37.1	Pers.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
(Winnipeg)						comm.[e]
Red River (Emmerson)	2013	2	<MDL	<MDL	<MDL	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3d. Concentrations of triclosan in surface water in British Columbia.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
Columbia River (at Waneta)	2009	1	NA	NA	<147	Pers. comm.[g]
Fishtrap Creek	2009-2010	2	<66	NA	<69	Pers. comm.[g]
Fraser River	2008	2	<236	NA	<240	Pers. comm.[g]
Mill Creek (Kelowna)	2008–2010	18	<63	NA	<249	Pers. comm.[g]
Okanagan River	2008–2010	16	<62	NA	<248	Pers. comm.[g]
Still Creek (Burnaby)	2008, 2010	3	<64	NA	<241	Pers. comm.[g]
Sumas River	2008–2010	4	<64	NA	<245	Pers. comm.[g]
BX Creek (Vernon)	2009–2010	3	<70	NA	<120	Pers. comm.[g]
Ellis Creek (Penticton)	2009–2010	4	<64	NA	<131	Pers. comm.[g]
Hastings Creek (North Vancouver)	2010	1	NA	NA	<63	Pers. comm.[g]
Osoyoos Lake	2009–2010	2	<67	NA	<111	Pers. comm.[g]
3 rivers and 3 lakes in British Columbia	2009–2010	12	<MDL	<MDL	<MDL	Pers. comm.[d]
Mill Creek (upstream)	2012–2014	15	<MDL	<MDL	7.7	Pers. comm.[e]
Mill Creek (middle)	2012–2014	15	<MDL	<MDL	20.7	Pers. comm.[e]
Mill Creek (reference)	2012–2014	11	<MDL	<MDL	35.3	Pers. comm.[e]

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
Okanagan River (North)	2012–2014	6	<MDL	NA	17	Pers. comm.[e]
Okanagan River	2012–2014	6	<MDL	<MDL	8.9	Pers. comm.[e]
Osoyoos Lake	2012–2013	4	<MDL	<MDL	<MDL	Pers. comm.[e]
Serpentine River	2012–2014	15	<MDL	<MDL	11.3	Pers. comm.[e]
Still Creek	2012–2014	18	<MDL	<MDL	20.2	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3e. Concentrations of triclosan in surface water in Saskatchewan.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
Wascana Creek (downstream of Regina)	2002–2003	23	12	87	602	Pers. comm.[g]
Wascana Creek (upstream to downstream of Regina)	2006	5	<MDL	139	178	Pers. comm.[g]
Wascana Creek (upstream to downstream of Regina)	2006–2007	10	<MDL	43	112	Waiser et al. 2011
Qu'Appelle River (upstream to downstream of confluence with Wascana Creek)	2006	5	<MDL	22	26	Pers. comm.[g]
Pasqua Lake	2006	1	NA	NA	15	Pers. comm.[g]
2 rivers in Saskatchewan	2009–2010	4	<MDL	<MDL	<MDL	Pers. comm.[d]
Wascana Creek (downstream)	2012–2014	12	<MDL	63.3	874	Pers. comm.[e]
Wascana Creek	2012–2013	9	<MDL	<MDL	<MDL	Pers.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
(upstream)						comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3f. Concentrations of triclosan in surface water in Alberta.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
1 lake and 3rivers in Alberta	2009–2010	8	<MDL	<MDL	<MDL	Pers. comm.[d]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3g. Concentrations of triclosan in surface water in Newfoundland.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
1 river and 2 lakes in Newfoundland	2009–2010	6	<MDL	<MDL	34	Pers. comm.[d]
Waterford River	2012–2014	12	<MDL	NA	17	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3h. Concentrations of triclosan in surface water in New Brunswick.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
1 river and 1 lake in New Brunswick	2009–2010	4	<MDL	<MDL	<MDL	Pers. comm.[d]
Napan River	2012–2013	7	<MDL	<MDL	<MDL	Pers. comm.[e]
St. John River (upstream)	2012–2014	16	<MDL	<MDL	8.0	Pers. comm.[e]
St. John River (downstream)	2012–2014	16	<MDL	<MDL	6	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3i. Concentrations of triclosan in surface water in Nova Scotia.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
2 lakes in Nova Scotia	2009–2010	4	<MDL	<MDL	<MDL	Pers. comm.[d]
Little Sackville River	2012–2013	5	<MDL	12	25.4	Pers. comm.[e]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3j. Concentrations of triclosan in surface water in Yukon.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
1 lake in Yukon	2009–2010	2	<MDL	<MDL	<MDL	Pers. comm.[d]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3k. Concentrations of triclosan in surface water in Northwest Territories.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
1 river and 2 lakes in Northwest Territories	2009–2010	6	<MDL	<MDL	<MDL	Pers. comm.[d]

Note: For table abbreviations and footnotes, see Table 4-3l.

Table 4-3l. Concentrations of triclosan in surface water in Nunavut.

Water body	Sampling period	No. of samples	Min. conc. (ng/L)[a]	Median conc. (ng/L)[a]	Max. conc. (ng/L)[a]	Reference
3 lakes in Nunavut	2009–2010	6	<MDL	<MDL	<MDL	Pers. comm.[d]

Abbreviations: conc., concentration; max., maximum; MDL, method detection limit; min., minimum; MQL, method quantification limit; NA, not available; No., number; SDL, sample detection limit; WWTP, wastewater treatment plant.
[a]**Ontario:** MQL = 4 ng/L for the Detroit River; MDL = 0.10 ng/L for the mouth and head of the Niagara River and St. Lawrence River; MDL = 5 ng/L for the Grand River and Hamilton Harbour values referenced as personal communication[c]; MDL = 20 ng/L for other water bodies referenced as personal communication[c]; MDL = 10 ng/L for water bodies referenced as personal communication[d]; MDL varied between sample batches and ranged from 4.06 to 41.9 ng /L (average of 6.02 ng/L) for water bodies referenced as personal communication[e]
Quebec: MDL = 6 ng/L for water bodies referenced as personal communication;[g] MDL = 10 ng/L for water bodies referenced as personal communication;[d] MDL varied between sample batches and ranged from 4.06 to 41.9 ng/L (average of 6.02 ng/L) for water bodies referenced as personal communication[e]
Manitoba: MDL = 10 ng/L for water bodies referenced as personal communication;[d] MDL varied between sample batches and ranged from 4.06 to 41.9 ng/L (average of 6.02 ng/L) for water bodies referenced as personal communication[e]
Saskatchewan: MDL = 25 ng/L (Waiser et al. 2011), MDL = 5 ng/L for water bodies referenced as personal communication;[h] MDL = 10 ng/L for water bodies referenced as personal communication;[d] MDL varied between

sample batches and ranged from 4.06 to 41.9 ng/L (average of 6.02 ng/L) for water bodies referenced as personal communication[e]
British Columbia: Values are presented as <SDL for water bodies referenced as personal communication.[h] The SDL varies by sample and can be lower or higher than the MDL depending on the sample's cleanness (i.e., presence or absence of interfering constituents). MDL = 10 ng/L for water bodies referenced as personal communication;[d] MDL varied between sample batches and ranged from 4.06 to 41.9 ng/L (average of 6.02 ng/L) for water bodies referenced as personal communication.[e]
Alberta, Newfoundland, New Brunswick, Nova Scotia, Yukon, Northwest Territories and Nunavut: MDL = 10 ng/L for water bodies referenced as personal communication;[d] MDL varied between sample batches and ranged from 4.06 to 41.9 ng/L (average of 6.02 ng/L) for water bodies referenced as personal communication[e]
[b]2006 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[c]2007 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[d]2014 personal communication from Environmental and Radiation Health Sciences Directorate, Health Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[e]2015 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[f]2010 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.
[g]2011 personal communication from Water Science and Technology Directorate, Environment Canada, to Science and Risk Assessment Directorate, Environment Canada; unreferenced.

In addition, methyl-triclosan monitoring data were identified for Ontario and Saskatchewan. Methyl-triclosan was measured at concentrations of approximately 1 ng/L and 0.1 ng/L in water samples from Hamilton Harbour and Lake Ontario, respectively (Andersen et al. 2007). In Saskatchewan, Waiser et al. (2011) measured concentrations ranging from 3 to 17 ng/L in Wascana Creek downstream of Regina's WWTP. The Wascana Creek downstream sampling location is associated with the highest measured levels of triclosan (see Table 4-3).

4.1.3.1.2 In other countries

Levels of triclosan have been monitored in the United Sates. In a national reconnaissance survey of 139 streams across 30 states during 1999 and 2000, the maximum and median measured concentrations of triclosan were 2300 ng/L and 140 ng/L, respectively (Kolpin et al. 2002). In Texas, Coogan et al. (2007) measured triclosan and methyl-triclosan concentrations of 60–120 ng/L and 50–80 ng/L, respectively, in a creek receiving an effluent from a WWTP.

Okumura and Nishikawa (1996) measured triclosan at concentrations of 50–150 ng/L in a river in Japan. In Switzerland, concentrations of triclosan in rivers and lakes ranged from 1.4 to 74 ng/L, as reported by Lindström et al. (2002). Still in Switzerland, Singer et al. (2002) measured a methyl-triclosan concentration of about 0.5 ng/L (between the method quantification limit [MQL] and MDL) in water sampled in both the epilimnion and hypolimnion of a lake.

Brausch and Rand (2011) reviewed all studies conducted on triclosan that were published before April 2010 and calculated that this compound has been detected in 56.8% of the surface water samples analyzed (*n* = 710), with a median concentration of 48 ng/L (range: < 0.1–2300 ng/L). Their review included data for surface water in the United States, Romania, the United Kingdom, the Republic of Korea and Switzerland, to name a few.

4.1.3.2 Measured concentrations in sediments

4.1.3.2.1 In Canada

Monitoring data for triclosan and methyl-triclosan are available for the years 2012 and 2013 (personal communication, 2015 email from Water Quality Monitoring and Surveillance Division, Environment Canada to Ecological Assessment Division, Environment Canada; unreferenced). Surface sediment samples were collected from the Pacific and Atlantic regions, Lake Erie, and St. Lawrence River. Overall, Canadian surface sediment concentrations of triclosan were in the range of <1–47 ng/g, and in the range of <2–22 ng/g for methyl-triclosan. Samples of core sediment at different depths from Lake Ontario were analyzed; the maximum concentrations of triclosan and methyl-triclosan were measured at 9 cm core depth, and were 9 and 15 ng/g, respectively. Suspended sediment was measured at varying distances from a WWTP located along the St. Lawrence River; the maximum triclosan concentration in the range of nearly 1000–2000 ng/g was found at a distance 4 km. Canadian monitoring data of triclosan and methyl-triclosan are presented in Table 4-4 below.

Table 4-4. Sediment monitoring data for triclosan and methyl-triclosan in Canada in 2012–2013[a]

Location (sample size)	Sample type	Triclosan range (ng/g)	Triclosan geometric mean (ng/g)	Methyl-triclosan range (ng/g)	Methyl-triclosan geometric mean (ng/g)
Pacific region (3)	Surface sediment	<1–9	2.1	<2	NA
Great Lakes (2)	Surface sediment	7	7.0	<2–14	NA
St. Lawrence River (7)	Surface sediment	14–47	27.4	<2–22	4.5
Atlantic region (9)	Surface sediment	<1–18	1.9	<2–3	NA
Lake Ontario (1)	Core sediment (1 cm depth)	7	NA	14	NA

Lake Ontario (1)	Core sediment (3 cm depth)	8	NA	<2	NA
Lake Ontario (2)	Core sediment (5–7 cm depth)	<1	NA	<2	NA
Lake Ontario (1)	Core sediment (9 cm depth)	9	NA	15	NA
Lake Ontario (11)	Core sediment (11–32 cm depth)	<1	NA	<2	NA
St. Lawrence River (2)	Suspended sediment (1 km from WWTP)	15–21	17.8	<2–9	NA
St. Lawrence River (2)	Suspended sediment (4 km from WWTP)	990–2000	1427	17–24	20.2
St. Lawrence River (4)	Suspended sediment (7 km from WWTP)	29–150	70.4	12–19	17
St. Lawrence River (6)	Suspended sediment (15 km from WWTP)	26–150	72	9–22	15.7

Abbreviations: NA, not available; WWTP, wastewater treatment plant.
[a]Source: Unpublished data, Quality Monitoring and Surveillance Division, Environment Canada.

4.1.3.2.2 In other countries

Sediment monitoring data for triclosan were available for Switzerland, Sweden, the United States and China. Singer et al. (2002) analyzed a sediment core taken from a lake in Switzerland that receives effluent from WWTPs. The profile in the core showed triclosan concentrations ranging from less than 5 ng/g dw in 1960–1961 to 53 ng/g dw in 1992–1993. In Sweden, Remberger et al. (2002) reported triclosan concentrations of 8–17 ng/g dw in sea sediments sampled in an industrial area. Triclosan was also detected by Miller et al. (2008) in cored estuarine sediments from Jamaica Bay, New York. The peak concentrations were 600–800 ng/g dw in sediments deposited between the mid-1960s and late 1970s; they then declined to less than 50 ng/g dw in the following years. Zhao et al. (2010) measured triclosan concentrations ranging from 56.5 to 739 ng/g dw in sediments sampled from three rivers flowing in a heavily populated area of China.

4.1.3.3 Measured concentrations in soils

No monitoring data for concentrations of triclosan or methyl-triclosan in soil were found for Canada. In Sweden, Remberger et al. (2002) measured triclosan concentrations in two contaminated (industrial) areas and in one pristine forest area. Triclosan concentrations in the contaminated sites ranged from less than 3 to 15 µg/kg dw, while they were less than 3 µg/kg dw (detection limit) in the forest soil. In the United States, Wu et al. (2010b) measured triclosan in soils that had been amended with biosolids. The concentrations of triclosan in amended soils ranged from 1.6 to 11 µg/kg dw.

4.2 Environmental Fate

This section contains information on the environmental distribution and fate of triclosan in the environmental media. Environmental distribution to water, soil, sediment and air is evaluated using the Multispecies Model (version 1.0; Cahill 2008), and considers the ionizing properties of triclosan at pH 7 and 8. Environmental persistence of triclosan is evaluated in water, sediment and soil using empirical data. Degradation of triclosan in air is evaluated using modelled data generated from AOPWIN (2008). Information on abiotic and biotic degradation pathways and transformation products is organized based on the environmental compartment.

4.2.1 Environmental distribution

When a substance is able to ionize in water at environmentally relevant pH, its neutral and ionic forms will co-exist in the environment (water, sediment and soil). With a pK_a of 8.1 (see Table 2-2), triclosan will ionize to some extent in most of the natural water bodies in Canada. The ionization of triclosan proceeds as the proton attached to the phenolic group dissociates from the structure forming an anionic molecule. At pH values of 6, 7, 8 or 9, the fraction of ionized triclosan in pure water will be 1%, 7%, 44% or 89%, respectively, using the equation $F_i = 1 - (1/(1+10^{pH-pK_a})) \times 100\%$, where F_i is the fraction ionized.

Table 4-5 summarizes the distribution of the neutral and anionic forms of triclosan among environmental compartments based on the Multispecies Model (version 1.0; Cahill 2008). More specifically, the results provide the proportion (fraction of the total mass emitted to the environment − 1000 g per hour to each of air, water and soil compartments, as default model input) of each form present in each compartment upon a continuous release to water or soil, at an environmental pH of 7. The model was also run at an environmental pH of 8, since this value is also relevant for many aquatic and terrestrial ecosystems in Canada. The proportion modelled is determined with respect to the total quantity released, so the sum of all proportions adds up to 100%. The physical/chemical properties and half-life values presented in Tables 2-2 and 4-6, respectively, were used as input for the model. The input values for the physical/chemical properties of the ionized form of triclosan were based on the corresponding values for the neutral form, after applying correction factors, while the

input values for half-lives were the same as for the neutral form. The results in Table 4-5 represent the net effect of chemical partitioning, intermedia transport and loss by both advection (out of the modelled region, but not out of the wider ecosystem) and degradation or transformation processes. In spite of loss processes, the sum of all proportions still adds up to 100% given that the predictions are based on the assumption that steady state is reached among the four compartments after triclosan is being released on a continuous basis.

Table 4-5. Distribution of the two forms of triclosan among environmental compartments at pH 7 and 8

Triclosan released to:	Form	Percentage of triclosan partitioning into each compartment			
Water (100%) at pH 7	Neutral	Air: 0.0	Water: 72.9	Soil: 0.0	Sediment: 19.8
Water (100%) at pH 7	Ionized	Air: 0.0	Water: 5.8	Soil: 0.0	Sediment: 1.5
Soil (100%) at pH 7	Neutral	Air: 0.0	Water: 0.1	Soil: 92.6	Sediment: 0.0
Soil (100%) at pH 7	Ionized	Air: 0.0	Water: 0.0	Soil: 7.3	Sediment: 0.0
Water (100%) at pH 8	Neutral	Air: 0.0	Water: 50.6	Soil: 0.0	Sediment: 5.2
Water (100%) at pH 8	Ionized	Air: 0.0	Water: 40.1	Soil: 0.0	Sediment: 4.1
Soil (100%) at pH 8	Neutral	Air: 0.0	Water: 0.2	Soil: 55.6	Sediment: 0.0
Soil (100%) at pH 8	Ionized	Air: 0.0	Water: 0.1	Soil: 44.1	Sediment: 0.0

In a scenario where triclosan is exclusively released to water, it is expected to reside in both water (79–91%) and sediment (9–21%) at pH 7 and 8. If released only to soil, triclosan remains almost exclusively in this compartment (>99%). At an environmental pH of 7, triclosan will mainly be present in its neutral form in water, sediment and soil. At a pH of 8 in these same compartments, about 55% of triclosan will be in its neutral form and about 45% in its ionized (anionic) form. In the prairie provinces, for instance, where soil is alkaline (pH 9), triclosan would be present primarily in its anionic form.

4.2.2 Fate in air

Modelled environmental distribution profile using the Multispecies Model (version 1.0; Cahill 2008) summarized in Table 4-5 indicated that triclosan in unlikely to partition to air if released into the environment. Model results using the model AOPWIN (2008) indicated that triclosan degrades fast via reactions with hydroxyl radicals, with a half-life of 0.66 day. Triclosan is not likely to be subject to long-range transport given its unlikely distribution into air, and the predicted short air residence time.

4.2.3 Fate in water

4.2.3.1 Abiotic processes

Triclosan is a phenolic compound that ionizes at environmentally relevant pH (pK_a of 8.1; see Table 2-2). The speciation, or ionization state, of a weak organic acid, such as triclosan, will influence its fate in the environment and its bioavailability. For instance, the ionized form of triclosan has a different light absorption spectrum than the neutral form. Also, organisms may more readily take up the neutral form; this was highlighted by Orvos et al. (2002), who showed that, for the same species, the toxicity of triclosan decreased with increasing pH. More generally, the results obtained by Erickson et al. (2006a, b) suggest that the ionized form of weak organic acids is also available for uptake through a variety of mechanisms. Hence, ionized triclosan could also accumulate in organisms.

In natural waters, triclosan may form complexes with dissolved organic matter, which could influence the concentrations of freely dissolved triclosan. Assuming that the dissolved organic matter–triclosan complexes cannot cross a cell membrane, only the fraction of total triclosan present in the freely dissolved form in the water column could be bioavailable. No studies quantifying the effect of dissolved organic matter on the bioaccumulation of triclosan in aquatic organisms could be found in the literature. According to a mass balance fish model, the predicted bioavailable fraction of triclosan in the water column is approximately 99%, based on its log K_{oc} of 4.7 (see Section 4.3.1).

Laboratory studies have shown that triclosan is hydrolytically stable at pH 4, 7 and 9 (US EPA 2008e). It is also stable against strong acids and bases (Singer et al. 2002). Its low Henry's law constant of 5.05×10^{-4} Pa·m^3/mol (see Table 2-2) indicates that it should not volatilize from a water surface.

Triclosan is susceptible to phototransformation in surface waters, as shown in many studies (Lindström et al. 2002; Singer et al. 2002; Tixier et al. 2002; Mezcua et al. 2004; Latch et al. 2005; Lores et al. 2005). Tixier et al. (2002) quantified the phototransformation of triclosan under laboratory and field conditions for a small lake in Switzerland. They highlighted the fact that pH, by affecting the speciation of triclosan (pK_a = 8.1), has an impact on its absorption of sunlight. Indeed, the direct phototransformation rate of triclosan increases with pH, i.e., with the proportion of the ionized form of triclosan present in solution. Indirect phototransformation (e.g., photosensitization by organic matter) was a negligible process. The study authors estimated that, during the summer season, direct phototransformation accounted for 80% of the observed total elimination of triclosan from the study lake. The remaining major sink for triclosan was the loss in the outflow. The authors also predicted triclosan phototransformation rates for a variety of environmental conditions, including time of year and latitude. The resulting primary degradation half-life values spanned from 2 to 2000 days. For latitudes modelled by the authors that are equivalent to southern Canada (~45–50°N) and for a pH of 8.0, the effective annualized phototransformation

half-lives obtained for triclosan in water were less than 100 days throughout the year. For water bodies with a lower pH, somewhat longer half-lives would be expected (but still less than 100 days), and the relative importance of other removal processes, such as biodegradation and sedimentation, would increase.

Latch et al. (2005) performed experiments in both natural and deionized water under natural sunlight and showed that triclosan was rapidly degraded by direct photolysis (half-life of 5 hours at pH 8, midsummer sunlight, 45°N latitude).

Lindström et al. (2002) conducted a photolysis experiment in which triclosan was exposed to natural sunlight in lake water at different pH values. While triclosan was stable at pH 5.6, it degraded rapidly at pH 8.0 (half-life of about 20 minutes). Methyl-triclosan, which reaches surface water as part of WWTP effluent, was also tested in this study; it did not photodegrade at either pH.

Different degradation products can be formed by the photolysis of triclosan. For instance, in addition to showing a short half-life for triclosan (41 minutes), a study conducted under laboratory conditions indicated that 2,4-DCP was formed as a major transformation product (up to 97%; US EPA 2008f). This substance has been the subject of a SIDS Initial Assessment Report under the OECD HPV Chemicals Programme. This report indicates that 2,4-DCP is likely not persistent, not bioaccumulative and moderately toxic to aquatic organisms (OECD 2007).

Mezcua et al. (2004) measured 2,7/2,8-DCDD as major phototransformation products of triclosan under natural sunlight. Two phototransformation experiments were conducted at two different pH values (pH 5 and 7). It was shown that triclosan transformed to dioxin at pH 7 only, confirming the results obtained by Tixier et al. (2002) regarding the high transformation rate of the ionized form compared with the neutral form. Mezcua et al. (2004) also measured 2,7/2,8-DCDD in the effluent of a WWTP (4–400 ng/L), thereby revealing its input to receiving surface waters. The phototransformation of triclosan to DCDD was confirmed by Lores et al. (2005) and by Sanchez-Prado et al. (2006) using photo-solid-phase microextraction. Latch et al. (2005) also measured 2,8-DCDD as well as 2,4-DCP as transformation products of triclosan in a photolysis experiment. Yields of these products ranged from 3% to 12%. Finally, the phototransformation of triclosan to 2,8-DCDD was also reported in seawater (Aranami and Readman 2007).

Data available on the degradation of 2,7/2,8-DCDD and the aquatic toxicity of 2,8-DCDD indicate that these compounds should be less harmful to the environment than other dioxins, such as their tetrachlorinated congeners (e.g., 2,3,7,8-TCDD). 2,7/2,8-DCDD are not on the list of 17 dioxins and furans that are of the greatest concern based on international toxicity equivalency factors (NATO 1988). The photolability of 2,7/2,8-DCDD is reported in several studies (Mezcua et al. 2004 [half-life < 20 hours]; Latch et al. 2005; Sanchez-Prado et al. 2006; Aranami and Readman 2007), as is the aerobic

microbial degradation of both 2,7- and 2,8-DCDD (e.g., 16–33% within 7 days; Field and Sierra-Alvarez 2008) (Parsons and Storms 1989; Parsons 1992). The toxicity of 2,8-DCDD to fish appears to be low, as suggested by the results of a study in which embryos of the Japanese medaka (*Oryzias latipes*) hatched and survived for 3 days post-hatch (full exposure duration) when exposed to 50 000 ng/L (Wisk and Cooper 1990). The toxicity of 2,7-DCDD is unknown. Given their probable transient state in the environment and low toxicity, these DCDDs are not likely to be of environmental concern.

Buth et al. (2009) showed that chlorinated triclosan derivatives formed during the disinfection of wastewater can further phototransform to PCDDs, as well as to 2,4-DCP, in natural water. These dioxin congeners (1,2,8-TriCDD, 2,3,7-TriCDD and 1,2,3,8-TCDD) were detected in sediments from the Mississippi River at levels that trended with the historical use of triclosan (Buth et al. 2010). These compounds may be more toxic than 2,7/2,8-DCDD due to their increased chlorine substitution. Buth et al. (2010) estimated that the mass contribution of triclosan-derived dioxins could represent up to 30% of the total dioxin pool in the sediment cores that they analyzed.

4.2.3.2 Biotic processes

4.2.3.2.1 WWTP-related conditions

Based on its chemical structure, triclosan is not expected to biodegrade rapidly. Results obtained for the standardized OECD test guideline 301C (modified MITI test (I)) test indicate that triclosan is not readily or inherently biodegradable (0% degradation after 4 weeks at a test concentration of 100 mg/L) (NITE 2002). In this kind of test, which measures ultimate degradation (measured by the formation of carbon dioxide), an aqueous solution of the test substance is inoculated and incubated under aerobic conditions in the dark or in diffuse light. These results are consistent with previous work by Voets et al. (1976), who observed no loss of triclosan in test systems that were inoculated with a soil extract. However, Federle et al. (2002) suggested that the negative results obtained in these tests are unreliable as a consequence of the likely bacterial toxicity of triclosan at the high concentrations used (1–100 mg/L). This statement is supported by the results of a ready biodegradability study in which triclosan was applied at a rate of 0.2 mg/L to a microbial inoculum in sandy loam soil and activated sludge. Triclosan degraded with an average half-life of 5.2 days (US EPA 2008e). Results of aerobic biodegradation tests conducted at various concentrations (10–500 000 µg/L) for various durations (21–91 days) indicated 18–70% degradation for triclosan (NICNAS 2009). More specifically, Stasinakis et al. (2008b) conducted a biodegradability test with triclosan (at 10 µg/L) using the OECD test guideline 301F method (manometric respirometry test). In this 28-day test, 52% ultimate degradation was achieved, and the calculated half-life was 1.8 days. Federle et al. (2002) conducted biodegradation tests with activated sludge at triclosan concentrations of 20–200 µg/L. By the end of the tests (71 days), 31–52% of triclosan had mineralized to carbon dioxide. For comparison purposes, concentrations of triclosan in the influent of WWTPs

in Canada are in the range of 0.102–20.7 µg/L (Table 4-1)—that is, much lower than those tested in the biodegradation tests mentioned above.

Voets et al. (1976) conducted tests with triclosan under anaerobic conditions for sludge digestion in WWTPs. Results of two anaerobic biodegradation tests conducted at 200 and 1000–5000 µg/L for 147 and 21 days, respectively, indicated 10% and 50% degradation, respectively.

4.2.3.2.2 Environmental conditions

In an aerobic aquatic metabolism study conducted at 20°C, triclosan disappeared rapidly from the water layer in river water–sandy loam sediment and pond water–silty clay loam sediment systems (US EPA 2008e). In the water layer (pH 7.2–7.3), [^{14}C]triclosan declined from an average 88–93% of the applied radioactivity at time 0 to 49–53% at 1 day to less than or equal to 0.3% at 56–104 days post-treatment. Volatilized carbon dioxide for the whole system was 21–29% of the applied radioactivity by study termination (day 104). [^{14}C]Triclosan dissipation half-lives for the water layer (resulting from degradation and partitioning) were 1.3–1.4 days based on extractable residues only. Half-lives for sediments and total systems were 54–60 days and 40–56 days, respectively. More details are provided in Section 4.2.4.2 below.

Considering the results above for ultimate biodegradation (i.e., mineralization to carbon dioxide) of triclosan under aerobic conditions, there is evidence that this substance is not persistent in water. Results from the aerobic aquatic metabolism study also indicate that triclosan is not persistent in this environmental compartment.

Table 4-6. Data on the persistence of triclosan in different media

Medium: fate process (test conditions)	Degradation value	Degradation endpoint (units)	Reference
Air: atmospheric oxidation	0.66[a]	Half-life (d)	AOPWIN 2008
Water: hydrolysis	Stable	NA	Singer et al. 2002
Water: hydrolysis (pH 4, 7 and 9, 50°C, for 5 d)	Stable	NA	US EPA 2008e
Water: photodegradation (field conditions, pH 8.0, year-round, 50°N)	<100	Primary half-life (d)	Tixier et al. 2002
Water: photodegradation (laboratory conditions, pH 8.0, summer sunlight, 45°N)	5	Primary half-life (h)	Latch et al. 2005
Water: photodegradation (laboratory conditions, pH 8.0, summer sunlight,	0.37	Primary half-life (h)	Lindström et al. 2002

Medium: fate process (test conditions)	**Degradation value**	**Degradation endpoint (units)**	**Reference**
47°N)			
Water: photodegradation (laboratory conditions, pH 7.0, artificial light)	41	Half-life (min)	US EPA 2008e
Water: biodegradation, WWTP-related conditions (aerobic conditions, various test concentrations and durations)	18–70	Degradation (%)	NICNAS 2009
Water: biodegradation and partitioning (aerobic conditions, 20°C, in darkness, for 104 d): • river water–sandy loam sediment system (pH 7.3) • pond water–silty clay loam sediment system (pH 7.2)	Range for both systems (water layer): 1.3–1.4[a]	Dissipation half-life (d)	US EPA 2008e
Sediment: biodegradation and partitioning (aerobic conditions, 20°C, in darkness, for 104 d): • river water–sandy loam sediment system (pH 7.3) • pond water–silty clay loam sediment system (pH 7.2)	Ranges for both systems: sediment: 54–60[a] whole system: 40–56	Dissipation half-life (d) Degradation half-life (d)	US EPA 2008e
Soil: biodegradation (aerobic conditions, 20°C, in darkness, for 124 d): • sandy loam (pH 7.1) • clay loam (pH 6.85) • loam (pH 7.3)	 2.9 3.8 3.7	Half-life (d)	US EPA 2008e
Soil: biodegradation (aerobic conditions, loam, pH 7.4, 22°C)	18[a]	Primary half-life (d)	Ying et al. 2007
Soil: biodegradation (aerobic conditions, room temperature): • silty clay (pH 4.7) • sandy loam (pH 4.1)	 58 32	Primary half-life (d)	Wu et al. 2009
Soil: biodegradation (aerobic conditions, 20°C in darkness, for 45 d): • loamy sand (pH 7.5) • silty clay (pH 7.5) • sandy loam (pH 7.1) • silt loam (pH 7.1)	 14 16 14 13	Primary half-life (d)	Xu et al. 2009

Medium: fate process (test conditions)	Degradation value	Degradation endpoint (units)	Reference
Soil: biodegradation (anaerobic conditions, loam, pH 7.4, 22°C)	>>70	Primary half-life (d)	Ying et al. 2007

Abbreviations: d, days; h, hours; NA, not available; WWTP, wastewater treatment plant.
[a]Value used for fugacity modelling with Multispecies Model.

4.2.4 Fate in sediment

4.2.4.1 Abiotic processes

Triclosan is susceptible to rapid oxidation by manganese oxides, which are present in aerobic sediments and soils (Zhang and Huang 2003). Under environmentally relevant pH and manganese dioxide concentrations, the primary degradation half-life of triclosan was calculated to be less than 21 hours. Degradation products were reported to include 2,4-DCP (< 1% of triclosan loss). However, dissolved metal ions and natural organic matter in water and soil would likely increase this value by competitively adsorbing and reacting with manganese dioxide.

Given its moderate log K_{oc} values of 3.34–4.67 (see Table 2-2), it can be expected that triclosan (especially the neutral form) will adsorb to organic matter present in effluent or in receiving surface waters. As the substance is released to aquatic ecosystems through WWTP effluent, a portion could be removed from the water column through sedimentation. Once in aerobic sediments, triclosan could react with manganese oxides to a certain extent. The balance of these two processes—i.e., input to sediment through sedimentation and output through oxidation—would be difficult to quantify.

4.2.4.2 Biotic processes

As noted previously, triclosan degraded rapidly in river water–sandy loam sediment and pond water–silty clay loam sediment systems under aerobic conditions (US EPA 2008e). In the water layer, [^{14}C]triclosan declined from an average 88–93% of the applied radioactivity at time 0 to less than or equal to 0.3% at 56–104 days post-treatment. In the sediment, [^{14}C]triclosan increased from an average 39–40% of the applied radioactivity at time 0 to 69–75% at 7–14 days and was 21–22% at 104 days post-treatment. In the total system, [^{14}C]triclosan decreased steadily from 88–93% of the applied radioactivity at time 0 to 52–68% at 28 days and to 21.5–21.8% at 104 days post-treatment. [^{14}C]Triclosan dissipation half-lives (degradation and partitioning) were 1.3–1.4 days (water layer) and 54–60 days (sediment) for both water–sediment systems; degradation half-lives were 40–56 days in total systems. Non-extractable residues (not included in half-life calculations) were 32–33% at study termination, and volatilized carbon dioxide was 21–29%. Methyl-triclosan was identified as a minor transformation product, with a maximum mean of 0.1% of the applied radioactivity at 28

days post-treatment in the water and a maximum mean of 3.4–4.8% at 104 days in the sediment and total system.

No experimentally measured half-lives for triclosan in sediments under anaerobic conditions could be found. However, evidence of the persistence of triclosan in buried anaerobic sediments is shown by monitoring data. Singer et al. (2002) analyzed a sediment core taken from a lake in Switzerland that receives effluent from WWTPs. The concentration profile in the core showed that triclosan has been accumulating in sediments, from less than 5 ng/g dw in 1960–1961 to 42 ng/g dw in 1970–1971 to 53 ng/g dw in 1992–1993. This increase was likely due to its continual input into the lake, showing that it accumulates in anaerobic sediments more rapidly than it degrades. The fact that a relatively high amount of triclosan was contained in the approximately 30-year-old sediment layer (1970–1971) points to a slow degradation rate for triclosan. Triclosan was also detected in cored estuarine sediments from Jamaica Bay, New York. Indeed, Miller et al. (2008) measured peak triclosan concentrations of 600–800 ng/g dw in sediments deposited in that bay between the mid-1960s and late 1970s. For the following years, the concentrations declined to less than 50 ng/g dw, probably due to the introduction of an activated sludge treatment process to the Jamaica Bay WWTP. In China, Zhao et al. (2010) measured triclosan concentrations ranging from 56.5 to 739 ng/g dw in sediments sampled from three rivers flowing in a heavily populated area. As a whole, these sediment core data point to the persistence of triclosan in buried anaerobic sediments.

Given that organisms live mostly under aerobic conditions (even endobenthic fauna), a greater weight is attributed to half-lives measured under these conditions. Triclosan that is present in buried anaerobic sediments is considered of less significance in terms of biological exposure. In addition, if triclosan in these sediments were to be resuspended, it would likely come in contact with oxygen as a result of mixing and could then be subject to biodegradation processes. Half-life values for ultimate degradation under aerobic conditions are not available for sediments. The study conducted with two water–sediment systems indicated half-lives of 40–56 days in those systems. These half-lives represent a mix of primary and ultimate degradation processes, since carbon dioxide was 21–29% of the applied radioactivity by study termination. In this study, a portion of triclosan is not available for biodegradation given its partitioning to sediments (i.e., bound to residues). Based on empirical evidence for rapid primary biodegradation in water and soil (half-lives of days to a few weeks; Table 4-6) and half-lives of approximately 30–70 days for ultimate degradation in water, it is expected that triclosan will not be persistent in sediment. Methyl-triclosan is a transformation product of triclosan in sediment.

4.2.5 Fate in soil

4.2.5.1 Abiotic processes

As mentioned previously, hydrolysis is not an important transformation process for triclosan. Also, its Henry's law constant value (see Table 2-2) indicates that it should not volatilize from moist soil surfaces. Its log K_{oc} values (3.34–4.67) suggest that it should generally not be mobile in soil, especially if the organic carbon content in soil is high. Other abiotic processes, such as phototransformation, have not been documented for triclosan in the soil compartment. Since its main entry route in soil would likely be through spreading of biosolids on agricultural fields followed by ploughing (see Section 4.5.3), a portion of triclosan will likely be incorporated in the deeper soil layers and hence would not be exposed to light. If spread on wood lots or in the forest, triclosan in biosolids could be exposed to light in the absence of ploughing. Prior to biosolid application, some WWTPs may have placed biosolids on a sludge pad or open field for further drying, leaving triclosan susceptible to phototransformation and possible production of degradation products that could be released in the environment.

The leaching potential of triclosan from soil was examined using both the criteria of Cohen et al. (1984) and the groundwater ubiquity score (Gustafson 1989). These two approaches allow for a semiquantitative determination of the leaching potential of a chemical. Table 4-7 shows how physical/chemical properties and certain fate data for triclosan compare with the values for the criteria of Cohen et al. (1984). This comparison does not allow for a clear indication regarding the leaching potential of triclosan. In the Prairies, where soils tend to be alkaline, the anionic form of triclosan is expected to predominate, thus increasing its potential for leaching.

Table 4-7. Comparison of the properties of triclosan with the leaching criteria of Cohen et al. (1984)

Property	Criteria of Cohen et al. (1984) indicating a potential for leaching	Triclosan value	Meets criterion for leaching
Solubility in water	>30 mg/L	10 mg/L	No
K_d	<5 and usually <1 or 2	10–282	No
K_{oc}	<300	2188–46 774	No
Henry's law constant	$<10^{-2}$ atm·m^3/mol (<1013 Pa·m^3/mol)	4.99×10^{-9} atm·m^3/mol (5.05×10^{-4} Pa·m^3/mol)	Yes
pK_a	Negatively charged (either fully or partially) at ambient pH	8.1	Yes (varies with ambient pH)
Hydrolysis half-life	>20 wk (>140 d)	Stable to hydrolysis	Yes
Soil	>1 wk (>7 d)	NA	NA

Property	Criteria of Cohen et al. (1984) indicating a potential for leaching	Triclosan value	Meets criterion for leaching
phototransformation half-life			
Half-life in soil	>2–3 wk (>14–21 d)	Aerobic: 2.9–58 d Anaerobic: >>70 d	Yes

Abbreviations: d, days; K_d, soil/water partition coefficient; K_{oc}, soil organic carbon/water partition coefficient; NA, not available; pK_a, dissociation constant; wk, week.

The method of Gustafson (1989) may also be used to estimate the leaching potential of chemicals. Gustafson's assessment method uses a groundwater ubiquity score (GUS), which is based on the persistence and mobility of the compound and is expressed as:

$$GUS = \log_{10}(t_{½\ soil}) \times (4 - \log_{10}(K_{oc}))$$

The GUS value indicates the leachability of the compound. The persistence term in the GUS equation, $t_{½\ soil}$, is the field dissipation time (DT_{50}), as determined in field dissipation studies, and is meant to include dissipation by volatilization, phototransformation and biological transformation. Instead of the field dissipation DT_{50}, however, the laboratory aerobic soil DT_{50} or $t_{½}$ value was used in the GUS equation; this is because the field dissipation DT_{50} may also include dissipation from leaching and runoff and therefore may underestimate leaching potential when used in the equation. The GUS classification scheme is as shown in Table 4-8.

Table 4-8. Leachability classification system based on calculated GUS indices

GUS	Probable attributes
>2.8	Leacher
>1.8 and <2.8	Borderline leacher
<1.8	Non-leacher

For triclosan, a half-life value of 58 days in aerobic soil and a K_{oc} value of 2188 were used to calculate a conservative value of the GUS index. According to the leachability classification presented in Table 4-8, triclosan is a non-leacher (GUS = 1.16).

$$GUS \text{ for triclosan} = \log_{10}(58) \times (4 - 3.34) = 1.16$$

When present in soil, triclosan is expected to have a low potential to leach based on the mobility classification (K_{oc}: 2188–46 774: immobile to slight mobility, as per McCall et al. 1981) and the GUS score indicating that it is a non-leacher. It should be noted, however, that triclosan has been detected in groundwater at low levels in various monitoring studies, suggesting that other mechanisms, such as facilitated transport (particle facilitated or macropore/fractures), may contribute to its detection in

groundwater (Gottschall et al. 2012; Edwards et al. 2009). In a national reconnaissance of contaminants present in groundwater in the United States in 2000, triclosan was detected in 15% of the 47 sites sampled by Barnes et al. (2008). The concentrations were all below the reporting level of 1 µg/L. The sampling sites consisted mainly of wells and of a few springs and sumps. They were located in areas suspected to be susceptible to contamination from either animal or human wastes (i.e., down-gradient of a landfill, unsewered residential development or animal feedlot). In China, Chen et al. (2011) measured triclosan in groundwater that served to irrigate agricultural fields; concentrations of 1.2–10.8 ng/L were measured at three different sites. Triclosan was below the LOQ (1.6 µg/kg) in the corresponding irrigated soils.

Triclosan may also enter into the terrestrial environment through the disposal of products in landfills. Leaching is expected to be limited for products in which triclosan is embedded into solid material, such as plastics. However, for materials like textiles, triclosan is more likely to leach out given its application on the surface of the material. Personal care products are also disposed of in landfills and are expected to contribute to triclosan residues in landfill leachate. Leachate from 94% of the larger landfills in Canada is collected and treated (on-site and/or off-site) before being released to the environment. Monitoring data were collected under the Government of Canada's Chemicals Management Plan monitoring program in 2010, 2011, 2012 and 2013 at 4 to 12 of the larger landfills in Canada. These data indicate that triclosan concentrations in leachate before any treatment ranged from below MDL to 1.4 µg/L. Three of the 12 overall landfills sampled are treating their leachate on-site before either sending it to a WWTP or releasing it to the environment. For these landfills, triclosan concentrations in leachate after treatment ranged from below MDL to 0.16 µg/L. For landfills that send their leachate (treated or not) to a WWTP, the removal of triclosan during wastewater treatment (primary or secondary) followed by the dilution of the WWTP effluent in the receiving watercourse will likely result in low releases of triclosan in aquatic ecosystems (Conestoga-Rovers and Associates 2015). Based on this information, landfills are not a likely source of triclosan to the environment.

There is also evidence that triclosan can reach surface water and groundwater through runoff and drainage. Following broadcast application of either liquid or dewatered wastewater biosolids to soil and simulating a rainfall, Topp et al. (2008) and Sabourin et al. (2009) measured triclosan concentrations in runoff of 258 ng/L and 110 ng/L, respectively, one day after biosolids application. In the study by Topp et al. (2008), the concentration of triclosan in runoff was still above the LOQ on day 266 following application. To explain this persistence, the authors suggested that sorptive and diffusive processes in the soil had sequestered a portion of the chemical, reducing its availability for biodegradation. Lapen et al. (2008) and Edwards et al. (2009) measured maximum triclosan concentrations of 3680 ng/L and 240 ng/L in tile drainage following application of liquid and dewatered wastewater biosolids, respectively, which points to the potential of triclosan to reach groundwater. Gottschall et al. (2012) detected triclosan in the tile water at 73 ng/L, and at 19 ng/L in ground water at the depth of 2

meters, but not at depths of 4 to 6 meters, following application of dewatered waste water biosolids. These studies on runoff and tile drainage were conducted in Ontario, Canada.

4.2.5.2 Biotic processes

In an aerobic soil metabolism study conducted at 20°C, triclosan degraded rapidly, with half-lives of 2.9 days (sandy loam), 3.8 days (clay loam) and 3.7 days (loam) (US EPA 2008e). [^{14}C]Triclosan declined from an average 92–95% of the applied radioactivity at time 0 to 42–58% at 2–3 days and to 1.1–4.3% at 61–124 days post-treatment. Non-extractable residues (not included in half-life calculations) were 61–76% of the applied radioactivity at study termination, and volatilized carbon dioxide was 11–16%. The major transformation product was methyl-triclosan, at maximum averages of 13–24% of the applied dose at 14–28 days post-treatment. Methyl-triclosan then decreased by study termination. Dissipation time (DT_{50}) values for methyl-triclosan in these soils, as provided in NICNAS (2009), ranged from 39 to 153 days. A supplementary experiment was conducted at 10°C with the sandy loam described above. The DT_{50} value obtained for triclosan was 10.7 days versus 2.5 days for the same soil at 20°C, as provided in NICNAS (2009). The former value is still low in terms of persistence of triclosan in soil.

Ying et al. (2007) studied the biological degradation of triclosan in soil under both aerobic and anaerobic conditions in the laboratory. For the aerobic experiments, triclosan was added to a loam soil (at 1 mg/kg), which was then incubated in darkness for 70 days. The anaerobic experiments were conducted the same way but were carried out in an anaerobic incubation chamber filled with nitrogen. At each sampling time during the experiment, soil samples were extracted with acetone, and triclosan present in the extracted fraction was measured by high-performance liquid chromatography. Sterile soil samples were also incubated to assess abiotic transformation processes; no degradation occurred in these samples. The results obtained showed that triclosan degraded in aerobic soil, with a half-life of 18 days. However, it had not degraded under anaerobic conditions by the end of the study period (i.e., half-life >> 70 days). Additional measurements indicated that triclosan did not have negative effects on soil microbial activity in the aerobic soil samples; similar measurements were not made in the anaerobic soil. This study indicates that triclosan is not persistent in aerobic soil; however, the extent to which it degrades was not characterized by the study authors (e.g., primary vs. ultimate degradation). Indeed, no attempts were made to identify or quantify degradation products in soil, and no traps were used to collect volatile degradation compounds, such as carbon dioxide. In addition, the fraction of triclosan bound to soil residues (i.e., not extracted with acetone) was not quantified; however, the figures provided in the paper indicate that concentrations of extractable triclosan in sterile soil were rather stable over the study duration. The fact that these concentrations remained stable indicates that the bound residues formed in the non-sterile soil were likely transformation products of triclosan and not parent triclosan, since the latter did not bind to the soil under sterile conditions. In a similar study, Wu et al. (2009)

incubated under aerobic conditions two types of soil to which triclosan had been added. The incubation period was 60 days. The half-lives obtained were 58 days and 32 days, respectively, for a silty clay and a sandy loam. The authors also measured the biodegradation rate of triclosan in the same soils that had been amended with biosolids; the corresponding half-lives were found to be 41 days and 20 days. Finally, Xu et al. (2009) incubated four types of soil with triclosan under aerobic conditions for 45 days and observed half-lives of 13–16 days.

In a study comparing the transformation of triclosan in soils that had never received biosolids application and in the same soils to which biosolids were applied in the laboratory, Kwon et al. (2010) observed that the presence of biosolids significantly slowed the transformation of triclosan, likely due to physical and chemical interactions such as adsorption. Half-lives in two different soils were 2 days and 13 days without biosolids; half-lives in the same two soils were 50 days and 108 days, respectively, following biosolids application. Because biosolids are likely the main source of triclosan to the terrestrial environment, these longer half-lives can be expected under field conditions. Lozano et al. (2010) reported a dissipation half-life of 107 days for triclosan for a field that had received one application of biosolids. An additional study by Lozano et al. (2012) studied triclosan and its transformation product methyl-triclosan over a period of three years following application of biosolids to a sandy loam soil under field conditions. Triclosan disappearance corresponded with methyl-triclosan appearance, suggesting *in situ* formation. Dissipation half-lives were estimated to be 104 days for triclosan and 443 days for methyl-triclosan, respectively.

Similarly to sediments, given that organisms live mostly under aerobic conditions in soil, a greater weight is attributed to half-lives measured under these conditions. Half-life values for ultimate degradation in soil are not available. The only aerobic soil metabolism study in which carbon dioxide was trapped and measured indicates triclosan half-lives of 2.9–3.8 days and a production of 11–16% carbon dioxide after 124 days. These half-lives represent a mix of primary and ultimate degradation processes. Generally, carbon dioxide is not expected to reach high levels, because a large proportion of triclosan partitions to soil residues and hence is not available for degradation. Based on the evidence for rapid primary biodegradation in the various aerobic soil studies described above (half-lives of 2.9–58 days), triclosan is not considered persistent in soils.

4.2.6 Relevance of environmental fate of triclosan

Residence time and fate of a chemical in the environment are factors that directly affect levels of exposure to that chemical and associated risk, i.e., the likelihood of adverse effects from contact or uptake of a chemical. In general, long persistence can contribute to prolonged exposure and thus greater risk (Mackay et al. 2014).

Triclosan is not likely to persist in the environment as indicated by its half-lives in the various environmental compartments and its environmental distribution in each compartment (Tables 4-5 and 4-6). For the aquatic compartment, however, its continual input to surface waters through WWTP effluent results in its continuous presence in the receiving aquatic ecosystems. As noted by Mackay et al. (2014), when there is a constant and widespread input of a chemical into the environment, it leads to its continuous presence in the environment near field (i.e., in proximity to emission sources), and exposure to a chemical can occur well before its degradation processes are able to take place. Therefore, in this case, the half-life of a chemical as an indicator of the overall persistence is largely irrelevant, because of the short time to exposure (Mackay et al. 2014). Indeed, for triclosan, time to exposure in aquatic ecosystems may be shorter than the time needed for its degradation. Therefore, long-term exposures to triclosan in water and sediments are expected, especially near field, closer to effluent sources. In terrestrial ecosystems, exposure to triclosan can occur from the periodic land applications of biosolids. Since the field dissipation half-lives measured for triclosan are relatively long (>100 days), exposure levels in soil are also expected to be somewhat constant.

Exposure to triclosan transformation products is also expected in the environment, and the associated risk is dependent on their properties. In water, photolysis of triclosan leads to formation of dichlorophenol (DCP), and other phototransformation products of triclosan include lower (di-) chlorinated dioxins. DCP and di-chlorinated dioxins are not likely to be of environmental concern due to their moderate toxicity and a transient state in the environment. Disinfection of wastewater can also lead to formation of DCP as well as tri-chlorinated dioxin congeners. While the tri-chlorinated dioxins may be more toxic than DCP and di-chlorinated dioxins due to higher chlorine substitution, they are not considered as harmful as the higher chlorinated dioxins such as the tetra-chlorinated congeners.

Methylation of triclosan during biological process at WWTPs and in soil and in sediments leads to formation of methyl-triclosan. This transformation product is known to have longer half-lives in the environment, and, similarly to triclosan, it is also highly toxic to aquatic organism. Methyl-triclosan is expected to be ubiquitous in the environment, and co-exposure to both triclosan and methyl-triclosan is likely in the environment.

Long-range transport of triclosan in the environment is not expected because of its relatively short half-life in aquatic ecosystems, the short modelled half-life in air, and its predicted distribution in the environment (results presented in Table 4-5).

4.3 Bioaccumulation

Bioaccumulation is the process that causes an increased chemical concentration in an organism through all routes of exposure, i.e., diet and ambient environmental sources,

compared to that in its environment (Arnot and Gobas 2006; Burkhard et al. 2012). It is the net result of competing processes of the chemical uptake into the organism, from the diet and bioconcentration from the respiratory and dermal surfaces, and of the chemical elimination from the organism, through metabolic biotransformation of the parent compound, respiratory exchange, fecal egestion, and growth dilution (Arnot and Gobas 2006). On the ecosystem level, bioaccumulation of a chemical in organisms can lead to its biomagnification across trophic levels.

Numerous metrics can be used to assess the bioaccumulation potential of a chemical including the bioconcentration factor (BCF), bioaccumulation factor (BAF), the log K_{ow} (the partition coefficient between *n*-octanol (a surrogate for lipid tissue) and water), and biomagnification factor (BMF). Bioavailability and biotransformation of the parent compound through metabolism are also important considerations in determining the extent and potential of a chemical to bioaccumulate. Characterization of the bioaccumulation potential of a chemical is also important in evaluating its toxicity. Bioaccumulation to levels that surpass the internal narcotic toxicity thresholds can lead to adverse effects and mortality in organisms.

Bioaccumulation potential of triclosan was characterized using its physical chemical properties, BCF and BAF studies, metabolism, fugacity ratio and fugacity capacity calculations, and modelling using the model BASL4 (2011). Data were available for numerous aquatic organisms, and some terrestrial species. Bioaccumulation of methyl-triclosan in aquatic species is also described. The available bioaccumulation studies in fish and the potential for metabolism of triclosan presented in this section were also reviewed in an unpublished report (Arnot 2015) submitted to Environment and Climate Change Canada. In addition, an unpublished report (Arnot 2016), also submitted to Environment and Climate Change Canada, describes the use of *in vitro* to *in vivo* extrapolations (IVIVE) to estimate the whole body biotransformation rate constants (*k*B) from published *in vitro* bioassay experiments for use in BCF calculations. According to Arnot (2016), the range of the calculated BCFs using the IVIVE data were comparable to the reliable quality measured BCFs, as well as the field BCFs from various species and to the BCF predictions from various models.

Triclosan is available for uptake by organisms as demonstrated by its presence in tissues of exposed aquatic organisms. Triclosan can also be readily metabolized by organisms. BCF values ranging from low to high were available for two fish species and a moderate BCF value was determined in mussels (Böttcher 1991; Schettgen et al. 1999; Schettgen 2000; NITE 2006; Gatidou et al. 2010; Gonzalo-Lumbreras et al. 2012). There are numerous uncertainties associated with some of the BCF studies; the highest reported BCF values are thought to be overestimated. Triclosan BAF values reported for algae and snails were low to moderate (Coogan et al. 2007; Coogan and La Point 2008). BAF values reported for methyl-triclosan were moderate to high (Coogan et al. 2007; Coogan and La Point 2008; Balmer et al. 2004). Moderate bioaccumulation of triclosan in fish can lead to concentrations that surpass the internal toxicity thresholds,

as demonstrated by the fugacity capacity calculations. Triclosan is unlikely to biomagnify in aquatic and terrestrial food webs, primarily because it can be metabolised by organisms.

4.3.1 Aquatic organisms

4.3.1.1 Concentrations measured in wild aquatic organisms

Although limited information could be found on the levels of triclosan in wild aquatic organisms in Canada, experimental data on the presence or bioaccumulation of triclosan in organisms were available in the literature for other countries. Adolfsson-Erici et al. (2002) reported accumulation of triclosan in the bile of fish exposed in different ways to effluent from WWTPs in Sweden (Table 4-9). Some fish were exposed to effluent in the laboratory for 3-4 weeks, whereas others were caged for three weeks downstream from a WWTP. Wild fish were also caught, for which the exposure period is uncertain. When taken together, the concentrations measured in the bile of fish for all exposure types ranged from 0.24 to 120 mg/kg wet weight (ww). The highest concentrations were measured for fish exposed to wastewater in the laboratory, followed by fish that were caged downstream a WWTP. The lowest concentrations were measured in wild fish collected downstream a WWTP. These measurements are for the bile, which likely overestimate the concentration that would be expected for the whole body. Although no bioaccumulation factor (BAF) can be calculated from this study, the results show that triclosan is bioavailable when released in water. The data also highlight the potential for excretion of unmetabolized triclosan by fish. Results reported by Valters et al. (2005) show that triclosan is present to a much lesser extent in the plasma of fish (0.750–10 ng/g ww; Table 4-9). Boehmer et al. (2004) measured triclosan concentrations up to 3.4 ng/g ww in the muscle of fish sampled in numerous rivers in Germany. Corresponding concentrations of methyl-triclosan in the same samples were up to about 90 times higher than the triclosan concentrations (Table 4-9).

Fair et al. (2009) collected blood plasma from wild bottlenose dolphins in South Carolina and Florida. Triclosan concentrations in plasma ranged from 0.025 to 0.27 ng/g ww, with up to 31% of the sampled individuals having detectable levels of triclosan.

For the marine environment, triclosan and methyl-triclosan tissue residue data are available for the mussel species *Mytilus galloprovincialis* (Kookana et al. 2013). Triclosan and methyl-triclosan were measured in mussels at the mean concentrations of 9.87 and 6.99 ng/g ww, respectively, following exposure for 70 days at four marine locations in Adelaide, South Australia, that receive effluents from WWTPs (Kookana et al. 2013).

Given its pK_a of 8.1, triclosan can be partly ionized at environmentally relevant pH values, which can influence its bioaccumulation potential. pH values were not available for the studies described above.

Table 4-9. Measured concentrations of triclosan in tissues of aquatic organisms

Test organism	Endpoint	Value (based on wet weight)	Reference
Rainbow trout (*Oncorhynchus mykiss*)	Concentration in bile	34–120 mg/kg[a]	Adolfsson-Erici et al. 2002
Rainbow trout (*Oncorhynchus mykiss*)	Concentration in bile	17–47 mg/kg[b]	Adolfsson-Erici et al. 2002
Roach (*Rutilus rutilus*)	Concentration in bile	4.4 mg/kg[c]	Adolfsson-Erici et al. 2002
Eelpout (*Zoarces viviparus*)	Concentration in bile	0.24–0.90 mg/kg[c]	Adolfsson-Erici et al. 2002
Perch (*Perca fluviatilis*)	Concentration in bile	0.44 mg/kg[c]	Adolfsson-Erici et al. 2002
13 fish species collected in the Detroit River (near Windsor, Ontario)	Concentration in blood plasma	0.750–10 ng/g	Valters et al. 2005
Bottlenose dolphins (*Tursiops truncatus*)	Concentration in blood plasma	0.025–0.27 ng/g	Fair et al. 2009
Bream (*Abramis brama*)	Concentration in muscle	<0.25–3.4 ng/g	Boehmer et al. 2004
Marine mussel (*Mytilus galloprovincialis*)	Whole body concentration	9.87 ng/g	Kookana et al. 2013

Abbreviation: WWTP, wastewater treatment plant.
[a]Fish exposed to effluent from WWTPs in tanks in laboratory.
[b]Test organisms caged downstream from a WWTP.
[c]Organisms in the wild collected downstream from WWTPs.

4.3.1.2 Molecular size and bioconcentration

Molecular size and cross-sectional diameters are useful parameters to consider as weight of evidence for bioaccumulation potential and are commonly used by international jurisdictions such as the EU (ECHA 2008). Recent investigations relating fish BCF data and molecular size parameters (Dimitrov et al. 2002, 2005) suggest that the probability of a molecule crossing cell membranes as a result of passive diffusion declines significantly with increasing maximum diameter. The probability of passive diffusion via the gills decreases appreciably when the maximum diameter of a chemical is greater than about 1.5 nm, and much more so for molecules having a maximum diameter greater than 1.7 nm. Sakuratani et al. (2008) also investigated the effect of cross-sectional diameter on passive diffusion in a BCF test set of about 1200 new and existing chemicals. They observed that substances that do not have a very high

bioconcentration potential (BCF < 5000 L/kg ww) often have a maximum diameter of greater than 2.0 nm and an effective diameter of greater than 1.1 nm. For triclosan, the maximum diameter of 1.3 nm and effective diameter of 0.81 nm were determined, and suggest that triclosan will be passively diffused without restriction through the lipid bilayer.

4.3.1.3 Metabolism and toxicokinetics in fish

Studies on the metabolism and distribution of triclosan in fish suggest that triclosan can be biotransformed, predominantly through Phase II glucuronide conjugate transformation, and subsequently cleared from the exposed organisms (James et al. 2012; Newsome et al. 1975). Mammalian metabolism and toxicokinetics studies are discussed in section 3.1.1; the glucuronide conjugate of triclosan was also noted to be the major metabolite of triclosan in numerous studies (US EPA 2008b; SCCP 2009; Sandborgh-Englund et al. 2006). In addition, it was estimated using ACD Labs Percepta software (ACD/Percepta c1997-2012), that triclosan has a low to moderate volume of distribution (Vd) at 2.4 L/kg compared with more hydrophobic compounds, and a high predicted potential for protein plasma binding (log K_a human serum albumin = 4.1). This suggests that triclosan may be distributed in blood as well as in lipophilic tissues. Using the same software, it was predicted that triclosan is highly permeable in human jejunum (intestine) tissues with a high rate of passive diffusion (k_a = 0.06 min^{-1} via a 100% transcellular route). This is consistent with the size of maximum and effective diameter estimates for triclosan discussed in subsection 4.3.1.2.

Newsome et al. (1975) investigated the absorption, distribution, metabolism and excretion of triclosan in goldfish (*Carassius auratus*). In the study, a group of six goldfish (weight of 4 g to 107 g) was exposed to radiolabelled triclosan at 2 mg/L for two hours, or at 0.5 mg/L for eight hours of uptake (pH 7.8 to 8.2). After the two-hour uptake of triclosan, the greatest concentration of radioactivity was found in the gall bladder, with a concentration factor of 2500 over the bathing solution, and approximately 60% of the activity was found in the bile. Triclosan was eliminated rapidly during the excretion period. After 24-hour excretion, 60% of activity in water was identified as metabolite(s), with 40% remaining as the parent compound. At least one metabolite was identified, which was speculated to be a glucuronide conjugate. Newsome et al. (1975) stated that both kidney and body reached equilibrium with the bathing solution about two hours after initial exposure, whereas the liver and gall bladder concentrations continued to rise steeply. It is thus likely that steady-state had not been reached in the liver and gall bladder. Although a whole body steady-state was not reached in this study, the results generally suggest a short half-life of triclosan in goldfish, estimated at approximately 1-2 days.

In an *in vitro* study, triclosan was found to be rapidly glucuronidated and sulfonated in the liver and intestine of channel catfish (*Ictalurus punctatus*) (James et al. 2012). Triclosan glucuronidation and sulfonation were assayed in the microsomal fraction from

liver and proximal intestine. The K_m values for methyl-triclosan ranged from 80 to 250 µM, with V_{max} values for O-demethylation ranging from 30 to 150 pmol/min/mg protein (at 21 ^{o}C). Triclosan at 1 µM could be glucuronidated at a rate of 23 pmol/min/mg protein in liver and 3.2 pmol/min/mg protein in intestine, and sulfonated at rates of 277 and 938 pmol/min/mg protein in liver and intestine, respectively. James et al. (2012) concluded that triclosan could be rapidly cleared in catfish tissues following dietary uptake based on these rates.

Metabolism of triclosan was also modelled using the BCF_{Max} Model with Mitigating Factors (Dimitrov et al. 2005); the potential metabolites predicted by the model are shown in Figure 4-2. The Phase II glucuronide conjugate transformation was the dominant pathway, characterized by a nearly 100% probability of occurrence of the glucuronide conjugate metabolite of triclosan or a complete transformation of the parent molecule (i.e., 1:1 molar ratio). Phase I arene oxidation was predicted to have a lower probability of occurrence, but it may also be a likely elimination pathway. Using SMARTCyp, a HTML-based Cytochrome P450 Quantitative Structure-Activity Relationship (QSAR) from the University of Copenhagen's Department of Drug Design and Pharmacology (Rydberg et al. 2010a, 2010b; Rydberg and Olsen 2012a, 2012b; Rydberg et al. 2013a, 2013b), 3-4 sites of Phase I arene oxidation were predicted with high likelihood on the structure of triclosan.

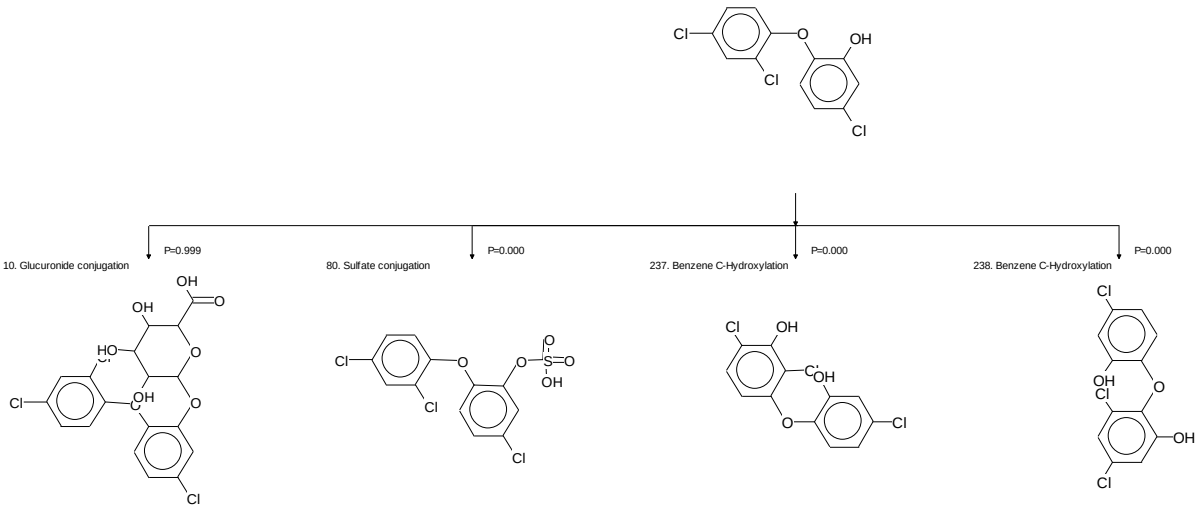


Figure 4-2. Prediction of potential metabolites from triclosan using the BCFMax Model with Mitigating Factors (Dimitrov et al. 2005)

4.3.1.4 Bioconcentration factors (BCF) and bioaccumulation factors (BAF) in aquatic species

Studies measuring the bioconcentration factors (BCF) in fish and mussels (Gonzalo-Lumbreras et al. 2012; Gatidou et al. 2010; Schettgen et al. 1999; Schettgen 2000; NITE 2006; Böttcher 1991), and the bioaccumulation factor (BAF) in algae and snails (Coogan et al. 2007; Coogan and La Point 2008) are described below and summarized in Table 4-10.

Table 4-10. Summary of bioconcentration (BCF) and bioaccumulation (BAF) data in aquatic species

Test organism	Endpoint	Value (L/kg, based on wet weight)	Reference
Zebrafish (*Danio rerio*) (larvae)	BCF	2018–2630 (based on 15% lipid content)	Gonzalo-Lumbreras et al. 2012
Zebrafish (*Danio rerio*)	BCF	2532–4157 (at pH 7.7–8.0)	Böttcher 1991
Zebrafish (*Danio rerio*)	BCF	3700–8700 (at pH 6, 7, 8 and 9)	Schettgen et al. 1999; Schettgen 2000
Common carp (*Cyprinus carpio*)	BCF	16–90	NITE 2006
Algae (field samples, various species)	BAF	900–2100[a]	Coogan et al. 2007
Daphnia resting eggs (ephippia)	BCF	74; 4970[b]	Chiaia-Hernandez et al. 2013
Mussel (*Mytilus galloprovincialis*)	BCF	1700[c]	Gatidou et al. 2010
Mussel (*Mytilus galloprovincialis*)	BCF	646;[c] 13 490[b]	Kookana et al. 2013
Snail (*Helisoma trivolvis*)	BAF	500[d]	Coogan and La Point 2008

Abbreviation: WWTP, wastewater treatment plant.
[a]Organisms in the wild collected downstream from WWTPs.
[b]Lipid normalized.
[c]Dry weight.
[d]Test organisms caged downstream from a WWTP.

Böttcher (1991) conducted a bioconcentration test with zebrafish (*Danio rerio*) in a flow-through test system based on methods modified from OECD test guideline 305C. Zebrafish were exposed to either 3 or 30 µg/L of triclosan in the test water. The test

compound concentrations were well maintained (at 2.95-3.18 µg/L and 26.4-27.66 µg/L for 3 and 30 µg/L nominal concentrations, respectively). Fish had an average weight of 0.33 g at study initiation. Uptake and depuration periods were 5 and 2 weeks, respectively. [^{14}C]Triclosan was used for the experiment, and results were based on total radioactivity measured in water and fish tissues. The experiment was conducted at pH 7.7-8.0; given the pK_a of 8.1 for triclosan, almost half of the test substance was dissociated resulting in exposure to both the neutral and ionogenic forms of triclosan. Steady state did not appear to be reached during the 5-week uptake period, as bioconcentration factor (BCF) values fluctuated during this period at both exposure concentrations. The maximum BCF values were reached at week 3, but then decreased until week 5. The causes for the decrease in BCF values are unknown, but are related to fluctuations in tissue residues rather than in exposure concentrations as the latter were very stable throughout the uptake phase. The average BCFs over the 5-week uptake period were calculated to be 4157 L/kg ww at 3 µg/L and 2532 L/kg ww at 30 µg/L (Table 4-10); maximum BCF values were 5337 L/kg ww and 3408 L/kg ww, respectively. Because such measurements based on total radioactivity cannot distinguish between the parent compound and possible metabolites, this might have led to overestimation of BCF values. Depuration rate constants (k_2) at 3 µg/L and 30 µg/L were 0.142/day and 0.141/day, respectively. It should be noted that the higher exposure concentration used in this test is 5.6% of the 96-hour median lethal concentration (LC_{50}) for zebrafish (540 µg/L; unreviewed study cited in NICNAS 2009). OECD test guideline 305 recommends that the highest concentration be set at 1% of the acute asymptotic LC_{50} to avoid toxic effects that could affect fish bioaccumulation kinetics. Given the deficiencies of this study, mainly the lack of equilibrium during the uptake phase, its results are uncertain and thus have questionable reliability. As such, these uncertainties were considered in the weight of evidence approach used to characterize the bioaccumulation potential of triclosan.

Schettgen et al. (1999) conducted a bioconcentration study with triclosan at different pH values (6–9) based on OECD test guideline 305E. Zebrafish (*Danio rerio*) were exposed to either 35 or 50 µg/L of triclosan for about 150 hours before being transferred to clean water for an additional 100 hours for the depuration phase. The average lipid content was 5.32%, 6.18%, 3.86% and 7.55% for fish tested at pH 6, 7, 8 and 9, respectively. Triclosan was dissolved in methanol, and the concentration of methanol was 0.05% in the accumulation tank (Schettgen 2000). This concentration exceeded the maximum solvent concentration of 0.01% (equivalent of 0.1 mL/L) specified in the OECD test guideline 305E. The high concentration of methanol might have increased the bioavailability of triclosan resulting in a higher degree of uptake than might be expected under natural conditions. Concentrations of triclosan in fish and water were analyzed by gas chromatography–electron capture detection, and rate constants for uptake (k_1) and clearance (k_2) were calculated. Based on the uptake and elimination curve obtained, equilibrium seems to have been reached during the experiment. The exposure period for the uptake phase (150 hours) exceeded the time to reach 80% of steady state (80% time to steady state = $1.6/k_2$ = 1.6/(0.0347/hour) = 46 hours), which is an additional

indication that steady state was reached. The BCF values (± standard deviation) were determined as the ratio of the rate constants and were as follows: 8700 (±2632) L/kg ww, 8150 (±1417) L/kg ww, 6350 (±963) L/kg ww and 3700 (±1232) L/kg ww at pH 6, 7, 8 and 9, respectively (Table 4-10). These values show the expected decrease in uptake rate with increasing ionization of triclosan from pH 6 to 9; the clearance rate constant had similar values for all pH values tested, ranging from 0.0347/hour to 0.0413/hour. The metabolic rate constant (k_M) will be slightly lower than these depuration values, but the half-life estimated based on the average depuration rate is approximately 18 days, somewhat longer than other studies. The uptake rate constants decreased from 356/hour to 129/hour with increasing pH values. As for one exposure concentration used in the study by Böttcher (1991), the exposure concentrations used in this test are higher than 1% of the acute asymptotic 96-hour LC_{50} for zebrafish (540 µg/L; unreviewed study cited in NICNAS 2009); the limit of 1% is recommended in the OECD test guideline 305 to avoid toxic effects that could affect fish bioaccumulation kinetics. In this experiment, the uptake and depuration processes, and hence the BCF values, may have been slightly affected by the concentrations of triclosan used. The recovery rate of triclosan was 168% in fish and was 93% in water; the greater than 100% recovery rate in fish suggests experimental error and possible tissue contamination, which might have led to overestimation of BCF. Because of the deficiencies in the experimental study, the reliability of this study is questionable, and this is considered in the weight of evidence approach used to characterize the bioaccumulation potential of triclosan.

A study using zebrafish larvae was conducted by Gonzalo-Lumbreras et al. (2012) as an alternative to the OECD technical guideline 305 based on ethical and economic considerations. Zebrafish larvae were exposed to 3 and 30 µg/L, corresponding to 0.1 and 1% of their LC_{50}, and similar to the concentrations used in studies by Böttcher (1991) and Schettgen et al. (1999), described above. The BCF values were determined as 2018 and 2630 at the lower and higher exposure concentrations, respectively, over 72 hours. Exposure solutions were changed every 24 hours as per the OECD 305 guideline requirement, to avoid fluctuations of the nominal exposure concentrations. Steady state was not reached during the uptake phase, and it was explained that a longer exposure time would be required. It is noted that at 15%, zebrafish larvae have a higher lipid content than adult fish which may impact the degree of bioaccumulation of hydrophobic chemicals, compared to results in adult fish which typically have 5% lipid content. A direct comparison with BCF values for adult fish would require application of a conversion factor to account for the differences in the lipid content. Given that in the natural environment fish would be exposed to triclosan at all life stages, this study is considered a valid representation for bioaccumulation potential at an early life stage.

The Japanese National Institute of Technology and Evaluation (NITE) conducted a bioconcentration study with carp (*Cyprinus carpio*) in which fish were exposed to either 3 or 30 µg/L of triclosan for 8 weeks under flow-through conditions (NITE 2006). The protocol followed the NITE test guideline for bioaccumulation in carp, which corresponds to OECD test guideline 305C. Measured concentrations of triclosan in test

water over the study duration slightly fluctuated from 22.4 to 26.0 µg/L and from 2.00 to 2.46 µg/L for the 30 µg/L and 3 µg/L exposure concentrations, respectively. The study report did not mention whether a depuration phase occurred during the experiment, but this is likely to have been performed. Also, the pH of the test water was not reported. Average BCF values at the 3 µg/L exposure concentration were 55, 69, 56, 39 and 80 L/kg ww at 1, 2, 4, 6 and 8 weeks, respectively. At the 30 µg/L exposure concentration, average BCF values were 36, 36, 30, 36 and 18 L/kg ww at 1, 2, 4, 6 and 8 weeks, respectively. The minimum and maximum BCF values were 16 and 90, respectively, when considering both exposure concentrations and all data (Table 4-10). As in the study by Böttcher (1991), BCF values fluctuated somewhat during the NITE study, but only nominally from the grand average BCF of 45. Since the measured concentrations in water were relatively stable, fluctuations in BCF values could be due to fluctuations in fish tissue concentrations; however, these data were not available. No values were reported for the uptake or depuration rate constants (k_1), but using the grand average BCF value from the test and extrapolating k_M using procedures outlined in Arnot et al. (2008), a metabolic rate constant would be approximately 8.8 d^{-1} or a half-life < 1 day.

The large differences observed between the fish BCF values reported by Böttcher (1991), Schettgen et al. (1999), Gonzalo-Lumbreras et al. (2012) and NITE (2006) could be due to differing uptake rates, metabolic rates, different weights of fish used, different lipid contents, etc., in addition to the study deficiencies mentioned.

There are no BAF values available for fish; however, the K_{oc} and K_{ow} of triclosan suggest that the BAF should closely approximate BCF. Indeed, at a log K_{oc} of 4.7, the predicted bioavailable fraction of triclosan in the water column according to mass balance fish models is approximately 99%, which means that practically all of the total water concentration of triclosan will be in the dissolved phase. This suggests that uptake from water via the gills is a very relevant exposure for this substance. This also suggests that the contribution of the diet to the total body burden of triclosan in aquatic organisms is likely quite low. In fact, the calculated BAF using the Arnot-Gobas mass balance (version 1.11) (Arnot and Gobas 2003) is only 3% greater than the BCF.

Two bioconcentration studies are available for a marine species, the mussel *Mytilus galloprovincialis*. Gatidou et al. (2010) measured a BCF of 1700 L/kg dry weight (reported as 1.7 L/g) for mussel *M. galloprovincialis*. Mussels were exposed to 300 ng/L of triclosan for 28 days (pH not reported), during which the tissue concentrations constantly increased, and steady state was not observed. The BCF was determined as the ratio of the uptake and depuration rate constants. The experiment revealed that the depuration rate of triclosan was lower than its uptake rate and the biological half-live of triclosan was reported as 12 days. Given this half-life value, a higher BCF would have been expected. Kookana et al. (2013) investigated bioconcentration of triclosan and methyl-triclosan in the same species of mussels. Mussels were exposed to triclosan at a concentration of 100 ng/L for 30 days is seawater aquaria. Steady state was reached at about 24-30 days. The lipid content of mussels remained constant, at about 5.4%. BCF

for triclosan was determined as 646, and 13 490 when lipid normalized. BCF (lipid normalized) for methyl-triclosan was determined as 15 488.

Bioconcentration in daphnia resting eggs (ephippia) were investigated by Chiaia-Hernandez et al. (2013). *Dapnia magna* ephippia were exposed to triclosan at concentrations between 150 and 250 µg/L for up to 120 hours. The lipid content of test organisms was measured as 1.5% of the wet weight. The BCF in ephippia was determined as 74 (wet weight), and 4970 when lipid normalized.

Coogan et al. (2007) calculated a BAF ranging from 900 to 2100 L/kg ww for algae collected in a creek receiving the effluent from a WWTP, while a BAF of 500 was calculated for snails that had been caged in the same creek for 2 weeks (Coogan and La Point 2008). It is unknown but likely that a steady state in triclosan concentration in snails was reached by the end of the exposure period. The exposure pH was not reported in either study.

4.3.1.5 Biota sediment accumulation factors (BSAF) in sediment species

The route and degree of uptake of triclosan by the sediment-dwelling worm, *Lumbriculus variegatus*, were investigated using ^{14}C-labelled triclosan (Karlsson et al. 2015). Feeding and non-feeding worms (where the head anterior segments were removed) were used in the study to assess the kinetics of uptake. Nominal triclosan exposure concentrations over 48-hours ranged between approximately 625 to 650 nmol/kg in sediment, and up to nearly 5 nmol/L in water. The ^{14}C activity of triclosan in the 48 hour uptake phase in the water column was observed to decrease, and was attributed to the uptake of the parent triclosan and any transformation products into the study organisms since the measurement of ^{14}C activity may represent not only the parent compound but also transformation products in the test systems. Significantly greater uptake of triclosan was observed in the feeding worms compared to the non-feeding worms; the increased observed uptake was attributed to the hydrophobicity of triclosan and resulting adsorption to sediments. The biota sediment accumulation factors (BSAF) were calculated based on the 48-hour uptake and depuration measurement using the first order one compartment model. The 48-hour BSAF for feeding worms was 9.0, and 6.6 for the non-feeding worms, for which uptake is thought to be dominated via the epidermis (Karlsson et al. 2015). These BSAF values represent a combination of parent and transformation products.

4.3.1.6 Water to biota fugacity ratio

Fugacity of a chemical is a thermodynamic equilibrium criterion that can be used to assess the relative chemical activity in a system comprised of multiple compartments or phases (such as water, sediment or diet). At equilibrium, the chemical fugacities in the different phases are equal, and fugacity ratios between an organism and a reference

phase are equal to one. A fugacity ratio between an organism and a reference phase that is greater than one indicates an increase (i.e., magnification) in the activity of the chemical in the organism compared to the reference phase. The fugacity ratio approach can be used to show a biomagnification potential of a chemical; fugacity ratios that exceed one indicate increases of chemical residues in organisms through trophic levels.

The fugacity ratio of triclosan for biota and water was calculated using the equation modified from Burkhard et al. (2012):

$F_{biota–water}$ = BCF (L/kg) × D_{biota} (kg/L) × Z_{water} ÷ Z_{biota}

where
BCF = bioconcentration factor
Z_{water}, fugacity capacity in water = 1/HLC (Henry's law constant)
Z_{biota}, fugacity capacity in biota = %lipid × (D_{biota} ÷ D_{lipid}) × K_{ow} × Z_{water}
D_{biota} = 1 kg/L and D_{lipid} = 0.9 kg/L (2012 personal communication from Frank A.P.C. Gobas, Simon Fraser University, to Science and Risk Assessment Directorate, Environment Canada; unreferenced).

A geometric mean of BCF values (from the whole body BCF fish studies by Böttcher (1991), Schettgen et al. (1999), Schettgen 2000, NITE (2006), summarized in Table 4-10) of 887 L/kg ww and a log K_{ow} (log D_{ow}) of 5.2 (at pH 7.4) were used in this calculation, resulting in a fugacity ratio of 0.13 at pH 7.4 (~blood). The result is less than one, and indicates that triclosan has a low potential for biomagnification (Burkhard et al. 2012). If maximum reported BCF values are used in this calculation, the fugacity ratio slightly exceeds one. Given that triclosan is readily metabolized by fish, and that the high BCF values (reported in Schettgen et al. 1999 and Schettgen 2000) are uncertain and may be overestimated due to experimental error, biomagnification across trophic levels is unlikely.

4.3.1.7 Bioaccumulation and the internal narcotic toxicity threshold

Bioaccumulation of a chemical to levels that surpass the internal toxicity thresholds can lead to mortality in the exposed organisms. The value of 5 mmol/kg is considered to be the internal neutral narcotic toxicity threshold for toxicity in fish from acute exposure. This value is based on findings from numerous studies which show that internal concentrations of neutral narcotic chemicals in fish causing death are fairly constant at about 2–8 mmol/kg for acute exposures, with a median of 5 mmol/kg, and 0.2–0.8 mmol/kg for chronic exposures (McCarty 1986, 1987a, 1987b, 1990; McCarty and Mackay 1993; McCarty et al. 1985, 1991, 2013; Van Hoogen and Opperhuizen 1988).

The equation for fugacity ($F = C \div Z$; Burkhard et al. 2012) and the fugacity ratio of biota to water ($F_{biota–water}$) (see section 4.3.1.4) can be used to calculate the maximum internal concentration of a chemical according to bioconcentration factor (BCF) data as follows:

$C = F \times Z_{biota}$

where
F = fugacity (Pa)
Z_{biota} = BCF (L/kg) × D_{biota} (kg/L) × $Z_{water} \div F_{biota-water}$ (see section 4.3.1.4)

This calculation assumes that octanol is a reasonable surrogate for lipids in fish and that the chemical's diffusion partitioning in fish is driven by hydrophobicity (i.e., no other mechanisms such as covalent binding, which is unlikely for triclosan).

For triclosan, if fugacity capacity using the vapour pressure of 0.00053 Pa is considered and 5% lipid in fish, the maximum concentration that can be achieved at pH 7.4 is approximately 30 mmol/kg (a fugacity of 0.000067 Pa), which is 6 times the median acute internal narcotic threshold of 5 mmol/kg. This indicates that based on its intrinsic properties, triclosan can bioaccumulate to levels exceeding internal narcotic thresholds.

4.3.1.8 Bioconcentration and bioaccumulation of methyl-triclosan in aquatic organisms

Given that methyl-triclosan has often been detected in aquatic organisms in waters contaminated with triclosan, BCF and BAF values for methyl-triclosan were also considered in the overall weight-of-evidence analysis. Miyazaki et al. (1984) were the first to report accumulation of methyl-triclosan in aquatic biota. They detected various levels of this compound in species of fish and shellfish sampled in the Tama River and Tokyo Bay in Japan. The concentrations ranged from 1 to 38 µg/kg and from 3 to 20 µg/kg in fish and shellfish, respectively (Table 4-11). The authors attributed the presence of this compound to biological methylation of triclosan in the environment.

Balmer et al. (2004) measured methyl-triclosan in white fish, roach and lake trout from lakes in Switzerland that receive effluents from WWTPs, as well as in reference lakes not influenced by WWTPs. They also sampled water using semipermeable membrane devices in order to derive a concentration for dissolved methyl-triclosan. The concentrations of methyl-triclosan in fish were up to 35 µg/kg on a wet weight basis and up to 365 µg/kg on a lipid basis. No methyl-triclosan was detected in fish from the reference lakes (< 1 and < 2 µg/kg). The concentrations of methyl-triclosan in fish correlated well (r^2 = 0.85) with the ratio of the human population in the watershed to the water flow of the lakes, which is considered to be a measure of the domestic burden from WWTPs to a lake. A BAF was estimated for methyl-triclosan using the concentrations in fish as well as the water concentrations derived from the semipermeable membrane devices; the resulting BAF was in the order of 100 000–260 000 L/kg (lipid basis). Assuming an average fat content in fish of 2%, the study authors estimated the BAF for methyl-triclosan to be 2000–5200 L/kg (log BAF of 3.3–3.7) on a wet weight basis.

BAF values of 700–1500 L/kg were reported for methyl-triclosan for algae collected in a creek receiving the effluent from a WWTP (Coogan et al. 2007), while a BAF of 1200 L/kg was calculated for snails that had been caged in the same creek for 2 weeks (Coogan and La Point 2008). It is unknown but likely that steady state was reached in this experiment, given the length of the exposure period.

Table 4-11. Experimental data on the presence or bioaccumulation of methyl-triclosan in aquatic organisms

Test organism	Endpoint	Value (based on wet weight)	Reference
Topmouth gudgeon (*Pseudorasbora parva*)	Concentration in whole body	1–38 µg/kg	Miyazaki et al. 1984
Goby (*Acanthogobius flavimanus*)	Concentration in whole body	<1–2 µg/kg	Miyazaki et al. 1984
Short-necked clam (*Tapes philippinarum*)	Concentration in whole body	3 µg/kg	Miyazaki et al. 1984
Thin-shelled surf clam (*Mactra veneriformis*)	Concentration in whole body	5 µg/kg	Miyazaki et al. 1984
Oyster (*Crassostrea gigas*)	Concentration in whole body	13 µg/kg	Miyazaki et al. 1984
Blue mussel (*Mytilus edulis*)	Concentration in whole body	20 µg/kg	Miyazaki et al. 1984
White fish (*Coregonus* sp.)	Concentration in whole body	4–211 µg/kg[a,b]	Balmer et al. 2004
Roach (*Rutilus rutilus*)	Concentration in whole body	<2–365 µg/kg[a,b]	Balmer et al. 2004
Lake trout (*Salmo trutta*)	Concentration in whole body	<1 µg/kg[a–c]	Balmer et al. 2004
13 fish species collected in the Detroit River (near Windsor, Ontario)	Concentration in plasma	<0.000 010 µg/kg	Valters et al. 2005
Bream (*Abramis brama*)	Concentration in muscle	3.8–26.1 ng/g	Boehmer et al. 2004
White fish (*Coregonus* sp.) and roach (*Rutilus rutilus*)	BAF	2000–5200 L/kg[a,b]	Balmer et al. 2004
Algae (field samples, various species)	BAF	700–1500 L/kg[b]	Coogan et al. 2007
Snail (*Helisoma trivolvis*)	BAF	1200 L/kg[d]	Coogan and La Point 2008

Abbreviation: WWTP, wastewater treatment plant.

[a]Values on a lipid basis.

[b]Wild fish caught, or algae collected, downstream from WWTPs. Levels in fish from reference lakes were <1 and <2 µg/kg.

[c]This species was only found in the reference lake.
[d]Snails caged downstream from a WWTP.

4.3.2 Bioaccumulation in terrestrial organisms

Kinney et al. (2008) sampled earthworms from agricultural soils that had been amended with biosolids from WWTPs. Based on the ratio of triclosan concentrations measured in earthworm tissues and in soil, BAF values of 10 and 27 (unitless) were calculated at 31 and 156 days following soil amendment, respectively. It is not known but likely that steady state in triclosan body concentrations was reached by 156 days, even though data are available for only two sampling times. Under field conditions similar to those in this case, the exposure is dynamic rather than static, given the pulses created by biosolids application followed by dissipation of triclosan through various processes. Pannu et al. (2012b) found similar BAF values (4.3 to 12, unitless) for earthworms exposed to biosolids-amended soils in the laboratory (28 days) and on the field.

Wu et al. (2010a) grew soybean plants in a sandy soil that had been either amended with biosolids or irrigated with wastewater containing triclosan. The BCF values (root/soil) measured after 60 and 110 days of growth in the soil amended with biosolids were about 2.5 and 5.9 (unitless), respectively. No BCF values could be calculated for plants grown in the soil irrigated with wastewater, as triclosan was not detected in the soil; however, triclosan did accumulate in plant tissues (root, stem, leaf and bean; 24.2–80.1 ng/g after 110 days). Again, it is unknown whether steady state was reached in this experiment.

The bioconcentration of triclosan in two species of wetland macrophytes was measured by Stevens et al. (2009). They exposed the organisms for 28 days to concentrations of triclosan ranging from 0.4 to 1000 µg/L in water-only flow-through systems. They measured BCF values ranging from 0.4 to 2.8 L/kg ww and from 1.4 to 101 L/kg ww in plant shoots and roots, respectively. These values would likely be different in a natural environment where plants would be rooted in soil.

Potential for secondary poisoning by triclosan in terrestrial food chains was assessed using the model BASL4 (BASL4 2011; see Section 4.5.3 for more details). In this model, the exposure of earthworms to triclosan present in soil following the application of biosolids to fields, and the subsequent accumulation of triclosan in earthworms, is estimated based on factors such as soil ingestion, lipid content and growth dilution, among others. As a conservative estimate, it is assumed that no metabolism of triclosan will occur in organisms. The bioaccumulation of triclosan in shrews consuming these earthworms is then estimated based on similar factors. Two biosolids application scenarios were run (a lower-end and an upper-end; see Section 4.5.3). In both scenarios, peak concentrations in soils (118 µg/kg dw and 222 µg/kg dw for lower-end and upper-end scenarios, respectively) occur right after biosolid application. Concentrations of triclosan in soil between biosolid applications averages 11 µg/kg dw

and 110 µg/kg dw, respectively, for these lower-end and an upper-end scenarios. Based on the highest modelled concentrations in soil, earthworms (~11 100 µg/kg dw and ~21 000 µg/kg dw for lower-end and upper-end scenarios, respectively) and shrews (~531 000 µg/kg dw and ~994 000 µg/kg dw for lower-end and upper-end scenarios, respectively), the modelled BAF values for earthworms (i.e., concentration in earthworms divided by concentration in soil) are approximately 95, while the modelled BAF values for shrews (i.e., concentration in shrews divided by concentration in soil) are approximately 4500. The modelled biomagnification factor values (i.e., concentration in shrews divided by concentration in earthworms) are ~48. Field data cited above indicate BAFs of 4.3–27 for earthworms sampled in biosolid-amended fields (Kinney et al. 2008, Pannu et al. 2012b). The model results indicate that triclosan concentrations will increase from soil to earthworms, and will further increase from earthworms to shrews. The modelled BAF values for shrew are unexpectedly high given that triclosan is extensively metabolized in mammals. Indeed, there is no evidence that triclosan bioaccumulates in mammals, although there may be retention of triclosan and/or its metabolites in the liver (NICNAS 2009, SCCP 2009). Triclosan is extensively metabolized via glucuronide and sulfate conjugation. The high modelled BAF values are probably due to the fact that BASL4 assumes that there is no metabolism occurring in organisms.

4.3.3 Relevance of triclosan bioaccumulation

The available information is reflective of the complex behaviour of triclosan in the environment and in organisms, and precludes precise description of the magnitude of bioaccumulation of triclosan. BCF studies conducted some time ago are of speculative reliability resulting in equivocal lines of evidence for determining an absolute factor for bioconcentration. What is more clear and consistent from the available evidence is that triclosan can be rapidly taken up in aquatic and terrestrial organisms and likely reaches steady-state within a few days given its low log K_{ow}, as is seen with many pharmaceuticals. Thus, triclosan is a highly bioavailable chemical *in vivo* with pH likely having a dramatic effect on the fugacity potential of triclosan and its distribution among tissues. In the environment, at pH of 7.0, triclosan will mostly occur in the neutral form and will tend to partition more readily into organisms than the ionized species. At pH 7.4 of blood, triclosan will occur largely in the neutral form as well, but will also occur at a lower fraction (20%) in the ionized state. Thus, triclosan is likely distributed between lipophilic and non-lipophilic tissues within biota and may undergo protein plasma binding in albumin due to its hydrogen donor/acceptor properties, particularly in the ionized form. The range of BCF values (noting their equivocal status) and field BAF values suggests that the rate of metabolism within and among higher and lower trophic level organisms naturally differs, and, given the high bioavailability of triclosan, is the predominant reason explaining the variation in bioaccumulation potential of triclosan as well as the pH of exposure waters. Considering the *in vivo*, *in silico* and *in vitro* information, there is a degree of consistency in the evidence to suggest that most

organisms can eliminate triclosan relatively quickly via Phase II and possibly Phase I metabolic transformations. The uptake of methyl-triclosan and subsequent demethylation can also add to the body burdens of triclosan, but this may be hard to distinguish from the uptake of triclosan itself in real world exposures.

There is evidence to suggest that the bioconcentration potential of triclosan from water can vary depending on the exposure conditions and organisms exposed. Compared with other chemicals of similar or more hydrophobic nature, the potential for triclosan to bioaccumulate is generally low to moderate, and it is predominantly mitigated by biotransformation (see for comparison Figure 7 in Arnot and Gobas (2006)). In this assessment, however, the absolute factor of bioconcentration or bioaccumulation is of less importance than triclosan's intrinsic ability to partition from water and into tissues. Importantly, triclosan has a sufficient bioconcentration potential and fugacity to result in internal body burdens that exceed narcotic or polar narcotic thresholds of toxicity, given a sufficient concentration in water. This becomes highly relevant because considering that the chemical activity[3] of triclosan in water in some cases can exceed the chemical activity of narcotic chemicals by more than a factor of ten, it suggests that the toxicity of triclosan can approach that of the more reactive chemicals (like some drugs) under chronic exposure. Thus, bioconcentration, even at low to moderate levels, becomes a critical factor for understanding the potential for adverse effects in the Canadian environment.

[3]Chemical activity (i.e., fraction of solubility in water eliciting adverse effects) can be used as a surrogate measure of the relative potency of a chemical according to its maximum solubility in water and is calculated here as the ratio of an effects concentration and the maximum solubility in water. Neutral organic chemicals have a chemical activity ranging from 1/10th to 1/200th of their solubility in water (Mackay et al. 2009, 2014).

4.4 Ecological Effects

4.4.1 Mode of action

Triclosan cellular modes of action (MOA) through binding molecular targets have been demonstrated in bacteria, plants, and rodents (Jang et al. 2008; McMurry et al. 1998; Heath et al. 1999; Hoang and Schweizer 1999; Levy et al. 1999; Zhang et al. 2006; Serrano et al. 2007). Triclosan has numerous intracellular and cytoplasmic target sites and may influence the transcription of genes involved in amino acid, carbohydrate and lipid metabolism as well as signalling pathways, as shown in the bacteria *Staphylococcus aureus* (Jang et al. 2008). Triclosan blocks lipid biosynthesis in bacteria by specifically inhibiting the enzyme enoyl–acyl carrier protein reductase, which is involved in type II bacterial fatty acid synthesis (McMurry et al. 1998; Heath et al. 1999; Hoang and Schweizer 1999; Levy et al. 1999). Plants share similar fatty acid synthesis pathways with bacteria (Zhang et al. 2006). Experiments conducted with the plant *Arabidopsis* (in the family Brassicaceae) have shown that enoyl–acyl carrier protein reductase is a possible target of triclosan (Serrano et al. 2007). In the mouse, activation of PPARα is the primary MOA for triclosan-induced hepatocarcinogenesis (see Section 3.1.8). Triclosan may also disrupt thyroid-mediated processes; triclosan has been shown to alter thyroid hormone-associated gene expression in amphibians *in vitro* (Veldhoen et al. 2006) (see Section 3.1.10 and Section 4.4.2.1). It is suspected that triclosan can uncouple oxidative phosphorylation (Newton et al. 2005; 2014 personal communication from Beate Escher, The University of Queensland, to the Science and Risk Assessment Directorate, Environment Canada; unreferenced).

The molecular structure of triclosan with its two phenol functional groups resembles those of several non-steroidal estrogens, such as diethylstilbestrol and bisphenol A. This suggests the potential to act as an endocrine-disrupting agent through estrogen receptor binding (Ishibashi et al. 2004; see Section 4.4.2). The Profiler function of the OECD QSAR Toolbox (QSAR 2008) identified structural alerts for high-toxicity classification for triclosan that suggest that triclosan exerts toxicity beyond a baseline narcotic MOA. These included estrogen receptor binding (strong binder), acute aquatic toxicity by OASIS (phenols and anilines) and high hazard class according to Cramer rules.

The chemical activity of triclosan (i.e., fraction of solubility in water eliciting adverse effects) is about 0.00004 (based on the predicted no-effect concentration (PNEC) for aquatic organisms; see Section 4.4.2.1 below), which is far less than the chemical activity expected for baseline narcotic chemicals (usually 0.1 to 0.01) (Mackay et al. 2014). The toxicity ratios are far greater than 10 indicating a specific mode of toxic action (Escher et al. 2011).

Triclosan ionizes at environmentally relevant pH levels. Some studies conducted with daphnids (*Ceriodaphnia dubia)* and algae *(Scenedesmus subspicatus*) have shown that the pH of the test solution may influence the toxicity of triclosan (Orvos et al. 2002; Roberts et al. 2014). Tests conducted at lower pH values, corresponding to a higher proportion of the neutral form of triclosan in solution, generally showed higher toxicity although this effect was not demonstrated consistently at all pH levels. This may be due to the fact that the bioavailability of the neutral form, in terms of its capacity to cross cellular membranes, is higher than that of the ionogenic form, due to an electronic barrier at the membrane surface for ionogenic species. Thus, the toxicokinetics of triclosan would be influenced by pH, but not its intra-cellular toxicity. At the site of toxic action, the pH of the cytoplasm matters due to an ion trapping phenomenon (Neuwoehner and Escher 2011) and thus this pH would govern the species of triclosan inducing the effect. This may explain the lack of a consistent relationship between exposure medium pH and effects in one of the two studies mentioned above (Roberts et al. 2014). Also, comparison of different studies conducted with the same species or other species does not clearly point to an influence of pH on toxicity. Given a strongly suspected MOA for triclosan as an uncoupler, an adjustment of ecotoxicity data for a pH-dependent effect (of the medium) was not done in this assessment. Weak acid uncouplers are known to have the highest potency when internal pH equals the pK_a (i.e., 50:50 ratio of neutral and ionized species) and thus both forms are believed to contribute to the toxicodynamics of triclosan. It is indeed believed that internal toxic effects are independent of pH of the test medium. It is acknowledged that the latter can affect the toxicokinetics of triclosan; however, the ultimate relationship between the pH of the test medium and the toxicity observed cannot be quantified.

4.4.2 Ecotoxicity

An extensive toxicity data set for triclosan was compiled by Environment and Climate Change Canada, and includes data for aquatic, benthic and terrestrial organisms. Studies with both acute and longer term or chronic exposure durations were available. The determination of whether an endpoint is acute or chronic was based on the lifespan of each species considered. Effects data for aquatic species are presented in subsection 4.4.2.1, for benthic organisms in subsection 4.4.2.2, and for terrestrial organisms in sub-section 4.4.2.3. Sub-section 4.4.2.1 also includes a description of the species sensitivity distribution (SSD) for aquatic species based on the chronic effects studies using the 2007 guidance protocol by the Canadian Council of Ministers of the Environment (CCME) (CCME 2007), a derivation of the predicted no-effect concentration (PNEC), and a summary of effects data for methyl-triclosan in aquatic species. Sub-section 4.4.2.3 also includes a derivation of the PNEC for terrestrial organisms. Antimicrobial resistance is addressed in section 3.6. There is indication that resistance to triclosan and multidrug resistance can increase in the environmental microbial communities exposed to triclosan (Carey and McNamara 2015); however few studies are available and they are generally limited to laboratory settings and high

exposure concentrations. Environmental hazard due to impacts from microbial resistance to triclosan based on the measured concentrations of triclosan has not been identified.

4.4.2.1 Aquatic organisms

4.4.2.1.1 Algae, macrophytes and bacterial communities

Single-species toxicity tests as well as community-level studies have been conducted with bacteria, algae and macrophytes exposed to triclosan. Orvos et al. (2002) tested five algal species. The blue-green alga *Anabaena flos-aquae* was the most sensitive species, with an EC_{10} value of 0.97 µg/L (Table 4-12). It is worth noting that the only marine species tested (the diatom *Skeletonema costatum*; 96-hour EC_{25} > 66 µg/L) was the least sensitive among the five algal species tested, which could suggest that the salinity of the test water may have had an impact on triclosan speciation and bioavailability (i.e., higher proportion of the ionized form). However, DeLorenzo and Fleming (2008) measured a 96-hour EC_{50} of 3.55 µg/L for a marine phytoplankton species (*Dunaliella tertiolecta*), which is comparable with the toxicity measured by Orvos et al. (2002) for certain freshwater algae. Yang et al. (2008) measured a 72-hour EC_{50} of 0.53 µg/L for *Pseudokirchneriella subcapitata*, which is much lower than the one reported by Orvos et al. (2002) for the same species (96-hour EC_{50} of 4.46 µg/L). This variation in toxicity values from different tests conducted with the same algal species is likely due to pH and illumination. Indeed, the test pH influences the fraction of neutral and ionized forms of triclosan present in solution, which may exert different levels of toxicity (Roberts et al. 2014). Also, illumination of the test medium induces quick photolysis of triclosan by UV rays, especially of the ionized form, causing exposure concentrations to decline during the test period. This may lead to underestimation of triclosan toxicity if concentrations are not measured throughout the test period. Fulton et al. (2009) obtained a similar 7-d MATC for growth inhibition for *Lemna gibba* as the one obtained in Study Submission (2013) (17 and 28 µg/L, respectively, Table 4-12).

Wilson et al. (2003) reported an algal community structure shift at triclosan levels as low as 0.015 µg/L. This study used natural algal assemblages as well as natural water, making the outcome of the bioassays more environmentally realistic. However, because insufficient data were reported, such as measurements of exposure concentrations, there is uncertainty about the actual threshold of effects and about the reliability of the study in general. Hence, the results of this study were not used for the derivation of a chronic toxicity threshold for triclosan. Lawrence et al. (2009) investigated the effects of triclosan on the structure and function of river biofilm communities, which are a key component of whole ecosystem function. Using South Saskatchewan River water as a source of inoculum and nutrients, they employed a variety of techniques, including microscale analyses, molecular probes and physiological determinations, to determine the effects of a continuous 8-week exposure to triclosan at 10 µg/L. Analyses of the biofilm communities indicated shifts in the algal and bacterial composition, as well as a

significant reduction in algal biomass, in test systems containing triclosan as compared with controls. The general shift observed was towards a more heterotrophic community, which may have significant ecological implications for carbon and energy flow. The actual exposure level in this study is however uncertain as triclosan concentration was not stable. Using pure cultures of protozoa, the same authors found effects of triclosan on certain species of algae, cyanobacteria and protozoa exposed to 0.5 and 10 µg/L for 14 days. However, the effects observed were not quantified and exposure concentrations were likely not maintained given the use of a static system. These results were not further considered. Miyoshi et al. (2003) reported deleterious effects of triclosan on two *Paramecium* species at concentrations of 1564 and 400 µg/L after 5 days. However, lack of experimental information, notably exposure concentrations, makes the reliability of this study questionable; hence, the results were not further considered.

Table 4-12. Chronic toxicity of triclosan to freshwater aquatic organisms[a]

Table 4-12a. Chronic toxicity of triclosan to freshwater algae and macrophytes

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
Scenedesmus subspicatus	MATC (72 h)	Growth	0.77	No	Orvos et al. 2002
Scenedesmus subspicatus	NOEC (96 h)	Growth	0.69	No	Orvos et al. 2002
Scenedesmus subspicatus	EC_{10} (72 h)	Growth	0.5	Yes	Roberts et al. 2014
Scenedesmus vacuolatus	EC_{10} (24 h)	Growth	1.09	Yes	Franz et al. 2008
Anabaena flos-aquae	EC_{10} (96 h)	Growth	0.97	Yes	Orvos et al. 2002
Pseudokirchneriella subcapitata	EC_{25} (96 h)	Growth	2.44	Yes	Orvos et al. 2002
Pseudokirchneriella subcapitata	MATC (72 h)	Growth	0.28	No	Yang et al. 2008
Pseudokirchneriella subcapitata	NOEC (72 h)	Growth	0.53	No	Tamura et al. 2012
Navicula pelliculosa	EC_{25} (96 h)	Growth	10.7	Yes	Orvos et al. 2002
Nitzschia palea	EC_{10} (72 h)	Photosynthetic activity	194	Yes	Franz et al. 2008
Closterium ehrenbergii	MATC (96 h)	Growth	354	Yes	Ciniglia et al. 2005
Lemna gibba	MATC (7 d)	Growth	28	Yes[b]	Study

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
					Submission 2013
Lemna gibba	MATC (7 d)	Growth	17	Yes[b]	Fulton et al. 2009

Note: For table abbreviations and footnotes, see Table 4-12f.

Table 4-12b. Chronic toxicity of triclosan to freshwater crustaceans

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
Hyalella azteca	LC_{10} (10 d)	Survival	5	Yes	Dussault et al. 2008
Hyalella azteca	EC_{10} (10 d)	Growth	50	No	Dussault et al. 2008
Ceriodaphnia dubia	MATC (7 d)	Reproduction	8.5	Yes[b]	Orvos et al. 2002
Ceriodaphnia dubia	MATC (7 d)	Survival and reproduction	177	Yes[b]	Tatarazako et al. 2004
Ceriodaphnia dubia	NOEC (8 d)	Survival and reproduction	30	No	Tamura et al. 2012
Daphnia magna	NOEC (21 d)	Survival of parental generation	200	No	Orvos et al. 2002
Daphnia magna	MATC (21 d)	Reproduction	89	Yes	Orvos et al. 2002

Note: For table abbreviations and footnotes, see Table 4-12f.

Table 4-12c. Chronic toxicity of triclosan to freshwater insects

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
Chironomus dilutus	LC_{10} (10 d)	Survival	20	Yes	Dussault et al. 2008
Chironomus dilutus	EC_{10} (10 d)	Growth	80	No	Dussault et al. 2008

Note: For table abbreviations, see Table 4-12f.

Table 4-12d. Chronic toxicity of triclosan to freshwater molluscs

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
Physa acuta	MATC (42 d)	Growth	3.2	Yes	Brown et al. 2012

Note: For table abbreviations, see Table 4-12f.

Table 4-12e. Chronic toxicity of triclosan to freshwater amphibians

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
African clawed frog (*Xenopus laevis*)	NOEC (32 d)	Growth and postembryonic development	>29.6	Yes	Fort et al. 2011
African clawed frog (*Xenopus laevis*)	NOEC (14 d)	Growth and endocrine biomarkers	>200	No	Matsumura et al. 2005
Bullfrog (*Rana catesbeiana*)	NOEC (18 d)	Growth and postembryonic development	>11.2	Yes	Veldhoen et al. 2006
Bullfrog (*Rana catesbeiana*)	LOEC (6 d)	Gene expression	0.12	No	Veldhoen et al. 2006
Pacific tree frog (*Pseudacris regilla*)	MATC (21 d)	Postembryonic development	0.95	Yes	Marlatt et al. 2013

Note: For table abbreviations, see Table 4-12f.

Table 4-12f. Chronic toxicity of triclosan to freshwater fish

Organism	Endpoint (duration)	Effect	Conc. (µg/L)	Used in SSD	Reference
Rainbow trout (*Oncorhynchus mykiss*)	MATC (61 d)	Fry survival	49.3	Yes	Orvos et al. 2002
Mosquitofish (*Gambusia affinis*)	MATC (35 d)	Sperm count	76.6	Yes	Raut and Angus 2010
Fathead minnow (*Pimephales promelas*)	NOEC (21 d)	Growth	>0.450	No	Schultz et al. 2012
Japanese medaka (*Oryzias latipes*)	NOEC (21 d)	Fecundity, fertility	>137	Yes	Ishibashi et al. 2004

Abbreviations: conc., concentration; EC_x, the concentration of a substance that is estimated to cause some effect on x% of the test organisms; LC_x, the concentration of a substance that is estimated to be lethal to x% of the test organisms; LOEC, lowest-observed-effect concentration; MATC, maximum allowable toxicant concentration, generally presented as the range between NOEC and LOEC or as the geometric mean of the two measures; NOEC, no-observed-effect concentration; SSD, species sensitivity distribution.

[a]All data in this table are from reliable studies as evaluated with Robust Study Summaries, which are available upon request from Environment and Climate Change Canada.

[b]Since these endpoints are equivalent and are for the same species, these values were used to calculate a geometric mean for these species (22 µg/L for *L. gibba* and 39 µg/L for *C. dubia*), which were used in the SSD.

4.4.2.1.2 Invertebrates

Regarding freshwater crustaceans, Orvos et al. (2002) measured acute and chronic toxic effects for daphnids at 390 µg/L and 89 µg/L, respectively. Their results for the reproduction of *Ceriodaphnia dubia* indicate a MATC of 8.5 µg/L (Table 4-12), while Tatarazako et al. (2004) obtained a MATC for the reproduction of the same species of 177 µg/L of triclosan. Flaherty and Dodson (2005) observed that *Daphnia magna* exposed to 10 µg/L of triclosan on a chronic basis produced more than twice as many male individuals as their control counterparts. However, when *Daphnia* was exposed to triclosan in a mixture of pharmaceuticals, there was a decrease in sex ratio, with 20% fewer male offspring. No endpoints could be calculated for the triclosan-only experiment because only one concentration was tested.

Borgmann et al. (2007) tested the effects of a mixture of pharmaceuticals, including triclosan, on the freshwater amphipod *Hyalella azteca*. Survival, mating, body size and reproduction were monitored over three generations. No effects were observed on any of the endpoints measured. The mean measured concentration of triclosan over the experiment was 127 ng/L. Dussault et al. (2008) conducted a chronic toxicity test with this amphipod and obtained LC_{10} and EC_{10} values of 5 µg/L and 50 µg/L for survival and growth, respectively. The same authors also tested larvae of the aquatic dipteran *Chironomus dilutus* and obtained similar LC_{10} and EC_{10} values (20 and 80 µg/L). Even though *Hyalella* and *Chironomus* are benthic organisms, the tests mentioned above were conducted using spiked water only (and not spiked sediments).

Triclosan was found to have genotoxic and cytotoxic effects *in vivo* in hemocytes of the freshwater zebra mussel (*Dreissena polymorpha*). Several biomarkers were assessed over a 96-hour exposure period. Significant increases in all genetic biomarkers (e.g., micronucleus test, apoptotic frequency) as well as a clear destabilization of lysosomal membranes were observed following exposure to triclosan at 290–870 ng/L (Binelli et al. 2009). Brown et al. (2012) exposed the freshwater snail *Physa acuta* to various concentrations of triclosan for 42 days. Snails exposed to 5 µg/L of triclosan and higher had decreased growth rate compared to control.

4.4.2.1.3 Amphibians

Fraker and Smith (2004) observed a decreased activity in *Rana pipiens* tadpoles exposed to triclosan for 24 days at concentrations of 0.230 µg/L and higher though not in a dose-response manner. Survival of tadpoles was significantly lower when exposed to 230 µg/L but it was similar to controls at 23 µg/L and below. In contrast, Smith and Burgett (2005) observed an increased activity in *Bufo americanus* tadpoles exposed to triclosan at 230 µg/L for 14 days. They did not observe any effect on growth or survival at the highest concentration tested (230 µg/L). However, exposure concentrations in both studies are uncertain since they were not verified analytically and the test medium was only renewed on a weekly basis. For these reasons, it is not possible to determine meaningful endpoints for growth and survival from these studies.

Based on acute LC_{50} values, Palenske et al. (2010) concluded that amphibian larvae were most sensitive to triclosan during early developmental stages. The study was conducted on one larval stage of three North American species, *Acris crepitans blanchardii*, *Bufo woodhousii woodhousii* and *Rana sphenocephala*, and on four larval stages of the African clawed frog, *Xenopus laevis*. The 96-hour LC_{50} values for these species were 367, 152, 562 and 259–664 µg/L (for four stages of *X. laevis*), respectively. There was a significant difference between the LC_{50} values for the North American species, and there was a significant difference between the LC_{50} values for the earlier versus later larval stages of *X. laevis*. Metabolic rate and heart rate in amphibian larvae were also monitored and seemed to be affected at various triclosan concentrations, but not in a clear dose-dependent manner.

Matsumura et al. (2005) showed no significant effect on growth and no significant difference in the levels of endocrine biomarkers such as plasma vitellogenin and testosterone in male adult clawed frogs exposed to 20–200 µg/L of triclosan in a 14-day waterborne exposure test.

Studies have also been conducted to assess the influence of triclosan on thyroid hormone–mediated metamorphosis in frogs. Veldhoen et al. (2006) studied the effects of triclosan on precocious metamorphosis in bullfrog (*Rana catesbeiana*) tadpoles. Premetamorphic tadpoles were either not injected or injected with T_3 to induce metamorphosis and were exposed to measured triclosan concentrations of 0.12–11.2 µg/L for 18 days. A reduction in body weight was observed after 18 days for the frogs exposed to 0.12 µg/L triclosan with T_3, but not in the frogs exposed to higher concentrations or to concentrations of triclosan alone. Snout-vent length (SVL) and tail length were not significantly affected in any of the triclosan treatment exposures. The development of tadpoles, based on differences in developmental stages as defined by Nieuwkoop and Faber (1994), was advanced in all T_3/triclosan exposures but not in triclosan-only exposures. Although *R. catesbeiana* is not the species used in standardized protocols for testing amphibian metamorphosis, this species is native to eastern Canada. Using a *X. laevis* cell line, the same authors reported that exposure to low levels of triclosan (30–300 ng/L) resulted in altered (i.e., increased) TRα and TRβ mRNA expression. An increase in TRβ transcript levels may be indicative of advanced metamorphosis.

In contrast, Fort et al. (2010, 2011) concluded that triclosan does not alter the normal course of metamorphosis of *X. laevis*. In a 21-day test where prometamorphic tadpoles (NF stage 51) were exposed to triclosan concentrations of 0.6, 1.5, 7.2 and 32.2 µg/L, Fort et al. (2010) observed that larval growth (i.e., whole body length and weight, snout-vent and hind limb length) was reduced at 1.5 µg/L, but not at the other treatment levels. Based on developmental stages, the postembryonic development of *X. laevis* was advanced, although not in a dose-related manner. Indeed, a significant induction in TRβ mRNA expression occurred in the 1.5 and 7.2 µg/L treatments only. Such a lack of a dose–response relationship is not unusual. For instance, in recent studies conducted

with chemicals that are known to alter endocrine function (reviewed in Welshons et al. 2003), the effects observed were not necessarily manifested following a linear dose–response relationship and, in several instances, were found to follow a non-monotonic response curve. In a similar 32-day test, NF stage 47 *X. laevis* (premetamorphic) tadpoles were exposed to triclosan concentrations of 0.3, 1.3, 5.9 and 29.6 µg/L (Fort et al. 2011). Effects on growth endpoints such as a significant increase in mean whole body length and weight as well as SVL were observed at concentrations of 0.3 µg/L and 1.3 µg/L, respectively. Such effects are not necessarily detrimental from an ecological perspective. Contrary to the 21-day study, the postembryonic development of *X. laevis* was delayed in the treatment groups when compared with the control, but no statistical significance was detected. Although minimal, occurrences of thyroid gland hypertrophy and congestion were noted in all treatment levels, with the number of cases increasing with exposure concentration. Thyroid histology (e.g., follicle count, follicle size, colloid content/follicle) was not significantly different from that of control; however, the variability among individuals was high in the highest treatment levels for some parameters. Finally, TRβ mRNA expression was not significantly affected at any of the concentrations tested in this 32-day test. The authors of these two studies concluded that triclosan seems capable of increasing tadpole growth during their development, but not advancing thyroid-mediated metamorphosis (Fort et al. 2011). The authors suggested that increased growth was due to non-thyroidal mechanisms, such as reduced bacterial stressors in culture. It can be noted that in this study, the tadpoles were not injected with thyroid hormones (like T_3 or T_4) to induce metamorphosis as was done in the study by Veldhoen et al. (2006).

Marlatt et al. (2013) observed disrupted coordination of postembryonic tadpole development in the Pacific tree frog (*Pseudacris regilla*) in a 21-day adapted Amphibian Metamorphosis Assay (AMA). AMA is a standard test guideline (OECD TG 231) that was developed for *X. laevis* and that is designed to identify chemicals that disrupt thyroid hormone-mediated biological processes. In this study, the test protocol was modified and applied to a frog species that is relevant to North America, *Pseudacris regilla*. Premetamorphic tadpoles were injected or not with T_4 and were exposed for 21 days to nominal concentrations of triclosan of 0.3, 3 and 30 µg/L. Significant effects of triclosan on progression of developmental stage and on morphological endpoints such as body length, hindlimb length, snout-vent ratio and wet weight were observed at various days during the experiment, for both the triclosan-only test concentrations and the combined T_4/triclosan test concentrations. In addition, the expression of thyroid-hormone-responsive genes was altered at all combination of exposure concentrations, especially at the beginning of the exposure period (day 2). Some of these effects were transient, yet necessary to metamorphosis, according to the authors. They suggested that triclosan was responsible for uncoupling in the timing and progression of tadpole tissues (acceleration). It can be noted that mean mortality was up to 17% in the tadpoles exposed to T_4 only or to a combination of T_4 and 0.3 µg/L of triclosan; this rate is higher than the 10% limit recommended in the test guideline. Triclosan did not seem to be the cause of the mortality. Based on the endpoints identified in the OECD TG 231

as indicators of thyroid activity, a MATC of 0.95 µg/L was determined for this study based on significant effects of triclosan (in absence of T_4; in line with OECD TG 231) on hindlimb length/SVL at day 7. Developmental stage was not affected by triclosan-only exposures at days 7 or 21.

Overall, these studies do not demonstrate a consistent effect of triclosan on thyroid-mediated amphibian metamorphosis. However, they demonstrated effects on developmental stage, certain morphological endpoints and gene expression. It seems like triclosan alone does not significantly alter thyroid-mediated processes, however it seems to alter these processes when metamorphosis is induced by T_4 and T_3 hormones. These effects suggest that triclosan may interfere with the action of natural thyroid hormone in amphibians. As mentioned by Marlatt et al. (2013), altered development may translate into decrease fitness for amphibians; however, long-term exposure to triclosan would need to be tested to evaluate development through complete metamorphosis.

4.4.2.1.4 Fish

Orvos et al. (2002) determined acute toxicity (96-hour LC_{50}) values of 260 µg/L and 370 µg/L of triclosan for the fathead minnow and bluegill sunfish, respectively. For chronic toxicity, they measured a no-observed-effect concentration (NOEC) and lowest-observed-effect concentration (LOEC) of 34.1 µg/L and 71.3 µg/L, respectively, for the rainbow trout in an early life cycle test. An acute study (Oliveira et al. 2009) concluded that triclosan had deleterious effects on adult and early life stages of zebrafish (*Danio rerio*). Effects included embryotoxicity and hatching delay. The authors attributed the high embryo mortality to the incorporation of triclosan into the eggs. The 96-hour LC_{50} value for embryo survival was 420 µg/L. Embryotoxicological effects, such as spine malformation and reduced size, were observed after 4 days of exposure to 500 µg/L of triclosan.

In a study conducted on male western mosquitofish (*Gambusia affinis*), Raut and Angus (2010) observed a significant increase in normally female-limited vitellogenin mRNA expression at a triclosan treatment of 101 µg/L. In this study, which suggested that triclosan has the potential to act as an endocrine disruptor in male mosquitofish, it was also found that triclosan both decreased sperm counts and increased the mean hepatosomatic index at 101 µg/L. Other concentrations tested were 29 and 58 µg/L. Decreased sperm counts could have an impact at the population level; hence, it is considered an ecologically relevant endpoint.

A few published studies (Tamura et al. 2012; Tatarazako et al. 2004; Ishibashi et al. 2004) were conducted following the OECD 212 test guideline “Fish, Short-term Toxicity Test on Embryo and Sac-fry Stages”. These studies were not considered to assess the effects of triclosan on fish growth and reproduction since an OECD report recommended that this test is no longer scientifically valid because the time to start feeding is too late and the test is considered relatively insensitive (OECD 2012). It is

also considered as a sub-chronic test rather than a true, life-cycle, chronic test for fish. That being said, some findings are still relevant to note. In particular, Ishibashi et al. (2004) observed that gonadosomatic and hepatosomatic indices were significantly higher in adult Japanese medaka (*Oryzias latipes*) exposed to concentrations of 20 µg/L and higher. Also, concentrations of hepatic vitellogenin were increased significantly in males exposed to 20 and 100 µg/L.

Investigations by Foran et al. (2000) of possible estrogenic properties of triclosan on Japanese medaka (*Oryzias latipes*) indicated that this substance does not display estrogenic activity at levels ranging from 1 to 100 µg/L. However, based on the evaluation of changes in secondary sexual characteristics (slight increase in dorsal and anal fins in the high treatment group), these authors suggested that triclosan is potentially weakly androgenic. The observed effects could also have been induced by an anti-estrogenic MOA.

4.4.2.1.5 Species sensitivity distribution

A species sensitivity distribution (SSD) was developed to identify the critical toxicity value (CTV) for triclosan according to the 2007 guidance protocol provided by the Canadian Council of Ministers of the Environment (CCME) (CCME 2007). The CCME guidance (2007) indicates that toxicity endpoints obtained through regression-based statistical data evaluation (i.e., EC_x values identifying no- or low-effects thresholds) are preferred over endpoints obtained through hypothesis-based statistical data evaluation (i.e., NOEC and LOEC values). In addition, endpoints representing no-effects thresholds for a given species are preferred over endpoints representing low-effects thresholds, when available. Given these two aspects (i.e., data evaluation technique and effects threshold), acceptable endpoints were considered using the following tiered approach: most appropriate EC_x/IC_x representing a no-effects threshold > EC_{10}/IC_{10} > $EC_{11\text{-}25}/IC_{11\text{-}25}$ > MATC > NOEC > LOEC > $EC_{26\text{-}49}/IC_{26\text{-}49}$ >non-lethal EC_{50}/IC_{50} (CCME 2007). Robust study summaries[4] were completed for all the endpoints included in the SSD to ensure that they came from reliable studies. Only chronic toxicity data were chosen to derive the SSD, given that chronic exposure to triclosan is expected in the receiving ecosystems. The SSD comprises endpoints for three fish, three amphibian, five invertebrate, one macrophyte and seven algal species; the resulting distribution is shown in Figure 4-3. When more than one endpoint was available for a single species, the most preferred endpoint according to the CCME guidance (2007) was chosen. If multiple similar endpoints were available, the lowest value was chosen, or the geometric mean of these endpoints was calculated if these endpoints were deemed the same (e.g., effect, duration).

[4]Available on request from Environment Canada.

Several of the data mentioned above were not used in the derivation of the SSD for reasons other than not being the preferred endpoint. The toxicity values for the algae *Skeletonema costatum* and *Dunaliella tertiolecta* were not considered for the SSD because they are marine species and the exposure data available are for fresh water. The toxicity value for *Hyalella azteca* from Borgmann et al. (2007) was not used, as this test was conducted with a mixture of substances. The EC_{10} values for growth inhibition of *Hyalella azteca* and of *Chironomus dilutus* from Dussault et al. (2008) were not used in the SSD since lethality (LC_{10}) occurred at lower concentrations for these organisms in this study. This means that amphipods and chironomids that survived exposure to triclosan were able to grow well up to their respective EC_{10}. The fathead minnow study (Schultz et al. 2012) was also not included in the SSD since it provided a very low unbounded NOEC (i.e., two orders of magnitude lower than NOEC for other fish species). This NOEC is not considered toxicologically meaningful, as concentrations of triclosan tested were most likely too low. For amphibians, the endpoints relevant to population dynamics (e.g., growth and development) were used in the SSD. Two of those endpoints were unbounded NOECs (i.e., "greater than" values); nonetheless, they were included in the SSD as they did not over-estimate toxicity, and were based on relatively high test concentrations.

Endpoints based on biochemical responses (e.g., gene expression) available for amphibians and molluscs were not used in the SSD because they are difficult to relate to and to evaluate impacts on population dynamics. Although they were excluded from the SSD, they were still used as a valuable line of evidence to characterize the ecological effects of triclosan.

The values chosen for the SSD were not adjusted for the pH to reflect the ionizing potential of triclosan in the environment (see section 4.4.2). This is because, such an adjustment could only be done if the relationship between the pH and the degree of toxicity of triclosan was known, or if it were assumed to be linear. Assumption of linearity is a gross simplification of the physical-chemical processes that can take place, and in effect, would lead to a great uncertainty with the calculated results.

The software SSD Master Version 3.0 (CCME 2013) was used to plot the SSD. Several cumulative distribution functions (normal, logistic, extreme value, Gumbell, and Weibull) were fit to the data using regression methods. Model fit was assessed using statistical and graphical techniques. The best model was selected based on consideration of goodness of fit and model feasibility. Model assumptions were verified graphically and with statistical tests. The normal model was selected (Anderson-Darling Statistic [A^2] for goodness of fit = 0.242), and the 5th percentile (HC_5, i.e., hazardous concentration to 5% of species) of the SSD plot is 376 ng/L, with lower and upper confidence limits of 263 and 538 ng/L, respectively. Figure 4-3 shows the plot for the triclosan SSD.

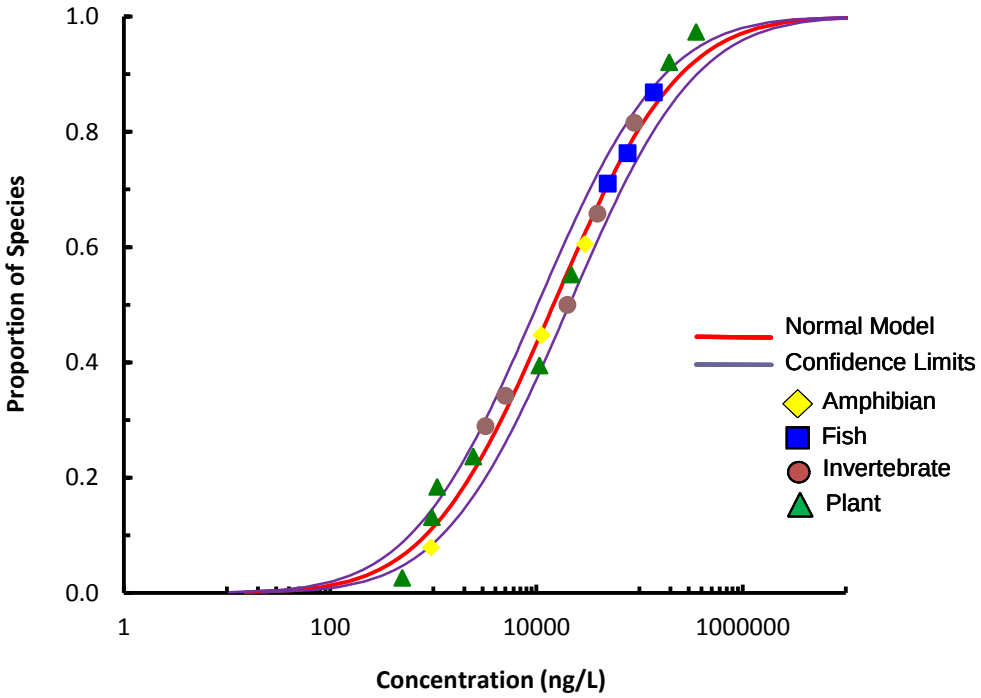


Figure 4-3. Species sensitivity distribution (SSD) for triclosan based on selected chronic toxicity data for freshwater aquatic organisms (Table 4-12). The normal model fit to the data is shown on the graph along with the 95% confidence intervals

It is noted that numerous SSDs for triclosan using endpoints for aquatic species were developed by other authors (Capdevielle et al. 2008; Lyndall et al. 2010; Belanger et al. 2013) using approaches other than the CCME guideline (2007). The HC_5 values obtained in these studies range from 534 to 1550 ng/L. Differences in the HC_5 values can be attributed to the selection of endpoints and species as well as different data-fitting approaches.

4.4.2.1.6 Derivation of the predicted no-effect concentration (PNEC) for aquatic species

The 5th percentile value (HC_5) of 376 ng/L calculated from the SSD for aquatic freshwater species was selected as the critical toxicity value (CTV) for triclosan. This value is below the lowest endpoint value used in the SSD (500 ng/L for *Scenedesmus subspicatus*).

Since the CTV was based on no- or low-effect chronic SSD that included toxicity endpoints for numerous species, an assessment factor (AF) of 1 was used to derive a

predicted no-effect concentration (PNEC). Consequently, the value of 376 ng/L was chosen as the PNEC in the risk analysis of triclosan (see section 4.5.1). It is noted that the SSD includes endpoints that may be susceptible to endocrine influence, including effects on growth and reproduction in fish and amphibians. Therefore, the PNEC is expected to be encompassing of endocrine disrupting effects.

The aim of the approach taken for the derivation of the PNEC for triclosan was to capture inter-species variation in sensitivity. It is considered that the PNEC of triclosan reflects accurately the observed no- to low-effect levels, and is not overly conservative.

4.4.2.1.7 Methyl-triclosan

A study conducted to assess the toxicity of methyl-triclosan to *Daphnia magna* indicates that the 48-hour NOEC for immobilization is greater than or equal to 180 µg/L. In another study, the 72-hour EC_{50} values for biomass and growth rate for the alga *Scenedesmus subspicatus* were 120 µg/L and 170 µg/L, respectively. The corresponding EC_{10} values were 55 µg/L and 76 µg/L, respectively (Study Submissions 2009). These results suggest that methyl-triclosan is less toxic to aquatic organisms than triclosan, but is nonetheless of high inherent toxicity.

4.4.2.2 Benthic organisms

The toxicity of triclosan to benthic organisms was assessed using a test with chironomids (*Chironomus riparius*) in accordance with OECD test guideline 218. After 28 days, no adverse effects were observed on the emergence ratio or development rate at any of the concentrations tested (Study Submissions 2009). Based on these results, the NOEC for triclosan is greater than or equal to 100 mg/kg dw, the highest concentration tested. The concentrations of triclosan in sediments were measured in the control, middle and highest treatment levels and were constant throughout the test. The concentrations of triclosan residues in the overlying water column were very low throughout the test period (< 1% of applied radiolabelled triclosan). Similarly, very low amounts of radioactivity were measured in the pore water samples (0.1% of applied radioactivity). This indicates that triclosan was mainly bound to the sediment, but most of this fraction was extractable.

There are differences in the observed triclosan binding with sediments. Results from the aerobic aquatic metabolism study described in Section 4.2.4.2, indicate that about one third of the triclosan that was bound to sediment by study termination (104 days) was not extractable. The differences between the metabolism study and the chironomid toxicity study may result from differences in protocols used in each study, study durations or different types of sediments. The sediments used in the toxicity study were mainly composed of sand silica, a substrate that has a low adsorption capacity.

4.4.2.3 Terrestrial organisms

Effects data for triclosan in several terrestrial organisms including microorganisms, plants, invertebrates, birds and small mammals were available. A summary of toxicity data for low level, chronic effects of triclosan on terrestrial organisms is presented in Table 4-13. Soil invertebrates were most sensitive to triclosan exposure followed by dicotyledonous plants (e.g., tomato, lettuce, soybean, and cucumber) and monocotyledonous plants (e.g., garlic chive, corn, wheat, rice) (Wang et al. 2015). The PNEC for the soil compartment was calculated based on a critical toxicity value (the most sensitive, reliable endpoint) divided by an assessment factor (see subsection 4.4.2.3.5).

Table 4-13. Toxicity of triclosan to terrestrial organisms

Table 4-13a. Toxicity of triclosan to soil microorganisms

Organism	Endpoint (duration)	Effect	Conc. (mg/kg dw)	Reference
Soil microorganisms	NOEC (1 h to 28 d)	Respiration, nitrification, phosphatase, glucosidase, chitinase	1	Waller and Kookana 2009

Note: For table abbreviations, see Table 4-13e.

Table 4-13b. Toxicity of triclosan to plants

Organism	Endpoint (duration)	Effect	Conc. (mg/kg dw)	Reference
Ryegrass (*Lolium perenne*)[a]	NOEC (21 d)	Root weight	0.162	Study Submissions 2009[b]
Corn (*Zea mays*)[a]	NOEC (21 d)	Root length; Shoot length; Fresh weight	30; 60; 60	Wang et al. 2015[c]
Corn (*Zea mays*)[a]	EC_{10} (21 d)	Root length; Shoot length; Fresh weight	26; 52; 41	Wang et al. 2015[c]
Garlic chives (*Allium tuberosum*)[a]	NOEC (21 d)	Root length; Shoot length; Fresh weight	40; 40; 40	Wang et al. 2015[c]
Garlic chives (*Allium tuberosum*)[a]	EC_{10} (21 d)	Root length; Shoot length; Fresh weight	40; 33; 25	Wang et al. 2015[c]
Wheat (*Triticum*	NOEC (21 d)	Shoot weight	0.162	Study

Organism	Endpoint (duration)	Effect	Conc. (mg/kg dw)	Reference
aestivum)[a]				Submissions 2009[b]
Wheat (*Triticum aestivum*)[a]	EC_{10} (21 d)	Survival	142	Amorim et al. 2010[c]
Rice (*Oryza sativa*)[a]	NOEC (20 d)	Root length; Shoot height	1; 70	Liu et al. 2009[c]
Rice (*Oryza sativa*)[a]	EC_{10} (20 d)	Root length; Shoot height	27; 37	Liu et al. 2009[c]
Soybean (*Glycine max*)[d]	NOEC (21 d)	Root length; Shoot length; Fresh weight	20; 20; 10	Wang et al. 2015[c]
Soybean (*Glycine max*)[d]	EC_{10} (21 d)	Root length; Shoot length; Fresh weight	20; 29; 22	Wang et al. 2015[c]
Field mustard (*Brassica rapa*)[d]	EC_{10} (21 d)	Survival	3	Amorim et al. 2010[c]
Lettuce (*Lactuca sativa*)[d]	NOEC (21 d)	Root length; Shoot length; Fresh weight	8	Wang et al. 2015[c]
Lettuce (*Lactuca sativa*)[d]	EC_{10} (21 d)	Root length; Shoot length; Fresh weight	4; 14; 6	Wang et al. 2015[c]
Cucumber (*Cucumis sativus*)[d]	NOEC (21 d)	Shoot length	0.065	Study Submissions 2009[b]
Cucumber (*Cucumis sativus*)[d]	NOEC (20 d)	Root length; Shoot height	10; 10	Liu et al. 2009[c]
Cucumber (*Cucumis sativus*)[d]	EC_{10} (20 d)	Root length; Shoot height	17; 6	Liu et al. 2009[c]
Tomato (*Solanum lycopersicum*)[d]	NOEC (21 d)	Root and shoot weight	0.162	Study Submissions 2009[b]
Tomato (*Solanum lycopersicum*)[d]	NOEC (21 d)	Root length; Shoot length; Fresh weight	8; 8; 8	Wang et al. 2015[c]
Tomato (*Solanum lycopersicum*)[d]	EC_{10} (21 d)	Root length; Shoot length; Fresh weight	11; 14; 9	Wang et al. 2015[c]

Note: For table abbreviations and footnotes, see Table 4-13e.

Table 4-13c. Toxicity of triclosan to invertebrates

Organism	Endpoint (duration)	Effect	Conc. (mg/kg dw)	Reference
Earthworm (*Eisenia fetida*)	NOEC (56 d)	Reproduction; Survival	2; >64	Wang et al. 2015[c]
Earthworm (*Eisenia fetida*)	EC_{10} (56 d)	Reproduction	1.05	Wang et al. 2015[c]
Earthworm (*Eisenia fetida*)	NOEC (14 d)	Survival	>1026	Reiss et al. 2009
Earthworm (*Eisenia fetida*)	NOEC (56 d)	Reproduction	10	Lin et al. 2014[c]
Earthworm (*Eisenia fetida*)	LOEC (56 d)	Reproduction	50	Lin et al. 2014[c]
Tiger worm (*Eisenia andrei*)	NOEC (14 d)	Survival	32	Amorim et al. 2010[c]
Tiger worm (*Eisenia andrei*)	EC_{10} (56 d)	Reproduction	0.6[e]	Amorim et al. 2010[c]
White worm (*Enchytraeus albidus*)	NOEC (42 d)	Reproduction; Survival	3.2	Amorim et al. 2010[c]
Collembolan (*Folsomia candida*)	NOEC (28 d)	Reproduction; Survival	3.2; ≥320	Amorim et al. 2010[c]
Terrestrial snail (*Achatina fulica*)	NOEC (28 d)	Inhibition of food intake; growth of biomass; growth of shell diameter	24	Wang et al. 2014
Terrestrial snail (*Achatina fulica*)	NOEC (28 d)	Survival	200	Wang et al. 2014

Note: For table abbreviations, see Table 4-13e.

Table 4-13d. Toxicity of triclosan to birds

Organism	Endpoint (duration)	Effect	Conc. (mg/kg bw per day)	Reference
Mallard duck (*Anas platyrhynchos*)	LD_{50} (14 d) (acute oral)	Survival	≥2150	US EPA 2008f
Bobwhite quail (*Colinus virginianus*)	LD_{50} (14 d) (acute oral)	Survival	825	US EPA 2008f
Bobwhite quail (*Colinus virginianus*)	LC_{50} (8 d) (dietary)	Survival	>5000	US EPA 2008f

Note: For table abbreviations, see Table 4-13e.

Table 4-13e. Toxicity of triclosan to mammals

Organism	Endpoint (duration)	Effect	Conc. (mg/kg bw per day)	Reference
Rat (*Rattus norvegicus*)	LD_{50} (acute oral)	Survival	>5000	NICNAS 2009
Rat (*Rattus norvegicus*)	NOAEL (90 d) (dietary exposure)	Survival, reproduction or growth	>433 (males) >555 (females)	NICNAS 2009
Mouse (*Mus musculus*)	NOAEL (90 d) (dietary exposure)	Decrease in body weight gain	750	NICNAS 2009
Mouse (*Mus musculus*)	LOAEL (90 d) (dietary exposure)	Decrease in body weight gain	900	NICNAS 2009

Abbreviations: conc., concentration; EC_x, the concentration of a substance that is estimated to cause some effect on x% of the test organisms; LC_x, the concentration of a substance that is estimated to be lethal to x% of the test organisms; LD_x, the dose of a substance that is estimated to be lethal to x% of the test organisms; LOEC, lowest-observed-effect concentration; NOAEL, no-observed-adverse-effect level; NOEC, no-observed-effect concentration; LOAEL, lowest-observed-adverse-effect level.
[a]Monocotyledonous plants.
[b]Based on time-weighted mean measured concentrations.
[c]Based on nominal concentrations.
[d]Dicotyledonous plants.
[e]EC_{10} = 0.6 mg/kg was chosen as the critical toxicity value (CTV) in derivation of the predicted no effect concentration (PNEC) for the soil compartment.

4.4.2.3.1 Microorganisms

The effect of triclosan on microbial activity was studied by Waller and Kookana (2009) in two types of soils (sandy loam and clay). Substrate-induced respiration and nitrification were decreased at a concentration of 50 mg/kg and 5 mg/kg, respectively. The activities of four enzymes – namely, the acid and alkali phosphatase, β-glucosidase and chitinase – were also measured, but did not seem affected by triclosan, except for the β-glucosidase in the sandy soil. No adverse effects were noted on any of the microbial processes at the lowest concentration tested of 1 mg/kg. In a study by Liu et al. (2009), soil respiration in a paddy soil was inhibited after 22 days of incubation at triclosan concentrations of 10 mg/kg and above. The phosphatase activity seemed to decrease with increasing triclosan concentrations in soil; however, the differences were not significant.

4.4.2.3.2 Plants

Triclosan effects studies were available for several terrestrial plant species. Wang et al. (2015) observed that dicotyledonous plants tend to be more sensitive to triclosan exposure than monocotyledonous plants, based on tests with corn, garlic chives, soybean, tomato and lettuce. Similar observations were made by Liu et al. (2009) and Amorim et al. (2010) in tests with cucumber, rice, field mustard, and wheat. Low level (i.e., NOEC, EC_{10}), chronic effects presented in Wang et al. (2015), Amorim et al. (2010) and Liu et al. (2009) were summarized in Table 4-13b. Observed effects on the root and shoot growth, and plant survival in these studies point to moderate toxicity of triclosan; effects ranged between 3 mg/kg (survival for the dicotyledonous field mustard) to 142 mg/kg (in the monocotyledonous common wheat).

In addition, three unpublished studies, submitted to Environment and Climate Change Canada (Study Submissions 2009), assessed the effects of triclosan on terrestrial plants, and show low toxicity of triclosan to the most sensitive species. In the first study, six plant species (corn, ryegrass, wheat, cucumber, soybean and tomato) were exposed to triclosan in quartz sand at nominal concentrations of 0.01–1 mg/kg dw for 21 days. Cucumber was the most sensitive species, with a measured time-weighted average NOEC of 0.065 mg/kg dw soil for shoot length (Study Submissions 2009). In the second study, the seed germination and seedling growth of cucumber exposed to triclosan in a sandy loam at nominal concentrations of 0.01–1 mg/kg dw were studied over 28 days. No adverse effects were observed at the highest concentration tested, resulting in a time-weighted average NOEC of 0.446 mg/kg dw based on measured concentrations (Study Submissions 2009). In the third study, 10 plant species (corn, ryegrass, wheat, cucumber, soybean, tomato, lettuce, radish, vetch and pea) were exposed for 14 days (post–median control emergence) to triclosan in a sandy loam at nominal concentrations ranging from 0.2 to 1000 mg/kg, following OECD test guideline 208 (Büche et al. 2009). The most sensitive species was lettuce, with NOEC and LOEC values for shoot weights of 50 and 75 mg/kg, respectively, based on nominal concentrations. The NOEC for shoot weight for all other tested species was 1000 mg/kg.

Lastly, the effects of triclosan on seed germination and seedling development of three wetland plants, *Sesbania herbacea*, *Euphorbia prostrata*, and *Bidens frondosa*, were studied by Stevens et al. (2009). These plants are also commonly found in terrestrial habitats. Plants were exposed to triclosan for 28 days at concentrations ranging from 0.0004 to 1 mg/kg in water-only flow-through systems. While germination and shoot weight were not affected at the highest concentration tested, root length was affected at 0.0006 mg/L for two of the species tested. Liu et al. (2009) found that in the plant growth test, the shoot growth was also a less sensitive endpoint than root elongation. Given that plants were tested in water flow-through systems, it is possible that the observed effects thresholds could be different if plants were rooted in soil.

4.4.2.3.3 Invertebrates

Soil invertebrates are sensitive to triclosan exposure. However, length of exposure and soil characteristics such as pH impact the extent of effects. Short and long-term effects studies were conducted for numerous species, including three soil-dwelling worms *Eisenia fetida*, *Eisenia andrei*, and *Enchytraeus albidus*, the collembolan *Folsomia candida,* and a terrestrial snail *Achatina fulica* (Reiss et al. 2009; Wang et al. 2014, 2015; Amorim et al. 2010; Lin et al. 2014).

Short-term 14-day exposure to triclosan does not cause mortality in earthworms, *E. fetida*, at the nominal exposure concentrations of up to 1026 mg/kg (dw soil) (Reiss et al. 2009), rather adverse effects of triclosan have been observed in long-term exposure studies. Wang et al. (2015) measured a 56-day EC_{10} of 1.05 mg/kg for reproduction in the earthworm, *E. fetida*. Similarly, a 56-day EC_{10} of 0.6 mg/kg for reproduction was determined for the tiger worm, *Eisenia andrei* (Amorim et al. 2010). The white worm, *E. albidus,* and the collembolan, *F. candida,* were also tested for effects on reproduction and survival in the Amorim et al. (2010) study. No clear dose–response curves were obtained for these two species; however, it is clear that juveniles were significantly affected at the highest concentration tested (320 mg/kg dw soil) based on a visual inspection of the curves representing results of chronic bioassays.

Lin et al. (2014) tested the effect of triclosan on the reproduction of the earthworm *E. fetida* exposed to a coastal alkali-saline soil (fine clay soil based on soil composition). The NOEC and LOEC values were 10 and 50 mg/kg, respectively, based on number of juveniles and cocoons produced after 56 days. This is much higher than the EC_{10} of 0.6 mg/kg obtained by Amorim et al. (2010) for *E. Andrei*. This difference in toxicity could be due to different sensitivity of the test species but also to the differences in test pH. The pH of the soil used by Amorim et al. (2010) and by Lin et al. (2014) were 5.8 and 8.1, respectively. This means that earthworms in the Amorim et al. (2010) study were likely exposed exclusively to the neutral form of triclosan. This form has been suggested to cause most of the toxicity in two aquatic species (Orvos et al. 2002; Roberts et al. 2014). Another factor to explain the difference in toxicity could be the difference in bioavailability due to binding of triclosan to organic matter. However, the percentage of organic matter in test soils would suggest a lower bioavailability in the soil used by Amorim et al. (2010) (4.4% versus 2.2% in the soil used by Lin et al. (2014)).

Effects of triclosan on the growth of biomass and shell-dimeter, inhibition of food intake and survival were studied in the terrestrial snail *A. fulica* (Wang et al. 2014). Moderate toxicity of triclosan was observed: the 28-day NOEC for growth, and inhibition of food intake was determined as 24 mg/kg, and the 28-day NOEC for survival was 200 mg/kg (Wang et al. 2014).

In addition, biochemical responses associated with oxidative stress and harmful stress conditions were studied in *A. fulica* (Wang et al. 2014) and in *E. fetida* (Lin et al. 2010, 2014), at triclosan exposure concentrations ranging from 1 to 300 mg/kg. Although indicative of specific cellular responses or pathways, these sublethal effects were observed at levels of triclosan unlikely to be reached in soils (i.e., ≥ 12.5 mg/kg).

4.4.2.3.4 Birds and mammals

Based on a limited data set, triclosan seems not toxic to slightly toxic to birds (median lethal dose [LD_{50}] ≥ 2150 mg/kg bw and 825 mg/kg bw for mallard duck and bobwhite quail, respectively) and not toxic to mammals (rat, LD_{50} > 5000 mg/kg bw) on an acute oral basis. Subchronic oral toxicity data indicate a NOAEL of 750 mg/kg bw per day based on decrease in body weight gain observed in mice. Oral toxicity studies were also conducted with dogs and baboons, but the results of these studies were not considered in this assessment due to a number of factors (see Section 3.2.3). There were no indications of adverse effects on thyroid function in mammals (see Section 3.1.10).

4.4.2.3.5 Derivation of the predicted no-effect concentration (PNEC) for terrestrial species

The calculation of a PNEC for the soil compartment is based on the most sensitive acceptable endpoint identified for terrestrial organisms (reproduction in the earthworm *E. andrei*, EC_{10} = 0.6 mg/kg; see Table 4-13). Another endpoint (growth in cucumber, 0.065 mg/kg) is lower than the one for earthworms; however, the cucumber study was conducted using quartz sand which, while it has low adsorption capacity and therefore maximizes the bioavailability of triclosan, is not representative of agricultural soils to which biosolids-borne triclosan would be applied. Agyin-Birikorang et al. (2010) measured similar partition coefficients (K_d and K_{oc}) for triclosan in soils and biosolids-amended soils, while these coefficients were higher in biosolids alone. This suggests that toxicity studies conducted with soils spiked with triclosan may adequately simulate the bioavailability of triclosan in biosolids-amended soils. No toxic effects of triclosan in soils amended with biosolids for six crop species were observed, suggesting a low bioavailability of triclosan in these soils (Prosser et al. 2014). The concentrations achieved in Prosser et al. (2014) were much lower than the concentrations tested in laboratory assays, but they were based on realistic agronomic rates. Overall, the EC_{10} of 0.6 mg/kg for earthworm reproduction selected as the critical toxicity value (CTV) is considered as being a conservative yet realistic endpoint. An assessment factor of 1 was applied since a no-effect, chronic endpoint is used. In addition, the test pH used in this study likely maximized the presence of the neutral form of triclosan in soil, which has proven to be the most toxic form to certain aquatic organisms (most likely due to greater bioaccumulation). The triclosan PNEC for soil is calculated as 0.6 mg/kg.

4.4.3 Relevance of the effects data for triclosan

Effects studies determine the ability a chemical to cause adverse effects in the tested species. Some effects studies can also help elucidate the mechanisms underlying the observed effects, i.e., the modes of action. Ecological effects of triclosan were characterized based on several toxicity data available for numerous species belonging to a variety of taxa. Toxicity of triclosan to the aquatic species was most extensively characterized through numerous studies on algae, invertebrates and vertebrates. Effects studies, particularly in aquatic species, served as one of the key lines of evidence in the risk assessment of triclosan. Predicted no-effect concentration (PNEC) values were determined for the aquatic and terrestrial species based on the available effects data.

There is consistency between the chemical activity, fugacity, and the measured toxicity values, all of which suggest that triclosan is a potent chemical acting through specific modes of action such as receptor mediated interactions. There is some uncertainty regarding the occurrence and the threshold for endocrine disruption in amphibians. Nonetheless, these subtle effects levels have likely been captured in the PNEC for the aquatic compartment, and it is difficult to determine if the current potency thresholds would change with additional new endocrine disrupting data. Effects data are available for only one benthic species and therefore, it is not fully representative of the potential effects in the sediment compartment.

Methylation of triclosan in aerobic soil and in WWTPs, leads to formation of methyl-triclosan. Limited effects data are available for methyl-triclosan; it seems to have a high inherent toxicity to aquatic organisms, and no toxicity data are available for terrestrial organisms. Co-exposure to both triclosan and methyl-triclosan is expected in the environmental media, but such combined effects data are also not available.

4.5 Ecological Exposure and Risk Assessment

Sources of triclosan in the Canadian environment and measured environmental concentrations of triclosan and methyl-triclosan in Canada and other countries were described in section 4.1. The main receiving environmental medium for triclosan is water; triclosan is released to the aquatic ecosystems via effluents from WWTPs. Once in the water column, results from the Multispecies Model (version 1.0; Cahill 2008) indicate that triclosan will to a large extent remain in water (79-91%) and will also partition to sediments (9-21%). Triclosan has been detected in surface water samples collected across Canada, and other countries. Triclosan can also reach soils through spreading of biosolids to agricultural lands. Monitoring data for soil were not available; therefore predicted environmental concentrations were modelled.

The environmental risk assessment includes risk quotients analysis. The risk quotient is an important line of evidence in characterizing the potential of a substance to cause

harm to ecosystems. A risk quotient is the ratio of a predicted environmental concentration (PEC) to a toxicity endpoint (predicted no-effect concentration [PNEC]) determined for each medium of concern.

For triclosan, a risk quotient analysis was done for key compartments of concern, namely water and soil. A qualitative risk assessment was done for sediment. Risk from exposure to methyl-triclosan was also evaluated for the aquatic compartment (see sections below).

Risk assessment of triclosan and methyl-triclosan is presented below, based on the environmental compartment.

4.5.1 Water

4.5.1.1 Risk analysis based on measured concentrations of triclosan in surface water

Because measured concentrations of triclosan in surface water are available for numerous water bodies in both densely and lightly populated areas of Canada, and because these concentrations integrate simultaneous fate processes occurring in surface water, these data are considered to provide a realistic representation of levels of triclosan in Canada (Table 4-3). It is recognized however that such measurements often provide only a snapshot of concentrations in time and space. For instance, Price et al. (2010) showed that triclosan concentrations measured over a single month at one site in a river in England varied from 21 to 195 ng/L. This was mainly due to variations in river discharges. The data available for Canada are based on sampling episodes that occurred at different sites on the same water body (except for small water bodies) and at different times over each sampling year. As such, it is believed that these data are representative of levels of triclosan in Canada. Several of the sampling sites are closely associated with WWTPs.

The data available date from 2002 to 2014, and the concentrations reported span almost four orders of magnitude, from below the lowest MDL (0.10 ng/L) to 874 ng/L; median concentrations for each site range from below the MDL to 139 ng/L. Most of the water bodies have relatively low maximum concentrations of triclosan. Five water bodies had maximum concentrations above the PNEC of 376 ng/L (Table 4-3). Recent data (2010 to 2013) collected for three of these five water bodies indicate that the maximum concentration of triclosan in two of them is now below the PNEC. The other water body has a maximum concentration (874 ng/L) much above the PNEC. There are no recent data available for the fourth and fifth water bodies. Data available for these two water bodies are from 2005 and show maximum concentrations of 433 ng/L and 599 ng/L. The water bodies where high concentrations of triclosan were measured are receiving effluent from WWTPs that have secondary treatment or that are lagoons.

The data presented in Table 4-3 are considered representative of conditions occurring across Canada, with no outliers identified. At those sites with high measured concentrations of triclosan, it is likely that there is a low dilution of the WWTP effluent by the receiving watercourse at certain times of the year and/or high inputs of triclosan. As noted in Anger et al. (2013), exposure to triclosan is dynamically linked to the size of the receiving water body and degree of wastewater impact, where a small-scale wastewater-impacted water body tends to be burdened with long-term exposure to the substance at elevated levels. Such variability with respect to the size and flow of the water bodies has been observed for the sampled WWTPs listed in Table 4-3.

Assuming that the data available for concentrations of triclosan in surface water are representative of those for the entire country, for some locations where triclosan is prevalent, i.e., near populated areas across Canada, the PEC values are expected to exceed the PNEC for triclosan.

4.5.1.2 Risk analysis based on quantities in industrial use

A survey conducted under section 71 of CEPA requested information on the manufacture, import, use and release of triclosan for the year 2011 (see Section 2.3.5). Results from this survey indicate that triclosan was not manufactured in Canada in 2011. Twenty-nine companies reported importing between 10 000 and 100 000 kg of triclosan as either the pure substance or in products. Some companies reported using triclosan to manufacture products such as antibacterial hand soap, dentifrice, cleaners, etc. This use of triclosan to manufacture products could result in releases of this substance to WWTPs through industrial wastewater as a result of washing residues from tanks, and spills. Depending on removal efficiency in WWTPs and on dilution in the receiving water bodies, the manufacturing facilities could represent sources of triclosan to the environment.

To assess whether these potential sources may be of ecological concern, locations of WWTPs for which data on measured concentrations of triclosan in influents are available (Table 4-1) were matched with locations of those facilities that reported the top quantities (>400 kg) for use of triclosan to manufacture products in 2011. Of these facilities, three could be matched with a WWTP having measured data. These three manufacturing facilities together used about 40% of the total quantity of triclosan reported as being used to manufacture products. The analysis indicated that the WWTP that has the highest triclosan concentration in its influent (20 750 ng/L, in 2011-2013; Table 4-1) receives wastewater from a soap manufacturer. In this case, due to high removal efficiency, the concentration of triclosan in the effluent was quite low (12 ng/L; Table 4-1). Two other WWTPs that receive industrial wastewater from facilities that used triclosan in 2011 had concentrations in their influent of 1260 and 1430 ng/L and concentrations in their effluent of 190 and 240 ng/L, respectively. These effluents would be further diluted once released to surface water. These effluent concentrations date

from 2004 so it is uncertain whether the facilities were actually using triclosan at that time and whether the quantities used were similar to the ones reported for 2011, however, these values are not particularly different from other WWTP effluent concentrations (Table 4-1). Based on these data, triclosan releases from the manufacturing facilities are not likely to be of ecological concern.

4.5.1.3 Risk analysis for methyl-triclosan

The potential risk posed by methyl-triclosan to aquatic ecosystems was also assessed, since this substance is released in WWTP effluent and there is evidence of its presence in certain water bodies in Canada. For this substance, the worst-case scenario would be equivalent to assuming 100% transformation of triclosan to methyl-triclosan. Although it was not quantified, the portion of triclosan actually biotransformed to methyl-triclosan is expected to be much lower than this, as suggested by the results of the studies conducted on the fate of triclosan in WWTPs. A more realistic scenario would be to take into account all the fate pathways—that is, to base the PEC on monitoring data for water. Monitoring data for methyl-triclosan in Canada were available only for Hamilton Harbour, Lake Ontario and Wascana Creek (Saskatchewan); the highest value was 17 ng/L for Wascana Creek. Therefore, the PEC for methyl-triclosan in water was chosen to be 17 ng/L. This is considered to be a realistic worst-case since Wascana Creek is known for its low capacity to dilute the WWTP effluent that it receives.

The results of only two aquatic toxicity studies are available for methyl-triclosan (acute tests with daphnids and algae). The lowest endpoint from these studies was selected as the CTV—that is, a 72-hour EC_{10} value of 55 µg/L for biomass of the alga *Scenedesmus subspicatus* (Study Submissions 2009).

An assessment factor of 100 was chosen to derive a PNEC from this value, given the very limited data set from which it was taken. Dividing the PEC of 17 ng/L by the PNEC of 550 ng/L results in a risk quotient (RQ) of 0.03, indicating that methyl-triclosan would be unlikely to represent a risk to aquatic organisms. However, this does not take into account the possible chronic toxicity of methyl-triclosan due to its bioaccumulation. Indeed, BAFs up to 5200 were measured for aquatic organisms (Table 4-11). It is also acknowledged that combined exposure to methyl-triclosan and triclosan is likely in certain aquatic ecosystems. The overall impact is uncertain, given the limited monitoring and effects data for methyl-triclosan. The risk associated with this co-exposure is likely somewhat higher than that from triclosan alone. Given that the PEC for triclosan is much higher, the realistic worse-case scenario presented in section 4.5.1.2 for triclosan likely encompasses risk from the potential combined exposure of methyl-triclosan and triclosan.

4.5.2 Sediment

The available toxicity data for triclosan in benthic organisms are limited to only one study using chironomids (*Chironomus riparius*). The NOEC in this study was established as ≥ 100 mg/kg dw (Study Submissions 2009). The available data are not fully representative of the sediment compartment as other benthic organisms could be more sensitive to triclosan.

Triclosan and methyl-triclosan were measured in surface, suspended and core sediment samples collected at different locations across Canada in 2012-2013 (see Table 4-4). The highest concentrations of triclosan were found in suspended sediment samples collected in the St. Lawrence River at different distances away from a WWTP. At 4 km away, triclosan was measured in two samples, at 990 and 2000 ng/g (0.99–2 mg/kg). At distances of up to 15 km away from the WWTP, the measured concentrations did not exceed 150 ng/g (0.15 mg/kg). It is noted that suspended sediment is not considered to be the primary route of exposure to sediment-dwelling organisms. Concentrations found in surface sediment were up to 47 ng/g (0.047 mg/kg), and in core sediment up to 9 ng/g (0.009 mg/kg). These measured concentrations are well below the NOEC value determined for a sediment-dwelling species (*Chironomus riparius*).

Methyl-triclosan was found in sediment samples at levels much lower than triclosan; the highest concentrations reported for surface, suspended and core sediment were 22, 24 and 15 ng/g, respectively (see Table 4-4). Due to the lack of suitable toxicity data on benthic organisms for methyl-triclosan, no further analysis was conducted.

4.5.3 Soil

4.5.3.1 Risk analysis for triclosan

The main release of triclosan to soil is via the spreading of biosolids from WWTPs. In Canada, about 40% of this type of biosolids is applied to various types of land (i.e., agricultural, forest or dedicated land) (Apedaile 2001). A PEC based on monitoring data (i.e., triclosan concentrations in soil) cannot be determined, as such data were not found for Canada. However, numerous monitoring data were available for triclosan in wastewater sludge and biosolids; these data can be used to derive a PEC for soil. As presented in Section 4.1.2.1, the concentration of triclosan in wastewater sludge and biosolids from various WWTPs across the country ranges from less than 1 to 46.4 µg/g dw. In Canada, the worst-case conditions for biosolids application to an agricultural soil are a maximum application rate of 8300 kg dw/ha per year (based on the highest existing provincial regulatory limit; such limits are only available for four provinces) with a mixing depth of 0.2 m (plough depth) and a soil density of 0.0017 kg/cm^3 (Environment Canada 2006). The following equation was used for deriving a soil PEC:

$$PEC = ([triclosan]_{sludge} \times \text{application rate}) \div (\text{depth} \times \text{density})$$

Taking the 95th percentile of triclosan concentrations found in biosolids (28 µg/g dw; Table 4-2) as a realistic worst-case concentration and the maximum application rate described above for biosolids spreading, a PEC of 68 µg/kg dw is obtained. Assuming a yearly application of biosolids over 10 years, the cumulative triclosan concentration in soil would be 684 µg/kg dw. This PEC value is based on the highly conservative assumption that triclosan will not degrade further once mixed into soil and that it will not leach or run off. In order to estimate more realistic PEC values, the Biosolids-Amended Soil Level 4 (BASL4) model was used (BASL4 2011). This model is a fugacity-based model and uses equilibrium partitioning principles to deduce the overall fate of a chemical in the soil. In this model, a chemical can be removed from the soil by volatilization, degradation, leaching, runoff and erosion processes.

Two scenarios were modelled in BASL4 to simulate the lower and upper ends of a range of possible PECs in soil based on two triclosan half-lives, two biosolids application rates and the 95th percentile of triclosan concentrations found in biosolids (28 µg/g dw). In the first scenario (lower-end), a half-life of 18 days was used based on results from laboratory biodegradation experiments (Table 4-6), and an application rate of 5000 kg dw/ha per year was used based on average existing provincial regulatory limits (such limits are only available for four provinces). BASL4 requires the use of a degradation half-life in soil that may represent biodegradation, photolysis, hydrolysis and oxidation. For triclosan, biodegradation is expected to be the major degradation process in soil (see Section 4.2.5). In the second scenario (upper-end), a half-life of 200 days was arbitrarily chosen as an estimate of a field degradation half-life. Lozano et al. (2010) reported a dissipation half-life of 107 days for a field that had received one application of biosolids. Chen et al. (2014) reported first-order dissipation half-lives of 258 and 106 days for a field that had received either one or repeated application of biosolids, respectively. Since these reported half-lives likely include contributions from processes such as leaching and volatilization, in addition to degradation processes, the value of 200 days was conservatively chosen to account for degradation only, as required for BASL4. Still in that second scenario, an application rate of 8300 kg dw/ha per year was used based on the highest existing provincial regulatory limit. A 10-year period was simulated with a yearly application during the first three years of this period. Yearly applications over ten years were also modelled; they generated similar results given that triclosan does not build up in soil.

The results obtained for the lower-end scenario show that the highest triclosan concentrations in soil would be reached at the time of ploughing, right after biosolid applications—i.e., on days 2, 367 and 732 (average of 118 µg/kg). This average is higher than the value of 68 µg/kg obtained above assuming no dissipation, probably because the equation used to calculate the latter assumes instantaneous mixing in the soil layer. The average triclosan concentration in soil between biosolid applications is estimated to be 11 µg/kg. There is no buildup in soil concentrations due to cumulative applications because of the relatively rapid rate of loss of triclosan from soil. The results

for the upper-end scenario show that the highest concentrations in soil would again be reached at the time of ploughing, right after biosolid applications (average of 222 µg/kg). The average triclosan concentration in soil between biosolid applications is estimated to be 110 µg/kg.

For comparison purposes, Fuchsman et al. (2010) conducted a terrestrial risk assessment for triclosan and modelled concentrations in soil using two half-lives (2 weeks, based on laboratory studies, and 16 weeks, based on soil dissipation studies) and two application frequencies (1 and 3 times a year; average application rate of 19 000 kg/ha per year). Their modelling exercise showed that there is no buildup of triclosan in soil, except for one of the four scenarios tested (one application and half-life of 16 weeks), in which the concentration of triclosan stabilizes over the years at approximately 110% of the initial soil concentration.

Measurements of triclosan in soils that were amended with biosolids are available from the literature. Wu et al. (2010b) measured triclosan in soils that had been amended with biosolids in Ohio. The soil for which the highest concentration of triclosan was measured (11 µg/kg dw in November 2008) is a clay that had historically received two biosolids applications (0.76 µg/g dw in biosolids), one in December 2006 and the other in November 2008. For comparison with the numbers provided above for Canada, the application rates for these two dates were 11 600 and 9900 kg dw/ha, respectively. In another study conducted in Virginia, Lozano et al. (2010) measured triclosan concentrations in soils that had been amended once with biosolids (average of 15.6 µg/g dw in biosolids) to vary between 4.1 and 4.5 µg/kg dw and between 24 and 67 µg/kg dw, 16 months and less than a year after application, respectively. In fields where there had been multiple applications of biosolids containing triclosan, there was a slight buildup in concentrations observed over the years, but these were much lower than the predictions made by the authors using an equation similar to the one above. In an additional study conducted by Lozano et al. (2012) in Maryland, triclosan concentration in a soil that was amended once with biosolids (average triclosan concentration of 19.1 µg/g dw in biosolids, and application rate of 72 000 kg ww/ha) peaked at 64 µg/kg dw two months after application. In the Midwestern United States, Kinney et al. (2008) found triclosan concentrations of 160 and 96 µg/kg dw in soil samples that were collected 31 and 156 days following biosolids application, respectively. The biosolids were applied once at a rate of 18 000 kg dw/ha, and its triclosan concentration was 10.5 µg/g dw. Finally, Sánchez-Brunete et al. (2010) measured triclosan concentrations of 4.7 and 1.7 µg/kg dw in agricultural soil sampled 1 day and 6 months following biosolids application (12 000 kg dw/ha; triclosan concentration in biosolids not mentioned), respectively. The same authors measured methyl-triclosan concentrations of 1.7 and 3.8 µg/kg dw in the same soil samples. Overall, when compared with results from soil biodegradation studies, these data suggest that the persistence of triclosan in soil is greater when it is applied in biosolids, likely because it is present as bound residues. As such, its bioavailability to soil organisms is probably lower as compared with laboratory conditions.

Use of treated wastewater to irrigate agricultural fields, as well as other types of field (e.g., golf courses), can also contribute to the introduction of triclosan in the terrestrial environment. This practice is used worldwide, including in Canada (Hogg et al. 2007). However, no data are available to quantify the relative importance of this source as compared with biosolids application.

The PNEC for the soil compartment of 0.6 mg/kg was based on the critical toxicity value, as the most sensitive acceptable endpoint identified for terrestrial organisms (reproduction in earthworm *E. andrei*, EC_{10} = 0.6 mg/kg (Amorim et al. 2010); see Table 4-13), divided by an assessment factor of 1 (see sub-section 4.4.2.3).

The risk quotients based on the average peak soil concentrations obtained for the lower-end and upper-end scenarios modelled in BASL4 are 118 µg/kg / 600 µg/kg = 0.20 and 222 µg/kg / 600 µg/kg = 0.37, respectively. Based on these results, there is low potential of risk to soil organisms from the application of biosolids that contain triclosan.

The potential risk of exposure of terrestrial wildlife to triclosan was not quantitatively assessed, since results from repeated oral dose toxicity studies in mammals showed low effects (e.g., NOAEL and LOAEL of 750 and 900 mg/kg bw per day, respectively, in mice; Table 4-13). Acute exposure also showed low toxicity to mammals (LD_{50} > 5000 mg/kg bw per day in rat; Table 4-13).

In addition, the BAF values in terrestrial organisms, such as earthworms and shrews (modelled BAFs of ~95 and ~4500 based on BASL4; see Section 4.3.2), coupled with some metabolism of triclosan that would occur following prey ingestion, would both mitigate exposure levels in top predators.

4.5.3.1 Risk analysis for methyl-triclosan

Methyl-triclosan is a major transformation product of triclosan in soil under aerobic conditions. A risk quotient analysis for terrestrial organisms was not performed due to lack of methyl-triclosan effects data for the soil compartment.

4.5.4 Characterization of ecological risk

Properties of triclosan relevant to ecological risk assessment have been described in this assessment report. Lines of evidence that characterize ecological risk of triclosan in Canada are summarized below.

In Canada, triclosan is used in many products used by consumers that end up in wastewater. A portion of triclosan is removed from wastewater before being released to

surface water as part of an effluent. During the wastewater treatment process, a portion of triclosan partitions to sludge in WWTPs. Biosolids from WWTPs may eventually be spread on land, hence potentially releasing triclosan to the terrestrial environment. A portion of triclosan may also be methylated during wastewater treatment to form methyl-triclosan. Methyl-triclosan is also formed in soils that receive application of biosolids.

When in surface water, triclosan is found either under a neutral or ionized form, depending on ambient pH. The ionized form is rapidly photodegraded (within hours) if exposed to sunlight. Potential transformation products resulting from this reaction include dichlorophenol (2,4-DCP) and lower chlorinated dioxins (2,7/2,8-DCDD).

Triclosan is not likely to persist in water and sediments in the long term, should releases of this chemical be halted. However, its continual input to surface water through WWTP effluents results in its continuous presence in receiving aquatic ecosystems. The relatively short half-life of triclosan in aquatic ecosystems means that triclosan will not be subject to long-range transport. Therefore, long-term exposures to triclosan in water and sediments are expected to be in the near field, closer to emission sources.

The evidence for bioaccumulation of triclosan in water is variable depending on exposure conditions and organisms exposed. Bioaccumulation of triclosan in organisms is partly dictated by its ionization state. The neutral form of triclosan has a greater potential for bioaccumulation compared to the ionized form. In fish, triclosan is rapidly taken up from the water phase. The physical and chemical properties of triclosan suggest that the contribution of the diet to the total body burden of triclosan in fish is likely quite low. While it bioconcentrates rapidly, triclosan also metabolizes rapidly. Triclosan also accumulates in algae and invertebrates with BCF/BAF ranging from 500 to 2100. BCF values ranging from 16 to 8700 have been reported for fish and have been shown to be influenced by pH of exposure and internal tissues. Fugacity ratio calculations in fish suggest that triclosan bioconcentrates sufficiently in fish to cause chronic adverse effects.

Triclosan is known to act through specific modes of action. Triclosan likely functions as an uncoupler of oxidative phosphorylation. The molecular structure of triclosan resembles that of several non-steroidal estrogens which suggests the potential to act as an endocrine-disrupting agent. Studies show that triclosan may disrupt the thyroid hormone in amphibians. Triclosan blocks fatty acids synthesis in bacteria. Plants share similar fatty acid synthesis pathways with bacteria, which may explain their high sensitivity to triclosan.

Triclosan is highly inherently toxic to aquatic organisms; observed adverse effects at very low exposure concentrations include reduction in growth, reproduction and survival. Triclosan may also interfere with the action of certain hormones in amphibians, fish and mammals. Algae are the most sensitive group of organisms, followed by invertebrates and vertebrates.

A species sensitivity distribution (SSD) based on no- to low-effects chronic endpoints for 19 aquatic species was used to determine a predicted no-effect concentration (PNEC) of 376 ng/L for triclosan. This SSD also includes endpoints which may be susceptible to endocrine influence such as growth, postembryonic development and reproduction in fish and amphibians. Because this PNEC is based on sensitive endpoints that were measured under chronic exposure, which likely allowed for bioaccumulation of triclosan and subsequent occurrence of adverse effects, it is not considered to be overly conservative.

The widespread use of triclosan in products used by consumers is reflected through its ubiquitous presence in water bodies located in populated areas across Canada. Of the available surface water monitoring data, a large number of the measured triclosan concentrations are below the toxic effects threshold (i.e., the PNEC of 376 ng/L), but there are a few instances where this level is exceeded. This indicates that the measured concentrations of triclosan in surface water in Canada can reach levels where there is a potential for triclosan to cause harmful effects to aquatic ecosystems.

A portion of triclosan partitions to sediments when released to the water compartment. Triclosan is expected to degrade relatively rapidly under aerobic conditions, but it degrades slowly in buried anaerobic sediment. Given its continuous presence in the water column, due to its continual release to surface water, and given its rapid partitioning to sediments, benthic organisms are likely exposed to triclosan on a steady-state long-term basis. Triclosan bioavailability in sediments may partly be mitigated by its partitioning to the solids phase. Based on the very limited data available for benthic toxicity and for levels of triclosan in sediments, there seems to be a low concern for triclosan to cause harmful effects to benthic organisms.

Generally, there is a similar level of toxicity of triclosan to marine algae and invertebrates compared to chronic toxicity for freshwater organisms. However, triclosan is not expected to cause harm to marine organisms, due to low exposure in marine ecosystems. Exposure concentrations of triclosan are expected to be lower than those for freshwater ecosystems because a high dilution is expected at many of these sites. Therefore, further risk assessment specific to marine ecosystems was not conducted.

The main route of entry of triclosan into soil is through the spreading of WWTP biosolids to agricultural lands. Experimental evidence shows that triclosan is not persistent in aerobic soil (half-life ranging from 3 to 58 days) under laboratory conditions. However, when applied as part of biosolids, field dissipation half-lives are 50 to 258 days. Releases of triclosan to terrestrial ecosystems are not continuous like those in aquatic ecosystems, but rather episodic. Even though triclosan is not expected to build-up in soil, it is likely to be present in this environmental compartment long enough to result in chronic exposure for soil organisms. Triclosan reaching small water bodies through runoff following broadcast application of biosolids to soil could be of concern. Indeed, as

mentioned previously in this report, triclosan concentrations up to 258 ng/L have been measured in runoff one day after biosolids application, which is close to the aquatic PNEC of 376 ng/L.

Triclosan does not bioaccumulate in soil organisms to a great extent based on BCF/BAF values of 2.5–27 measured for earthworms and soybean plants. BAF values modelled for earthworms and shrews were approximately 95 and 4500 (assuming no metabolism), respectively. Toxicity of triclosan to soil organisms varies depending on the species; observed effects include reduction in growth and reproduction, at both low and high levels of exposure. Triclosan is slightly toxic to birds and of low toxicity to mammals on an acute and subchronic oral basis. Risk quotients of ≤0.37 were calculated for terrestrial organisms based on measured concentrations of triclosan in biosolids in Canada and measured half-lives in soil, as well as on effects data for the most sensitive organism (earthworm). Based on the toxicity levels (NOAEL of 750 mg/kg bw per day in mice), effects in wildlife are not likely to occur. Overall, there is a low concern for triclosan to cause harmful effects in terrestrial organisms.

Transformation products of triclosan have been characterized. Triclosan is a precursor to lower chlorinated dioxins, namely 2,7/2,8-DCDD. Given their probable transient state in aerobic environments and their low inherent toxicity, 2,7/2,8-DCDD are not likely to be of environmental concern. Other persistent polychlorinated dioxins, e.g., 1,2,8-TriCDD, 2,3,7-TriCDD and 1,2,3,8-TCDD, present in sediments as a result of the phototransformation of chlorinated triclosan derivatives formed during wastewater disinfection, could be of concern, depending on their inherent toxicity (Buth et al. 2010).

Another transformation product of triclosan in water–sediment systems and in soil is methyl-triclosan. Methyl-triclosan seems to be persistent in wastewater sludge, likely as bound residues due to the high organic carbon content in sludge, and it also seems persistent in anaerobic sediments. Limited data on effects to aquatic organisms indicated that methyl-triclosan is highly toxic. It is also highly bioaccumulative, with a reported BAF greater than 5000 in fish (Balmer et al. 2004). In a field study in which both triclosan and methyl-triclosan were measured in fish muscles, the latter was found at concentrations 90 times higher than triclosan (Boehmer et al. 2004). Methyl-triclosan is likely present in surface waters over wide areas associated with triclosan, since it is formed in WWTPs. Methyl-triclosan can reach soil through the application of biosolids to land. Triclosan and methyl-triclosan were measured in two field studies; triclosan and methyl-triclosan ranged from less than the MDL to 112 ng/L and from 3 to 17 ng/L, respectively, in Wascana Creek in Saskatchewan (Waiser et al. 2011). The risk quotient analysis for aquatic ecosystems suggests that methyl-triclosan does not reach levels that would be harmful to aquatic organisms, but would contribute somewhat to the total toxicity of triclosan and its transformation products. A risk quotient analysis could not be done for terrestrial ecosystems due to a lack of effects data on methyl-triclosan for terrestrial organisms.

4.6 Consideration of the Lines of Evidence and Uncertainties

Technical information for various lines of evidence for ecological risk of triclosan was examined to develop a conclusion as required under CEPA. A weight of evidence approach, where several lines of evidence are used in the decision-making in all portions of the risk assessment, as well as precaution (as appropriate) were applied. Uncertainties underlying the lines of evidence were identified and their impacts on the assessment were considered. Uncertainties often result from data gaps characteristic of limited or incomplete data sets, or lack of data; assumptions, grounded in sound science, have to be made to address the data gaps. This in turn can lead to an over or underestimation of risk, or impacts can remain unknown.

The fate of triclosan in the environment, its bioaccumulation potential, ecological effects, environmental levels and risk quotient analyses for key environmental compartments were described in the assessment report to characterize the potential of triclosan to cause adverse effects in the Canadian environment. Consideration of the lines of evidence in an integrated manner led to the risk assessment conclusion under CEPA (see sections 4.7 and 5.1).

To effectively assess the impacts of the identified uncertainties on the risk assessment of triclosan, qualitative criteria were used. This qualitative analysis served to determine the overall confidence in the decision-making process that led to the assessment conclusion. The level of uncertainty was judged based on the abundance and quality of data, and its suitability. The analysis also included consideration of the relevance of each line of evidence and the qualitative assessment of the weight for each line of evidence to determine their impact on the overall conclusion. Qualifiers used in the analysis ranged from low to high.

Lines of evidence in the assessment of triclosan, associated uncertainties, and their analysis using the qualitative criteria are presented in Table 4-14.

Table 4-14. Uncertainty characterization and analysis of the weight of evidence in the risk assessment of triclosan

Theme	Line of evidence	Level of uncertainty	Relevance in assessment[a]	Weight assigned[b]
Environmental Fate	Primary half-life in water	Moderate	Moderate	Moderate
Environmental Fate	Primary half-life in sediments	Moderate	Moderate	Moderate
Environmental Fate	Primary half-life in soil	Low	Moderate	Moderate to High
Environmental Fate	Impact of transformation product – methyl-triclosan	Moderate to high	Moderate	Low to moderate

Theme	Line of evidence	Level of uncertainty	Relevance in assessment[a]	Weight assigned[b]
Environmental Fate	Impact of transformation products – PCDDs	Moderate to high	Moderate	Low to moderate
Bioaccumulation	Bioconcentration in aquatic organisms	Moderate	High	Moderate to high
Bioaccumulation	Critical body residue analysis in aquatic organisms	Moderate	High	Moderate to high
Bioaccumulation	Bioaccumulation in terrestrial organisms	Moderate	Moderate	Moderate
Toxicity	Mode of toxic action/receptor binding/chemical activity	Low	High	High
Toxicity	PNEC aquatic	Low	High	High
Toxicity	PNEC soil	Moderate	High	Moderate to high
Toxicity	Mammalian and avian toxicity	Low	Low to moderate	Moderate
Environmental exposure	Exposure in water	Low	High	High
Environmental exposure	Exposure in soil	Moderate to high	Moderate to high	Moderate
Risk quotient analysis	RQ aquatic	Low	High	High
Risk quotient analysis	RQ soil	Moderate to high	High	Moderate

Abbreviations: PCDD, polychlorinated dibenzodioxin; PNEC, predicted no-effect concentration; RQ, risk quotient.
[a]Relevance refers to the impact of the evidence in the assessment, from a scientific and a regulatory point of view.
[b]Weight is assigned to each line of evidence and it is directly related to its relevance in the assessment and to its uncertainty.

The themes described in Table 4-14 are interconnected in how they contribute to the overall risk, where characteristics stemming from one contribute to or influence others. Some of these relationships are the nature of release; the residence time and fate of the substance which can affect levels of exposure; the transformation and degradation products or metabolites with toxic profiles that can add to exposure thorough co-exposure or similar mode of action; the bioaccumulation which can contribute to overall toxicity when internal toxicity thresholds levels are surpassed; and the specific modes of action that can trigger toxicity responses in numerous species at low exposure concentrations. Considerations of the relevance of these the themes for triclosan are presented in sections 4.2.6 (Fate), 4.3.3 (Bioaccumulation) and 4.4 (Ecological Effects), and summarized in section 4.5.4 (Characterization of Ecological Risk).

Although triclosan is unlikely to persist in the environment, based on a relatively robust set of degradation data, chronic exposure to triclosan is expected in water, as triclosan is continuously released from products used by consumers that get released down-the-drain. Measured concentrations of triclosan in water and in sediment samples across Canada indicate the ubiquitous and dispersive nature of this chemical. In soil, triclosan half-lives are known to be longer and, even though exposure in this medium results from intermittent rather than continuous releases, chronic exposure to triclosan is also expected for terrestrial organisms.

Triclosan transforms to methyl-triclosan and lower chlorinated dioxins in the environment. Limited data characterizing these compounds, including their potential for exposure in the Canadian environment, are available. Methyl-triclosan seems to be highly toxic to aquatic species and has a longer residence time in the environment than triclosan. Similarly to triclosan, chronic exposure is expected in the aquatic compartment; ultimately, organisms are expected to be co-exposed to both triclosan and methyl-triclosan. The overall impact is uncertain, but the risk associated with this co-exposure is likely somewhat higher than that from triclosan alone. Lower chlorinated dioxins formed from triclosan are generally characterized by low toxicity and tend to be transient in the environment.

Triclosan is a bioavailable chemical, readily taken up by organisms. It is highly toxic to aquatic organisms, as demonstrated by a wealth of reliable studies for numerous species. There is also convincing evidence, based on toxicity studies, fish kinetics studies, and QSAR modelling, that triclosan is a very reactive chemical with specific modes of action. These factors are highly relevant in the risk assessment of triclosan and demonstrate that triclosan causes adverse effects at low exposure concentrations. Despite its ability to rapidly biotransform in fish, triclosan likely accumulates sufficiently to result in body burdens that exceed thresholds of toxicity, based on robust calculations of fugacity capacity. This is also highly relevant to the overall impact of triclosan in aquatic ecosystems because under chronic exposure, even at low to moderate levels, bioconcentration of a reactive chemical like triclosan will lead to adverse effects in aquatic organisms.

Triclosan shows high toxicity in chronic studies with soil organisms, although data are available for only a few species and results are variable. It is uncertain whether triclosan accumulates to exceed internal toxicity thresholds in terrestrial organisms; fugacity capacity and critical body residue calculations are currently not possible to verify. Measured and modelled bioaccumulation (BAF) and bioconcentration (BCF) factors are low to moderate, except for one modelled BAF in mammals where metabolism was not considered, likely resulting in an overestimation.

Predicted no-effect concentrations (PNECs) were determined for the aquatic and soil compartments and serve as very important lines of evidence in the risk assessment of

triclosan. For the aquatic compartment, the fifth percentile value of a species sensitivity distribution, representative of the level that affects 5% of species, was used as the critical toxicity value, to obtain the PNEC value. This approach considers the inter-species variation in sensitivity, and is based on a broad range of data. Considering this and recognizing that the PNEC is based on no- and low-effects endpoints, it is not overly conservative. Due to a more limited data set for soil organisms, the most sensitive endpoint was chosen as the critical toxicity value to determine the PNEC in soil. Finally, there is evidence that shows that triclosan is moderately toxic to birds and mammals. Effects data for these organisms are limited but results are robust. Since low environmental exposure to triclosan is expected for birds and mammals, this line of evidence is overall less relevant in the risk assessment of triclosan.

There are numerous, reliable, and consistent measurements of triclosan in water bodies and in wastewater at WWTPs across Canada. As triclosan is present in biosolids from WWTPs, soil amendment of biosolids can result in exposure to soil organisms. Concentrations of triclosan in soils in Canada were modelled due to the lack of monitoring data. There are uncertainties associated with the modelling as well as the soil amendment practices across Canada.

Risk quotient analyses for aquatic and terrestrial ecosystems are of high importance in the risk assessment of triclosan. For the aquatic compartment, there is high confidence associated with the risk quotient analysis as both the exposure levels of triclosan in water and the PNEC for aquatic organisms have low uncertainty. This analysis indicated that the higher exposure levels of triclosan determined for aquatic ecosystems in Canada slightly exceed the PNEC; however, given the high potency of triclosan, precaution is needed when interpreting the aquatic risk quotient analysis in terms of the potential for triclosan to cause harm in the environment. For terrestrial ecosystems, more assumptions were used in the risk quotient analysis due to limitations in exposure data and in information on soil amendment practices. The impact of these conservative but realistic assumptions is uncertain, but may ultimately contribute to an overestimation of risk for the terrestrial ecosystems.

Overall, exposure in the aquatic compartment is of high importance in the risk assessment of triclosan. Therefore, a higher weight was assigned to those lines of evidence that describe continuous release of triclosan to the aquatic environment in Canada (Table 4-14). Given that triclosan is a very potent chemical acting through specific modes of action, low levels of exposure and bioconcentration can cause harm in organisms. The level of uncertainty associated with the key lines of evidence is viewed as low and therefore has little impact on the characterization of risk for triclosan.

4.7 Conclusion of Risk to the Environment

Triclosan is a man-made chemical that has been measured in numerous water bodies across Canada at concentrations in the range of ng/L. Though it tends to degrade

relatively quickly in the environment, it is always present in aquatic ecosystems near sources of release across the country because it is continuously released when products containing triclosan are disposed of or washed down-the-drain. Triclosan is a very potent chemical that can cause effects in organisms even at low exposure levels in the environment in the ng/L range. These effects include reduction in growth, reproduction and survival, as have been observed in studies with aquatic invertebrates and vertebrates, and terrestrial organisms including plants. Triclosan is known to have anti-microbial properties. There is evidence that triclosan can elicit effects associated with endocrine disruption at environmentally relevant concentrations. Triclosan is also known to accumulate in aquatic organisms to levels that can cause adverse effects.

While it is recognized that there are uncertainties in the exposure assessment of triclosan, a precautionary approach is required considering the potency of this biocide and its ubiquitous presence in the Canadian environment. In addition, the combined exposure from its transformation product, methyl-triclosan, and from chemicals such as triclocarban that have similar mode of action and use patterns, could also contribute to the potential for harm.

Considering the potency of triclosan and current exposure levels observed in the Canadian environment, it is concluded that a potential for harm exists from exposure to triclosan in aquatic ecosystems.

It is considered that sufficient robust data are available for the key lines of evidence that support the conclusion. Considering both the sources of uncertainty and overall confidence in the available data, it is anticipated that the above conclusion would not be highly sensitive to refinement if additional data were provided for the key lines of evidence. Additional data to elucidate other modes of toxic action or receptor mediated effects for triclosan and its transformation product methyl-triclosan would be beneficial for better understanding of the endocrine disruption potential of this substance.

5. Conclusion

5.1 Conclusion under CEPA

Based upon the adequacy of the MOEs between estimates of aggregated exposure to triclosan and critical effect levels, it is concluded that triclosan is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health, and thus does not meet the criteria under paragraph 64*(c)* of CEPA.

Considering all available lines of evidence presented in this assessment, there is risk of harm to organisms but not to the broader integrity of the environment from triclosan. It is concluded that triclosan meets the criteria under paragraph 64(*a*) of CEPA as it is entering or may enter 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. However, it is concluded that triclosan does not meet the criteria under paragraph 64(*b*) of CEPA as it is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, it is concluded that triclosan meets one or more the criteria set out in section 64 of CEPA.

Even though it is continuously present in the environment, triclosan has been determined not to meet the persistence criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA. Similarly, while triclosan accumulates in organisms to levels that can cause adverse effects, it does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

5.2 Status under PCPA

The Canadian registrants voluntarily discontinued the sale of pest control products containing triclosan. Consequently, as of December 31, 2014, triclosan is no longer registered in Canada as a pest control product. This assessment report does not include a conclusion under PCPA for these products.

References

Abduljilil K, Furness P, Johnson TN, Rostami-Hodjegan A, Soltani H. 2012. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy. Clin Pharmacokinet. 51(6):365-396.

Abudu N. 2011. Detection of prenatal drug abuse in meconium. Warde Medical Laboratory. 22(1). Available from: http://www.wardelab.com/22-1.html

ACD/Percepta [Prediction Module]. c1997-2012. Toronto (ON): Advanced Chemistry Development. [cited 2014 July]. Available from: www.acdlabs.com/products/percepta/

Addis T, Watanabe CK. 1916. The volume of urine in young healthy adults on a constant diet. J Biol Chem. 27:267-272.

Adolfsson-Erici M, Pettersson M, Parkkonen J, Sturve J. 2002. Triclosan, a commonly used bactericide found in human milk and in the aquatic environment in Sweden. Chemosphere. 46(9-10):1485-1489.

Aggarwal R, Deorari A, Paul VK. [date not specified]. Fluid and electrolyte management in term and preterm neonates [Internet]. New Delhi (IN): All India Institute of Medical Sciences, Department of Paediatrics, Division of Neonatology. [cited 2011 Sep]. Available from: www.newbornwhocc.org/pdf/fluid_electrolytes_bablance.pdf

Agying-Birikorang S, Miller M, O'Connor GA. 2010. Retention-release characteristics of triclocarban and triclosan in biosolids, soils, and biosolids-amended soils. Environ Toxicol Chem. 29(9):1925-1933.

Aiello AE, Larson EL, Levy SBl. 2007. Consumer antibacterial soaps: effective or just risky? Clin Infect Dis. 45(Suppl 2):S137-S147.

Alcorn J, McNamara PJ. 2002. Ontogeny of hepatic and renal systemic clearance pathways in infants, part I. Clin Pharmacokinet. 41(12):959-998.

Allmyr M, Adolfsson-Erici M, McLachlan MS, Sandborgh-Englund G. 2006. Triclosan in plasma and milk from Swedish nursing mothers and their exposure via personal care products. Sci Total Environ. 372:87-93.

Allmyr M, Panagiotidis G, Sparve E, Diczfalusy U, Sandborgh-Englund G. 2009. Human exposure to triclosan via toothpaste does not change CYP3A4 activity or plasma concentrations of thyroid hormones. Basic Clin Pharmacol Toxicol. 105:339-344.

Amorim MJB, Oliveira E, Soares AMVM, Scott-Fordsmand JJ. 2010. Predicted no effect concentration (PNEC) for triclosan to terrestrial species (invertebrates and plants). Environ Int. 36:338-343.

Andresen JA, Muir D, Ueno D, Darling C, Theobald N, Bester K. 2007. Emerging pollutants in the North Sea in comparison to Lake Ontario, Canada, data. Environ Toxicol Chem. 26(6):1081-1089.

Anger CT, Sueper C, Blumentritt DJ, McNeill K, Engstrom DR, Engstrom DR, Arnold WA. 2013. Quantification of triclosan, chlorinated triclosan derivatives, and their dioxin photoproducts in lacustrine sediment cores. Envrion Sci Technol. 47:1833-1843.

[AOPWIN] Atmospheric Oxidation Program for Windows [Estimation Model]. 2008. Version 1.92. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. [cited 2011 Nov]. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Apedaile E. 2001. A perspective on biosolids management. Can J Infect Dis Med Microbiol. 12(4):202-204.

Aranami K, Readman JW. 2007. Photolytic degradation of triclosan in freshwater and seawater. Chemosphere. 66:1052-1056.

Arbuckle TE, Fraser WD, Fisher M, Davis K, Liang CL, Lupien N, Bastien S, Velez MP, von Dadelszen P, Hemmings DG, et al. 2013. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr Perinat Epidemiol. 27(4):415-425. doi: 10.1111/ppe.12061

Arbuckle TE, Marro L, Davis K, Fisher M, Ayotte P, Bélanger P, Dumas P, LeBlanc A, Bérubé R, Gaudreau E, et al. 2015a. Exposure to free and conjugated forms of bisphenol A and triclosan among pregnant women in the MIREC cohort. Environ Health Perspect. 123:277-284.

Arbuckle TE, Weiss L, Fisher M, Hauser R, Dumas P, Bérubé R, Neisa A, LeBlanc A, Ayotte P, Calafat A, et al. 2015b. Maternal and infant exposure to phenols as measured in multiple matrices. Sci Total Environ. 508:575-584.

Arnot J (Arnot Research and Consulting). 2015. A review of the bioaccumulation of triclosan in fish and other species. Final report. Unpublished report prepared for BASF SE. 32 p.

Arnot J (Arnot Research and Consulting). 2016. Estimating bioconcentration factors for triclosan using in vitro biotransformation rate data from catfish liver. Final report. Unpublished report prepared for BASF SE. 19 p.

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.

Arnot JA, Gobas FAPC. 2006. A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms. Environ Rev. 14:257-297.

Arnot JA, Mackay D, Bonnell M. 2008. Estimating metabolic biotransformation rates in fish from laboratory data. Environ Toxicol Chem. 27(2):341-351.

Asimakopoulos A, Thomaidis NS, Kannan K. 2014. Widespread occurrence of bisphenol A diglycidyl ethers, p-hydroxybenzoic acid esters (parabens), benzophenone type-UV filters, triclosan, and triclocarban in human urine from Athens, Greece. Sci Total Environ. 470-471:1243-1249.

Axelstad M, Boberg J, Vinggaard AM, Christiansen S, Hass U. 2013. Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and in directly exposed offspring. Food Chem Toxicol. 59:534-540.

Azzouz A, Jurado-Sánchez B, Souhail B, Ballesteros E. 2011. Simultaneous determination of 20 pharmacologically active substances in cow's milk, goat's milk, and human breast milk by gas chromatography–mass spectrometry. J Agric Food Chem. 59:5125–5132.

Balmer ME, Poiger T, Droz C, Romanin K, Bergqvist PA, Müller MD, Buser HR. 2004. Occurrence of methyl triclosan, a transformation product of the bactericide triclosan, in fish from various lakes in Switzerland. Environ Sci Technol. 38(2):390-395.

Barnes KK, Kolpin DW, Furlong ET, Zaugg SD, Meyer MT, Barber LB. 2008. A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States. I. Groundwater. Sci Total Environ. 402(2-3):192-200.

Barr DB, Wilder LC, Caudill SP, Gonzalez AJ, Needham LL, Pirkle JL. 2005. Urinary creatinine concentrations in the US population: Implications for urinary biologic monitoring measurements. Environ Health Perspect. 113(2):192-200.

[BASL4] Biosolid-Amended Soil: Level IV Model. 2011. Version 2. Peterborough (ON): Trent University, Canadian Centre for Environmental Modelling and Chemistry (CCEMC). Prepared for Environment Canada by CCEMC (Contract No.: K8A43-10-0015).

Belanger S, Carr G, Capdevielle M, DeLeo P, Pawlowski S, Ayala-Fierro F, Montemayor B. 2013. SSD analysis of high quality triclosan chronic ecotoxicity data – roles of data quality and quantity to derive appropriate PNECs. Presentation at the 34th annual meeting of the Society for Environmental Toxicology and Chemistry (SETAC) – North America, Nashville, USA, 17-21 November 2013.

Bertelsen RJ, Longnecker MP, Løvik M, Calafat AM, Carlsen K-H, London SJ, Lødrup Carlsen KC. 2013. Triclosan exposure and allergic sensitization in Norwegian children. Allergy. 68:84-91.

Bester K. 2003. Triclosan in a sewage treatment process—balances and monitoring data. Water Res. 37(16):3891-3896.

Bester K. 2005. Fate of triclosan and triclosan-methyl in sewage treatment plants and surface waters. Arch Environ Contam Toxicol. 49(1):9-17.

Binelli A, Cogni D, Parolini M, Riva C, Provini A. 2009. *In vivo* experiments for the evaluation of genotoxic and cytotoxic effects of triclosan in zebra mussel hemocytes. Aquat Toxicol. 91:238-244.

Biomonitoring California. 2013. Maternal and Infant Environmental Exposure Project. Available from: http://www.biomonitoring.ca.gov/results/chemical/64

Black JG, Howes D. 1975. Percutaneous absorption of triclosan from toilet preparations. J Soc Cosmet Chem. 26:205-215.

Blair BD, Crago JP, Hedman CJ, Klaper RD. 2013. Pharmaceuticals and personal care products found in the Great Lakes above concentrations of environmental concern. Chemosphere. 93(9):2116-2123.

Boehmer W, Ruedel H, Wenzel A, Scroeter-Kermani C. 2004. Retrospective monitoring of triclosan and methyl-triclosan in fish: results from the German Environmental Specimen Bank. Organohalogen Compd. 66:1516-1521.

Borgmann U, Bennie DT, Ball AL, Palabrica V. 2007. Effect of a mixture of seven pharmaceuticals on *Hyalella azteca* over multiple generations. Chemosphere. 66(7):1278-1283.

Böttcher J. 1991. Report on the bioaccumulation test of FAT-80’023/Q. Test No. G 069 09 [Place of Publication unknown]: Ciba-Geigy Ltd., D&C Product Ecology, FC 6.13. 26 p.

Bound JP, Voulvoulis N. 2005. Household disposal of pharmaceuticals as a pathway for aquatic contamination in the United Kingdom. Environ Health Perspect. 113(12):1705-1711.

Bourget C, Femino A, Franz C, Hastings S, Longcope C. 1987. The effects of l-thyroxine and dexamethasone on steroid dynamics in male cynomologous monkeys. J Steroid Biochem. 28(5):575-579.

Braid JJ, Wale MC. 2002. The antibacterial activity of triclosan-impregnated storage boxes against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus cereus* and *Shewanella putrefaciens* in conditions simulating domestic use. J Antimicrob Chemother. 49(1):87-94.

Brausch JM, Rand GM. 2011. A review of personal care products in the aquatic environment: environmental concentrations and toxicity. Chemosphere. 82(11):1518-1532.

Brown J, Bernot MJ, Bernot R. 2012. The influence of TCS on the growth and behavior of the freshwater snail, *Physa acuta*. J Environ Sci Health. A 47:1626-1630.

Büche C, Fort DJ, Navarro LT, Peter R, Hauk A, Inauen J. 2009. Effects of triclosan on seedling emergence and growth. Poster presented at the 19th annual meeting of the Society for Environmental Toxicology and Chemistry (SETAC) – Europe, Göteborg, Sweden, 31 May – 4 June 2009.

Burkhard L, Arnot JA, Embry MR, Farley KJ, Hoke RA, Kitano M, Leslie HA, Lotufo GR, Parkerton TF, Sappington KG, et al. 2012. Comparing laboratory and field measured bioaccumulation endpoints. Integr Environ Assess Manag. 8(1):17-31.

Buth JM, Grandbois M, Vikesland PJ, McNeill K, Arnold WA. 2009. Aquatic photochemistry of chlorinated triclosan derivatives: potential source of polychlorodibenzo-*p*-dioxins. Environ Toxicol Chem. 28(12):2555-2563.

Buth JM, Steen PO, Sueper C, Blumentritt D, Vikesland PJ, Arnold WA, McNeill K. 2010. Dioxin photoproducts of triclosan and its chlorinated derivatives in sediment cores. Environ Sci Technol. 44(12):4545-4551.

Cahill T. 2008. Multispecies Model, version 1.0. Glendale (AZ): Arizona State University, Department of Integrated Natural Sciences.

Calafat A, Weuve J, Ye X, Jia L, Hu H, Ringer S, Huttner K, Hauser R. 2009. Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. Environ Health Perspect 117(4):639-644.

Canada. 1985. *Food and Drugs Act*, R.S.C. 1985, c. F-27. Available from: www.canlii.org/ca/sta/f-27/whole.html

Canada. 1990. Polychlorinated dibenzodioxins and polychlorinated dibenzofurans (Priority substances list assessment report no. 1) [Internet]. Ottawa (ON): Environment Canada; Health Canada. Available from: www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/dioxins_furans_dioxines_furannes/dioxins_furans_e.pdf

Canada. 1999. *Canadian Environmental Protection Act, 1999*. S.C., 1999, c. 33. Canada Gazette, Part III, vol. 22, no. 3. Available from: www.gazette.gc.ca/archives/p3/1999/g3-02203.pdf

Canada. 2001. Chloroform (Priority substances list assessment report) [Internet]. Ottawa (ON): Environment Canada; Health Canada. Available from: www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/chloroform/chloroform-eng.pdf

Canada. 2002. *Pest Control Products Act, 2002*. S.C., 2002, c. 28. Available from: www.gazette.gc.ca/archives/p3/2003/g3-02503.pdf

Canada. 2007. *Food and Drugs Regulations: Cosmetic Regulations*, C.R.C., c. 869. Available from: http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._869/FullText.html

Canada. 2012. *Fisheries Act: Wastewater Systems Effluent Regulations*. P.C. 2012-942, 2012 June 28, SOR/2012-139. Available from: http://laws-lois.justice.gc.ca/eng/regulations/sor-2012-139/index.html

Canada, Environment Canada. 1995. Toxic Substances Management Policy. Ottawa (ON): Environment Canada. 2004 reprint of original 1995 ed. Available from: http://www.publications.gc.ca/site/eng/305088/publication.html

Canada, Dept. of the Environment. 2013. Canadian Environmental Protection Act, 1999: Notice with respect to triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol). Canada Gazette, Part I, vol. 147, no. 6, p. 175–188. Available from: http://gazette.gc.ca/rp-pr/p1/2013/2013-02-09/html/notice-avis-eng.html#d101

Canosa P, Rodriguez I, Rubi E, Cela R. 2007a. Determination of parabens and triclosan in indoor dust using matrix solid-phase dispersion and gas chromatography with tandem mass spectrometry. Anal Chem. 79(4):1675-1681.

Canosa P, Pérez-Palacios D, Garrido-López A, Tena M, Rodríguez I, Rubi E, Cela R. 2007b. Pressurized liquid extraction with in-cell clean-up followed by gas chromatography–tandem mass spectrometry for the selective determination of parabens and triclosan in indoor dust. J Chromatogr A. 1161:105-112.

Capdevielle M, Egmond RV, Whelan M, Versteeg D, Hofmann-Kamensky M, Inauen J, Cunningham V, Woltering D. 2008. Consideration of exposure and species sensitivity of triclosan in the freshwater environment. Integr Environ Assess Manag. 4(1):15-23.

Carey DE, McNamara PJ. 2015. The impact of triclosan on the spread of antibiotic resistance in the environment. Front Microbiol. 5:780.

Caudal F, Grimault D, Sioufi A. 1974. Urinary excretion (free and glucuronide) in man after topical application of CGP. 433 cream. C.R.B. R 4/1974. Ciba-Geigy Biopharmaceutical Research Center. [cited in SCCP 2009].

[CCME] Canadian Council of Ministers of the Environment. 2007. A protocol for the derivation of water quality guidelines for the protection of aquatic life. Winnipeg (MB): Canadian Council of Ministers of the Environment.

[CCME] Canadian Council of Ministers of the Environment. 2010a. Emerging substances of concern in biosolids: concentrations and effects of treatment processes. Final report—Field sampling program; CCME Project No. 447-2009. PN 1448. Winnipeg (MB): Canadian Council of Ministers of the Environment.

[CCME] Canadian Council of Ministers of the Environment. 2010b. A review of the current Canadian legislative framework for wastewater biosolids. PN 1446. Winnipeg (MB): Canadian Council of Ministers of the Environment.

[CCME] Canadian Council of Ministers of the Environment. 2013. Determination of hazardous concentrations with species sensitivity distributions: SSD Master, Version 3.0 (unpublished). Available from National Guidelines and Standards Office, Environment Canada, Gatineau (email: cegg-rcqe@ec.gc.ca).

[CDC] Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals: Updated Tables, February 2015. Atlanta (GA): Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Available from: http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf

Chen F, Ying G-G, Kong L-X, Wang L, Zhao J-L, Zhou L-J, Zhang L-J. 2011. Distribution and accumulation of endocrine-disrupting chemicals and pharmaceuticals in wastewater irrigated soils in Hebei, China. Environ Pollut. 159:1490-1498.

Chen F, Ying G-G, Ma Y-B, Chen Z-F, Lai H-J, Peng F-J. 2014. Field dissipation and risk assessment of typical personal care products TCC, TCS, AHTN and HHCB in biosolid-amended soils. Sci Total Environ. 470-471:1078-1086.

Chen M, Tang R, Fu G, Xu B, Zhu P, Qiao S, Chen X, Xu B, Qin Y, Lu C, et al. 2013. Association of exposure to phenols and idiopathic male infertility. J Hazard Mater. 250-251:115-121.

Chen M, Zhu P, Xu B, Zhao R, Qiao S, Chen X, Tang R, Wu D, Song L, Wang S, Xia Y, Wang X. 2012. Determination of nine environmental phenols in urine by ultra-high-performance liquid chromatography-tandem mass spectrometry. J Anal Toxicol. 36:608-615.

Cheung C, Akiyama TE, Ward JM, Nicol CJ, Feigenbaum L, Vinson C, Gonzalez FJ. 2004. Diminished hepatocellular proliferation in mice humanized for the nuclear receptor peroxisome proliferator-activated receptor-α. Cancer Res. 64:3849-3854.

Chiaia-Hernandez AC, Ashauer R, Moest M, Hollingshaus T, Jeon J, Spaak P, Hollender J. 2013 Bioconcentration of organic contaminants in *Daphnia* resting eggs. Envrion Sci Technol. 47:10667-10675

Choksi NY, Jahnke GD, St Hilaire C, Shelby M. 2003. Role of thyroid hormones in human and laboratory animal reproductive health. Birth Defects Res B Dev Reprod Toxicol. 68(6):479-491.

Chu S, Metcalfe CD. 2007. Simultaneous determination of triclocarban and triclosan in municipal biosolids by liquid chromatography tandem mass spectrometry. J Chromatogr A 1164:212-218.

Chun Hong HS, Kurz ND, Wolf T, De Salva SJ. 1976. Chemical analysis of hexachlorophene (HCP), tribromsalan (TBS), triclosan (DP-300), triclocarban (TCC) and cloflucarban (CF3) in tissues, blood and urine of animals and humans. Oral presentation at the March 16, 1976, meeting of the Society of Toxicology in Atlanta, GA. [cited in SCCP 2009].

Ciba-Geigy. 1974. 21-day inhalation study on the rat. Basel (CH): Ciba-Geigy Ltd.

Ciba-Geigy. 1976a. Investigations of percutaneous absorption in the rat and the rabbit. GP 41 353 (Triclosan). Basel (CH): Ciba-Geigy Ltd. [cited in SCCP 2009].

Ciba-Geigy. 1976b. Isolation and identification of the main metabolites in the blood of the beagle dog and the baboon and in the urine of the latter following oral administration of ^{14}C-labelled triclosan (Report No. B 14/1976). Basel (CH): Ciba-Geigy Ltd. [cited in SCCP 2009].

Ciniglia C, Cascone C, Lo Giudice R, Pinto G, Pollio A. 2005. Application of methods for assessing the geno- and cytotoxicity of triclosan to *C. ehrenbergii*. J Hazard Mater. 122:227-232.

Clayton EM, Todd M, Dowd JB, Aiello AE. 2011. The impact of bisphenol A and triclosan on immune parameters in the U.S. population, NHANES 2003–2006. Environ Health Perspect 119(3):390–396.

[CMA] Chemical Manufacturers' Association (US). 1990. Antimicrobial exposure assessment study. Study No. Q626. BCH No. 03691. Washington (DC): Chemical Manufacturers' Association.

Cohen SZ, Creeger SM, Carsel RF, Enfield CG. 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. In: Krueger RF, Seiber JN, editors. Treatment and disposal of pesticide wastes. Washington (DC): American Chemical Society. ACS Symp Ser 259:297–325.

Cole EC, Addison RM, Rubino JR, Leese KE, Dulaney PD, Newell MS, Wilkins J, Gaber DJ, Wineinger T, Criger DA. 2003. Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. J Appl Microbiol. 95(4):664-676.

Conestoga-Rovers and Associates. 2015. Compiling and interpreting chemical data from municipal solid waste landfill leachate. Report Number 10. Unpublished report prepared for Environment Canada. 318 p.

Coogan MA, La Point TW. 2008. Snail bioaccumulation of triclocarban, triclosan, and methyl-triclosan in a North Texas, USA, stream affected by wastewater treatment plant runoff. Environ Toxicol Chem 27(8):1788–1793.

Coogan MA, Edziyie RE, La Point TW, Venables BJ. 2007. Algal bioaccumulation of triclocarban, triclosan, and methyl-triclosan in a North Texas wastewater treatment plant receiving stream. Chemosphere 67:1911–1918.

Cooke GM. 2014. Biomonitoring of human fetal exposure to environmental chemicals in early pregnancy. Journal of Toxicology and Environmental Health, Part B. 17:205-224.

Cottell A, Denyer SP, Hanlon GW, Ochs D, Maillard JY. 2009. Triclosan-tolerant bacteria: changes in susceptibility to antibiotics. J Hosp Infect. 72(1):71-76.

Crofton KM, Paul KB, DeVito MJ, Hedge JM. 2007. Short-term *in vivo* exposure to the water contaminant triclosan: evidence for disruption of thyroxine. Environ Toxicol Pharmacol 24:194–197.

Cullinan MP, Palmer JE, Carle AD, West MJ, Seymour GJ. 2012. Long term use of triclosan toothpaste and thyroid function. *Science of the Total Environment*. 416:75-79.

Cullinan MP, Bird PS, Heng N, West MJ, Seymore GJ. 2013. No evidence of triclosan-resistant bacteria following long-term use of triclosan-containing toothpaste. J Periodont Res. doi: 10.1111/jre.12098.

Davison JM, Noble MCB. 1981. Serial changes in 24 hour creatinine clearance during normal menstrual cycles and the first trimester of pregnancy. British Journal of Obstetrics and Gynaecology. 88:10-17.

Dayan A. 2007. Risk assessment of triclosan [Irgasan®] in human breast milk. Food Chem Toxicol 45:125–129.

DeLorenzo ME, Fleming J. 2008. Individual and mixture effects of selected pharmaceuticals and personal care products on the marine phytoplankton species *Dunaliella tertiolecta*. Arch Environ Contam Toxicol 54:203–210.

Den Hond E, Paulussen M, Geens T, Bruckers L, Baeyens W, David F, Dumont E, Loots I, Morrens B, Nemery de Bellevaux B, et al. 2013. Biomarkers of human exposure to personal care products: Results from the Flemish Environment and Health Study (FLEHS 2007-2011). Sci Total Environ. 463-464:102-110.

Dimitrov S, Dimitrova N, Walker J, Veith G, Mekenyan O. 2002. Predicting bioconcentration potential of highly hydrophobic chemicals. Effect of molecular size. Pure Appl Chem 74(10):1823–1830.

Dimitrov S, Dimitrova N, Parkerton T, Comber M, Bonnell M, Mekenyan O. 2005. Baseline model for identifying the bioaccumulation potential of chemicals. SAR QSAR Environ Res 16(6):531–554.

[DPD] Drug Product Database [database on the Internet]. 2016. Ottawa (ON): Health Canada. [cited 2016]. Available from: http://webprod.hc-sc.gc.ca/dpd-bdpp/start-debuter.do?lang=eng

Drury B, Scott J, Rosi-Marshall EJ, Kelly JJ. 2013. Triclosan exposure increases triclosan resistance and influences taxonomic composition of benthic bacterial communities. Environ Sci Technol 47(15):8923-8930.

Dussault EB, Balakrishnan VK, Sverko E, Solomon KR, Sibley PK. 2008. Toxicity of human pharmaceuticals and personal care products to benthic invertebrates. Environ Toxicol Chem 27(2):425–432.

[ECHA] European Chemicals Agency. c2007-2014. Registered Substances database. Search results for CAS RN [3380-34-5]. Helsinki (FI): ECHA. [updated 2012 Nov 27; cited 2014 August]. Available from: www.echa.europa.eu/information-on-chemicals/registered-substances

[ECHA] European Chemicals Agency. 2008. Guidance on information requirements and chemical safety assessment. Chapter R.11: PBT assessment. May 2008. Guidance for the implementation of REACH. Helsinki (FI): European Chemicals Agency.

Edwards M, Topp E, Metcalfe CD, Li H, Gottschall N, Bolton P, Curnoe W, Payne M, Beck A, Kleywegt S, Lapen DR. 2009. Pharmaceuticals and personal care products in tile drainage following surface spreading and injection of dewatered municipal biosolids to an agricultural field. Sci Total Environ. 407:4220-4230.

Engel LS, Buckley JP, Yang G, Liao LM, Satagopan J, Calafat AM, Mattews, CE, Cai Q, Ji B, Cai H, Engel SM, Wolff MS, Rothman N, Zheng W, Xiang Y, Shu X, Gao Y, Chow W. 2014. Predictor and variability of repeat measurements of urinary phenols and parabens in a cohort of Shanghai women and men. Environ Health Persp. 122 (7): 733-740.

Environment Canada. 2006. Guidance for conducting ecological assessments under CEPA, 1999: Science resource technical series, Technical guidance module: Sludge amendment. Working document. Gatineau (QC): Environment Canada, Ecological Assessment Division.

Environment Canada. 2007. 2007 municipal water use report—municipal water use, 2004 statistics. Gatineau (QC) Environment Canada. Available from: www.ec.gc.ca/Publications/default.asp?lang=En&xml=8D951F7A-3866-47AA-98D6-1C49AB04E1BA

Environment Canada. 2013. Data for triclosan collected under Canadian Environmental Protection Act, 1999, Section 71: Notice with respect to triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol). Data prepared by: Environment Canada, Existing Substances Program.

Erickson RJ, McKim JM, Lien GJ, Hoffman AD, Batterman SL. 2006a. Uptake and elimination of ionizable organic chemicals at fish gills: I—Model formulation, parameterization, and behavior. Environ Toxicol Chem 25(6):1512–1521.

Erickson RJ, McKim JM, Lien GJ, Hoffman AD, Batterman SL. 2006b. Uptake and elimination of ionizable organic chemicals at fish gills: II—Observed and predicted effects of pH, alkalinity, and chemical properties. Environ Toxicol Chem 25(6):1522–1532.

Escher BI, Ashauer R, Dyer S, Hermens JLM, Lee J-H, Leslie HA, Mayer P, Meador JP, Warne MSJ. 2011. Crucial role of mechanisms and modes of toxic action for understanding tissue residue toxicity and internal effect concentrations of organic chemicals. Integrated Environ Assess Manage 7(1): 28-49.

European Commission. 2002. Opinion on triclosan resistance: Adopted by the Scientific Steering Committee at its meeting of 27–28 June 2002. European Commission, Health & Consumer Protection Directorate-General. Available from: http://ec.europa.eu/food/fs/sc/ssc/out269_en.pdf

European Parliament. 2014. Notices from European Union institutions, bodies, offices and agencies. Written questions with answers. Official Journal of the European Union. 2014/C 11 E/01. Available from: (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2014:040E:FULL:EN:PDF

Fair PA, Lee H-B, Adams J, Darling C, Pacepavicius G, Alaee M, Bossart GD, Henry N, Muir D. 2009. Occurrence of triclosan in plasma of wild Atlantic bottlenose dolphins (*Tursiops truncatus*) and their environment. Environ Pollut. 157:2248–2254.

Fan X, Kubwabo C, Rasmussen P, Jones-Otazo H. 2010. Simultaneous quantitation of parabens, triclosan, and methyl triclosan in indoor house dust using solid phase extraction and gas chromatography–mass spectrometry. J Environ Monit. 12:1891–1897.

Federle TW, Kaiser SK, Nuck BA. 2002. Fate and effects of triclosan in activated sludge. Environ Toxicol Chem. 21(7):1330–1337.

Field JA, Sierra-Alvarez R. 2008. Microbial degradation of chlorinated dioxins. Chemosphere. 71:1005–1018.

Fisher DA, Brown RS. 2000. Thyroid physiology in the perinatal period and during childhood. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia (PA): Lippincott, Williams & Wilkins. p. 959–972.

Flaherty CM, Dodson SI. 2005. Effects of pharmaceuticals on *Daphnia* survival, growth, and reproduction. Chemosphere. 61(2):200–207.

Foran CM, Bennett ER, Benson WH. 2000. Developmental evaluation of a potential non-steroidal estrogen: triclosan. Mar Environ Res. 50:153–156.

Fort DJ, Rogers RL, Gorsuch JW, Navarro LT, Peter R, Plautz JR. 2010. Triclosan and anuran metamorphosis: no effect on thyroid-mediated metamorphosis in *Xenopus laevis*. Toxicol Sci. 113:392–400.

Fort DJ, Mathis MB, Hanson W, Fort CE, Navarro LT, Peter R, Buche C, Unger S, Pawlowski S, Plautzk JR. 2011. Triclosan and thyroid-mediated metamorphosis in anurans: differentiating growth effects from thyroid-driven metamorphosis in *Xenopus laevis*. Toxicol Sci. 121:292–302.

Fraker SL, Smith GR. 2004. Direct and interactive effects of ecologically relevant concentrations of organic wastewater contaminants on *Rana pipiens* tadpoles. Environ Toxicol. 19(3):250–256.

Francis WJA. 1960. Disturbances of bladder function in relation to pregnancy. The Journal of Obstetrics and Gynaecology of the British Empire. LXVII(3):353-366.

Franz S, Altenburger R, Heilmeier H, Schmitt-Jansen M. 2008. What contributes to the sensitivity of microalgae to triclosan? Aquatic Toxicol. 90: 102–108.

Frederiksen H, Aksglaede L, Sorensen K, Nielsen O, Main KM, Skakkebaek NE, Juul A, Andersson A-M. 2013a. Bisphenol A and other phenols in urine from Danish children and adolescents analyzed by isotope diluted TurboFlow-LC–MS/MS. Int J Hyg Environ Health. 216:710-720.

Frederiksen H, Sogaard Nielsen J, Aeroe Morck T, Winton Hansen P, Fangel Jensen J, Nielsen O, Andersson AM, Knudsen LE. 2013b. Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother-child pairs. Int J Hyg Environ Health. 216:772-783.

Fuchsman P, Lyndall J, Bock M, Lauren D, Barber T, Leigh K, Perruchon E, Capdevielle M. 2010. Terrestrial ecological risk evaluation for triclosan in land-applied biosolids. Integr Environ Assess Manag. 6:405-418.

Fulton BA, Brain RA, Usenko S, Back JA, King RS, Brooks BW. 2009. Influence of nitrogen and phosophorous concentrations and ratios on *Lemna gibba* growth responses to triclosan in laboratory and field experiments. Environ Toxicol Chem. 28:2610-2621.

Gatidou G, Vassalou E, Thomaidis NS. 2010. Bioconcentration of selected endocrine disrupting compounds in the Mediterranean mussel, *Mytilus galloprovincialis*. Mar Pollut Bull. 60:2111-2116.

Geens T, Roosens L, Neels H, Covaci A. 2009. Assessment of human exposure to bisphenol-A, triclosan and tetrabromobisphenol-A through indoor dust intake in Belgium. Chemosphere 76:755–760.

Glinoer D. 1997. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 18(3):404–433.

Gonzalo-Lumbreras R, Sanz-Landaluze J, Guinea J, Cámara C. Miniaturized extraction methods of triclosan from aqueous and fish roe samples. Bioconcentration studies in zebrafish larvae (*Danio rerio*). 2012. Anal Bioanal Chem 403: 927-937.

Gottschall N, Topp E, Metcalfe C, Edwards M, Payne M, kleywegt S, Russell P, Lapen DR. 2012. Pharmaceutical and personal care products in groundwater, subsurface

drainage, soil, and wheat grain, following a high single application of municipal biosolids to a field. Chemosphere. 87:194-203

Greyshock AE, Vikesland PJ. 2006. Triclosan reactivity in chloraminated waters. Environ Sci Technol 40(8):2615–2622.

Guerra P, Kim M, Shah A, Alaee M, Smyth SA. 2014. Occurrence and fate of antibiotic, analgesic/anti-inflammatory, and antifungal compounds in five waste water treatment processes. Sci Total Envrion. 473-474:235-243

Guiliano CA and Rybak MJ. 2015. Efficacy triclosan as an antimicrobial hand soap and its potential impact on antimicrobial resistance: a focused review. Pharmacotherapy. 35(3):328-336.

Gustafson DI. 1989. Groundwater ubiquity score: a simple method for assessing pesticide leachability. Environ Toxicol Chem 8:339–357.

Haddow JE, Knight GJ, Palomaki GE, Neveux LM, Chilmonczyk BA. 1994. Replacing creatinine measurements with specific gravity values to adjust urine cotinine concentrations. Clin Chem. 40(4):562-564.

Haraszthy VI, Sreenivasan PK, Zambon JJ. 2014. Community-level assessment of dental plaque bacteria susceptibility to triclosan over 19 years. BMC Oral Health. 14:61.

Health Canada. 2005. Dioxins and furans (It's Your Health factsheet). [published 2001 Nov; updated 2005 Sep]. Ottawa (ON): Health Canada. Available from: www.hc-sc.gc.ca/hl-vs/alt_formats/pacrb-dgapcr/pdf/iyh-vsv/environ/dioxin-eng.pdf

Health Canada. 2006. Antiseptic skin cleansers [Internet]. [cited 2011 Sep]. Available from: www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodnatur/mono_antiseptic_antiseptique-eng.pdf

Health Canada. 2011. The cosmetic ingredient hotlist—March 2011 [Internet]. Ottawa (ON): Health Canada, Consumer Product Safety. [cited 2011 Dec]. Available from: www.hc-sc.gc.ca/cps-spc/cosmet-person/indust/hot-list-critique/index-eng.php

Health Canada. 2013. Second report on human biomonitoring of environmental chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 2 (2009-2011). Ottawa (ON): Health Canada. Available from: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/chms-ecms-cycle2/index-eng.php

Health Canada 2014. Pesticide Product Infromation Database. Available from http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php

Health Canada. 2015. Third report on human biomonitoring of environmental chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 3 (2012-2013). Ottawa (ON): Health Canada. Available from http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/chms-ecms-cycle3/index-eng.php

Heath RJ, Rubin JR, Holland DR, Zhang E, Snow ME, Rock CO. 1999. Mechanism of triclosan inhibition of bacterial fatty acid synthesis. J Biol Chem 16:11 110–11 114.

Heath RJ, Yu YT, Shapiro MA, Olsen E, Rock CO. 1998. Broad spectrum antimicrobial biocides target the FabI component of fatty acid synthesis. J Biol Chem. 273(46):30316-30320.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2008. Version 3.20. 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

Higby K, Suiter CR, Phelps JY, Siler-Khodr T, Langer O. 1994. Normal values of urinary albumin and total protein excretion during pregnancy. Am J Obstet Gynecol. 171:984-989.

Hoang TT, Schweizer HP. 1999. Characterization of *Pseudomonas aeruginosa* enoyl–acyl carrier protein reductase (Fab I): a target for the antimicrobial triclosan and its role in acylated homoserine lactone synthesis. J Bacteriol. 181:5489–5497.

Hogg TJ, Weiterman G, Tollefson LC. 2007. Effluent irrigation: Saskatchewan perspective. Outlook (SK): Agriculture and Agri-Food Canada, Canada–Saskatchewan Irrigation Diversification Centre. [cited 21 Jan 2011]. Available from: www4.agr.gc.ca/resources/prod/doc/pfra-arap/csidc-crdi/pdf/effluent_eng.pdf

[HSDB] Hazardous Substances Data Bank [database on the Internet]. 1983– . Bethesda (MD): National Library of Medicine (US). [cited 2007 Nov 9]. Available from: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

Hua W, Bennett ER, Letcher RJ. 2005. Triclosan in waste and surface waters from the upper Detroit River by liquid chromatography–electrospray–tandem quadrupole mass spectrometry. Environ Int 31:621–630.

Huber DR, Blount BC, Mage DT, Letkiewicz FJ, Kumar A, Allen RH. 2011. Estimating perchlorate exposure from food and tap water based on US biomonitoring and occurrence data. J Expo Sci Environ Epidemiol. 21:395-407.

Hwang J, Suh SS, Chang M, Park SY, Ryu TK, Lee S, Lee TK. 2014. Effects of triclosan on reproductive parameters and embryonic development of sea urchin, *Stronylocentrotus nudus*. Ecotox Environ Safety. 100:148-152.

[ICRP] International Commission on Radiological Protection. 2003. Basic anatomical and physiological data for use in radiological protection: Reference values. ICRP Publication 89. Ann. ICRP 32(3-4).

Ingelfinger J. 1991. Renal conditions in the newborn period. In: Cloherty JP, Stark AR, editors. Manual of neonatal care. 2nd ed. Boston (MA): Little Brown & Co. p. 477–495.

Ishibashi H, Matsumura N, Hirano M, Matsuoka M, Shiratsuchi H, Ishibashi Y, Takao Y, Arizono K. 2004. Effects of triclosan on the early life stages and reproduction of medaka *Oryzias latipes* and induction of hepatic vitellogenin. Aquat Toxicol 67:167–179.

James M O, Marth C J, Rowland-Faux L. 2012. Slow O-demethylation of methyl triclosan to triclosan, which is rapidly glucuronidated and sulfonated in channel catfish liver and intestine. Aquat Toxicol. 124-125:72-82.

Jang HJ, Chang MW, Toghrol F, Bentley WE. 2008. Microarray analysis of toxicogenomic effects of triclosan on *Staphylococcus aureus.* Appl Microbiol Biotechnol 78:695–707.

Jannini EA, Ulisse S, D'Armiento M. 1995. Thyroid hormone and male gonadal function. Endocr Rev 16:443–459.

Junker LM, Hay AG. 2004. Effects of triclosan incorporation into ABS plastic on biofilm communities. J Antimicrob Chemother. 53:989–996.

Karlsson MV, Marshall S, Gouin T, Boxall ABA. 2015. Routes of uptake of diclofenac, fluoxetine, and triclosan into sediment-dwelling worms. Envrion Toxicol Chem. doi: 10.1002/etc.3020

Karnjanapiboonwong A, Morse AN, Maul JD, Anderson TA. 2010. Sorption of estrogens, triclosan, and caffeine in a sandy loam and a silt loam soil. J Soils Sediments 10:1300–1307.

Kim K, Park H, Yang W, Lee JH. 2011. Urinary concentrations of bisphenol A and triclosan and associations with demographic factors in the Korean population. Environ Res. 111(8):1280-1285.

Kinney CA, Furlong ET, Kolpin DW, Burkhardt MR, Zaugg SD, Werner SL, Bossio JP, Benotti MJ. 2008. Bioaccumulation of pharmaceuticals and other anthropogenic waste indicators in earthworms from agricultural soil amended with biosolid or swine manure. Environ Sci Technol. 42(6):1863–1870.

Klaunig JE, Babich MA, Baetcke KP, Cook JC, Corton JC, David RM, DeLuca JG, Lai DY, McKee RH, Peters JM, et al. 2003. PPAR-alpha agonist-induced rodent tumors: modes of action and human relevance. Crit Rev Toxicol. 33(6):655-780.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2008. 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

Koburger T, Hübner NO, Braun M, Siebert J, Karmer A. 2010. Standardized comparison of antiseptic efficacy of triclosan, PVP–iodine, octenidine dihydrochloride, polyhexanide and chlorhexidine digluconate. J Antimicrob Chemother. 65(8):1712-1719.

Koch HM, Aylward LL, Hays SM, Smolders R, Moos RK, Cocker J, Jones K, Warren N, Levy L, Bevan R. 2014. Inter- and intra-individual variation in urinary biomarker concentrations over a 6-day sampling period. Part 2: Personal care product ingredients. Toxicol Lett. 231:261-269.

Koeppe ES, Ferguson KK, Colacino JA, Meeker JD. 2013. Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007-2008. Sci Total Environ. 445-446:299-305.

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(6):1202–1211.

Kookana RS. Shareef A, Fernandes MB, Hoare S, Gaylard S, Kumar A. 2013. Bioconcentration of triclosan and methyl-triclosan in marine mussels (*Mytilus galloprovincialis*) under laboratory conditions and in metropolitan waters of Gulf St Vincent, South Australia. Marine Pollut Bull. 74:66-72

Krassas GE. 2000. Thyroid disease and female reproduction. Fertil Steril. 74(6):1063–1070.

Krishnan K, Gagné M, Nong A, Aylward LL, Hays SM. 2010. Biomonitoring equivalents for triclosan. Regul Toxicol Pharmacol. 58:10–17.

Kumar V, Chakraborty A, Kural MR, Roy P. 2009. Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reprod Toxicol. 27:177-185.

Kwon J-W, Armbrust KL, Xia K. 2010. Transformation of triclosan and triclocarban in soils and biosolids-applied soils. J Environ Qual 39:1139–1144.

Lajeunesse A, Gagnon C. 2007. Determination of acidic pharmaceuticals and carbamazepine in roughly treated sewage by solid phase extraction and gas chromatography– tandem mass spectrometry. Int J Environ Anal Chem. 87:565–578.

Lakind JS, Naiman DQ. 2008. Bisphenol A (BPA) daily intakes in the United States: Estimates from the 2003-2004 NHANES urinary BPA data. J Expo Sci Environ Epidemiol. 18: 608-615.

Lan Z, Kim TH, Bi KS, Chen XH, Kim HS. 2013. Triclosan exhibits a tendency to accumulate in the epididymis and shows sperm toxicity in male Sprague-Dawley rats. Environ Toxicol. DOI 10.1002/tox:1-9.

Langdon KA, Warne MS, Smernik RJ, Shareef A, Kookana RS. 2011. Selected personal care products and endocrine disruptors in biosolids: an Australia-wide survey. Sci Total Environ. 409:1075–1081.

Lanini S, D'Arezzo S, Puro V, Martini L, Imperi F, Piselli P, Montanaro M, Paoletti S, Visca P, Ippolito G. 2011. Molecular epidemiology of a hospital outbreak driven by a contaminated disinfectant-soap dispenser. PLoS One. 6:e17064.

Lapen DR, Topp E, Metcalfe CD, Li H, Edwards M, Gottschall N, Bolton P, Curnoe W, Payne M, Beck A. 2008. Pharmaceutical and personal care products in tile drainage following land application of liquid municipal biosolids. Sci Total Environ. 399:50–65.

Larson EL, Gomez-Duarte C, Lee LV, Della-Latta P, Kain DJ, Keswick BH. 2003. Microbial flora of hands of homemakers. Am J Infect Control. 31(2):72-79.

Latch DE, Packer JL, Stender BL, VanOverbeke J, Arnold WA, McNeill K. 2005. Aqueous photochemistry of triclosan: formation of 2,4-dichlorophenol, 2,8-dichlorodibenzo-*p*-dioxin, and oligomerization products. Environ Toxicol Chem. 24(3):517–525.

Lawrence JR, Zhu B, Swerhone GDW, Roy J, Wassenaar LI, Topp E, Korber DR. 2009. Comparative microscale analysis of the effects of triclosan and triclocarban on the structure and function of river biofilm communities. Sci Total Environ. 407:3307–3316.

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

Lee HB, Peart TE, Svoboda ML. 2003. Acidic pharmaceuticals in sewage—Methodology, stability test, occurrence, and removal from Ontario samples. Water Qual Res J Can. 38(4):667–682.

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 1094:122–129.

Lee HB, Kohli J, Peart TE. 2013. Selected chloro and bromo derivatives of triclosan – syntheses and their occurrence in Candian sewage and biosolid samples. Environ Sci Pollut Res. Published online: 14 June 2013.

Lentner C, editor. 1981. Geigy scientific tables volume 1: Units of measurement, body fluids, composition of the body, nutrition. 8th ed. Basel (CH): Ciba-Geigy Ltd.

Levy CW, Roujeinikova A, Sedelnikova S, Baker PJ, Stuitje AR, Slabas AR, Rice DW, Rafferty JB. 1999. Molecular basis of triclosan activity. Nature. 398(6726):383–384.

Li X, Ying G-G, Zhao J-L, Chen Z-F, Lai H-J, Su H-C. 2013. 4-Nonylphenol, bisphenol-A and triclosan levels in human urine of children and students in China, and the effects of drinking these bottled materials on the levels. Environ Int. 52:81-86.

Lin D, Zhou Q, Xie X, Liu Y. 2010. Potential biochemical and genetic toxicity of triclosan as an emerging pollutant on earthworms (*Eisenia fetida*). Chemosphere. 81:1328–1333.

Lin D, Li Y, Zhou Q, Xu Y, Wang D. 2014. Effect of triclosan on reproduction, DNA damage and heat shock protein gene expression of the earthworm *Eisenia fetida*. Ecotoxicology DOI 10.1007/s10646-014-1320-9.

Lindström A, Buerge IJ, Poiger T, Bergqvist PA, Müller MD, Buser HR. 2002. Occurrence and environmental behavior of the bactericide triclosan and its methyl derivative in surface waters and in wastewater. Environ Sci Technol. 36(11):2322–2329.

Lishman L, Smyth SA, Sarafin K, Kleywegt S, Toito J, Peart T, Lee B, Servos M, Beland M, Seto P. 2006. Occurrence and reductions of pharmaceuticals and personal care products and estrogens by municipal wastewater treatment plants in Ontario, Canada. Sci Total Environ. 367(2–3):544–558.

Liu F, Ying G-G, Yang L-I, Zhou Q-X. 2009. Terrestrial ecotoxicological effects of the antimicrobial agent triclosan. Ecotoxicol Environ Saf. 72:86–92.

[LNHPD] Licensed Natural Health Products Database [database on the Internet]. 2016. Ottawa (ON): Health Canada. [cited 2016]. Available from: www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/lnhpd-bdpsnh-eng.php

Longcope C. 2000. The male and female reproductive systems in hypothyroidism. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia (PA): Lippincott, Williams & Wilkins. p. 824–828.

Lores M, Llompart M, Sanchez-Prado L, Garcia-Jares C, Cela R. 2005. Confirmation of the formation of dichlorodibenzo-*p*-dioxin in the photodegradation of triclosan by photo-SPME. Anal Bioanal Chem 381(6):1294–1298.

Lozano N, Rice CP, Ramirez M, Torrents A. 2010. Fate of triclosan in agricultural soils after biosolids applications. Chemosphere 78:760–766.

Lozano N, Rice CP, Ramirez M, Torrents A. 2012. Fate of triclosan and methyltriclosan in soil from biosolids application. Environ Poll. 160:103-108.

Lozano N, Rice CP, Ramirez M, Torrents A. 2013. Fate of triclocarban, triclosan and methyl-triclosan during wastewater and biosolids treatment processes. Water Res. 47(13): 4519-4527.

Lucker PW, Wetzelsberger N, Sturm Y. 1990. Safety (tolerance) and pharmacokinetics of triclosan (TCS) (study report). Study No. 27419. Grunstadt (DE): Institut für Klinische Pharmakologie Bobenheim. [cited in SCCP 2009].

Lyndall J, Fuchsman P, Bock M, Barber T, Lauren D, Leigh K, Perruchon E, Capdevielle M. 2010. Probabilistic risk evaluation for triclosan in surface water, sediments, and aquatic biota tissues. Integr Environ Assess Manag. 6(3):419-440.

Macherius A, Eggen T, Lorenz WG, Reemtsma T, Winkler U, Moeder M. 2012. Uptake of galazolide, tonalide, and triclosan by carrot, barley, and meadow fescue plants. J Agric Food Chem. 60: 7785-791.

Mackay D, Arnot JA, Petkova EP, Wallace KB, Call DJ, Brooke LT, Veith GD. 2009. The physicochemical basis of QSARs for baseline toxicity. SAR QSAR Environ Res. 20: 393-414.

Mackay D, Hughes DM, Romano ML, Bonnell M. 2014. The role of persistence in chemical evaluations. Integr Environ Assess Manage. 10(4):588-594.

Maibach HI. 1969. Percutaneous penetration of Irgasan® CH 3565 in a soap solution. San Francisco (CA): University of California Medical Center, Department of Dermatology.

Marlatt VL, Veldhoen N, Lo BP, Bakker D, Rehaume V, Vallee K, Haberl M, Shang D, van Aggelen GC, Skirrow RC, et al. 2013. Triclosan exposure alters postembryonic development in a Pacific tree frog (*Pseudacris regilla*) amphibian metamorphosis assay (TREEMA). Aquat Toxicol. (126): 85–94.

Marshall BM, Robleto E, Dumont T, Levy SB. 2012. The frequency of antibiotic-resistant bacteria in homes differing in their use of surface antibacterial agents. Curr Microbiol. 65(4):407-415.

Matos V, Drukker A, Guinard JP. 1999. Spot urine samples for evaluating solute excretion in the first week of life. Arch Dis Child Fetal Neonatal Ed. 80: F240-F242.

Matsumura N, Ishibashi H, Hirano M, Nagao Y, Watanabe N, Shiratsuchi H, Kai T, Nishimura T, Kashiwagi A, Arizono K. 2005. Effects of nonylphenol and triclosan on production of plasma vitellogenin and testosterone in male South African clawed frogs (*Xenopus laevis*). Biol Pharm Bull. 28(9):1748–1751.

McAvoy DC, Schatowitz B, Jacob M, Hauk A, Eckhoff WS. 2002. Measurement of triclosan in wastewater treatment systems. Environ Toxicol Chem 21(7):1323–1329.

McBain AJ, Bartolo RG, Catrenich CE, Charbonneau D, Ledder RG, Price BB, Gilbert P. 2003. Exposure of sink drain microcosms to triclosan: population dynamics and antimicrobial susceptibility. Appl Environ Microbiol. 69(9):5433-5442.

McBain AJ , Ledder RG, Sreenivasan P, Gilbert P. 2004. Selection for high-level resistance by chronic triclosan exposure is not universal. J Antimicrob Chemother. 53(5):772-777.

McCall PJ, Laskowski DA, Swann RL, Dishburger HJ. 1981. Measurement of sorption coefficients of organic chemicals and their use in environmental fate analysis. In: Test protocols for environmental fate and movement of toxicants. Proceedings of a symposium. 94th annual meeting of the Association of Official Analytical Chemists, October 21–22, 1980, Washington (DC). p. 89–109.

McCarty LS. 1986. The relationship between aquatic toxicity QSARs and bioconcentration for some organic chemicals. Environ Toxicol Chem. 5:1071-1080.

McCarty LS. 1987a. Relationship between toxicity and bioconcentration for some organic chemicals: I Examination of the relationship. In: QSAR in Environmental Toxicology-II, KLE Kaiser (ed). D Reidel Publishing Co, Dordecht, The Netherlands. 207-220 pp.

McCarty LS. 1987b. Relationship between toxicity and bioconcentration for some organic chemicals: II Application of the relationship. In: QSAR in Environmental Toxicology-II, KLE Kaiser (ed). D Reidel Publishing Co, Dordecht, The Netherlands . 221-229 pp.

McCarty LS. 1990. A kinetics-based analysis of quantitative structure-activity relationships in aquatic toxicity and bioconcentration bioassays with organic chemicals. [Ph.D. thesis]. University of Waterloo. Waterloo, Ontario, Canada.

McCarty LS, Hodson PV, Craig GR, Kaiser KLE. 1985. On the use of quantitative structure-activity relationships to predict the acute and chronic toxicity of chemicals to fish. Environ Toxicol Chem. 4:595-606.

McCarty LS, Mackay D, Smith AD, Ozburn GW, Dixon DG. 1991. Interpreting aquatic toxicity QSARs: the significance of toxicant body residues at the pharmacologic endpoint. Sci Total Environ, Special Issue: QSAR in Environ Toxicol 109:515-525.

McCarty LS, Mackay D. 1993. Enhancing ecotoxicological modeling and assessment: critical body residues and modes of toxic action. Environ Sci Technol. 27:1719-1728.

McCarty LS, Arnot JA, Mackay D. 2013. Evaluation of critical body residue for acute narcosis in aquatic organisms. Environ Sci Technol. 32(10):2301-2314.

McClellan K, Halden RU. 2010. Pharmaceuticals and personal care products in archived U.S. biosolids from the 2001 EPA national sewage sludge survey. Water Res. 44:658–668.

McMurry LM, Oethinger M, Levy SB. 1998. Triclosan targets lipid synthesis. Nature. 394(6693):531.

McMurry LM, McDermott PF, Levy SB. 1999. Genetic evidence that InhA of *Mycobacterium smegmatis* is a target for triclosan. Antimicrob Agents Chemother. 43(3):711-713.

McNamara PJ, LaPara TM, Novak PJ. 2014. The impacts of triclosan on anaerobic community structures, function, and antimicrobial resistance. Envrion Sci Technol. 48:7393-7400

McPhedran K, Seth R, Song M, Chu S, Letcher RJ. 2013. Fate and mass balances of triclosan (TCS), tetrabromobisphenol A (TBBPA) and tribromobisphenol A (Tri-BBPA) during the municipal wastewater treatment process. Water Qual Res J Can. 48.3:255-265.

Meeker JD, Cantonwine DE, Rivera-Gonzalez LO, Ferguson KK, Mukherjee B, Calafat AM, Ye X, Anzalota Del Toro LV, Crespo-Hernandez N, Jimenez-Velez B, et al. 2013. Distribution, variability, and predictors of urinary concentrations of phenols and parabens among pregnant women in Puerto Rico. Environ Sci Technol. 47:3439-3447.

Mezcua M, Gómez MJ, Ferrer I, Aguera A, Hernando MD, Fernández-Alba AR. 2004. Evidence of 2,7/2,8-dibenzodichloro-*p*-dioxin as a photodegradation product of triclosan in water and wastewater samples. Anal Chim Acta. 524(1–2):241–247.

Miller RC, Brindle E, Holman DJ, Shofer J, Klein NA, Soules MR, O'Connor KA. 2004. Comparison of specific gravity and creatinine for normalizing urinary reproductive hormone concentrations. Clin Chem. 50(5): 924-932.

Miller TR, Heidler J, Chillrud SN, Delaquil A, Ritchie JC, Mihalic JN, Bopp R, Halden RU. 2008. Fate of triclosan and evidence for reductive dechlorination of triclocarban in estuarine sediments. Environ Sci Technol. 42:4570–4576.

Miyazaki T, Yamagishi T, Matsumoto M. 1984. Residues of 4-chloro-1-(2,4-dichlorophenoxy)-2-methoxybenzene (triclosan methyl) in aquatic biota. Bull Environ Contam Toxicol. 32:227–232.

Miyoshi N, Kawano T, Tanaka M, Kadono T, Kosaka T, Kunimoto M, Takahashi T, Hosoya H. 2003. Use of *Paramecium* species in bioassays for environmental risk management: determination of IC_{50} values for water pollutants. J Health Sci. 49:429–435.

Moore LB, Parks DJ, Jones SA, Bledsoe RK, Consler TG, Stimmel JB, Goodwin B, Liddle C, Blanchard SG, Wilson TM, et al. 2000. Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands. J Biol Chem. 275(20):15122-15127.

Morimura K, Cheung C, Ward JM, Reddy JK, Gonzalez FJ. 2006. Differential susceptibility of mice humanized for peroxisome proliferator-activated receptor α to Wy-14,643-induced liver tumorigenesis. Carcinogenesis. 27:1074–1080.

Mortensen ME, Calafat AM, Ye X, Wong, L, Wright DJ, Pirkle JL, Merrill LS, Moye J. 2014. Urinary concentrations of environmental phenols in pregnant women in a pilot study of the National Children's study. Environ Res. 129: 32-38

Møretrø T, Høiby-Pettersen GS, Habimana O, Heir E, Lanqsrud S. 2011. Assessment of the antibacterial activity of a triclosan-containing cutting board. Int J Food Microbiol. 146(2):157-162.

Morrissey I, Oggioni MR, Knight D, Curiao T, Coque T, Kalkanci A, Martinez JL. 2014. BIOHYPO Consortium. Evaluation of epidemiological cut-off values indicates that biocide resistant subpopulations are uncommon in natural isolates of clinically-relevant microorganisms. PLoS ONE 9(1): e86669.

Moss T, Howes D, Williams F. 2000. Percutaneous penetration and dermal metabolism of triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether). Food Chem Toxicol. 38:361–370.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [Estimation Model]. 2008. Version 1.43. 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

[MSDS] Material Safety Data Sheet. 2014. Liquid hand dishwashing detergents and antibacterial hand soaps (MSDS No.: RQ1309635/RQ1310080/RQ1310594) [Internet]. Cincinnati (OH): Procter and Gamble Company. [cited 2015 March 25]. Available from: http://www.pgproductsafety.com/productsafety/search_results.php?searchtext=Ultra+down+2011&category=msds&submit=Search&submit=Search

[NATO] North Atlantic Treaty Organization. 1988. Pilot study on international information exchange on dioxins and related compounds: international toxicity equivalency factor (I-TEF) method of risk assessment for complex mixtures of dioxins and related compounds. Report No. 176. North Atlantic Treaty Organization, Committee on the Challenges of Modern Society. 26 p.

[NCI] National Chemical Inventories [database on CD-ROM]. 2011. Issue 1. Columbus (OH): American Chemical Society, Chemical Abstracts Service. [cited 2011 Aug]. Available from: www.cas.org/products/cd/nci/index.html

Neithardt AB, Dooley SL, Borensztajn J. 2002. Prediction of 24-hour protein excretion in pregnancy with a single voided urine protein-to-creatinine ratio. Am J Obstet Gynecol. 186:883-886.

Neuwoehner J, Escher BI. 2011. The pH-dependent toxicity of basic pharmaceuticals in the green algae *Scenedesmus vacuolatus* can be explained with a toxicokinetic ion-trapping model. Aquat Toxicol. 101(1):266-275.

Newsome CS, Howes D, Hoar D. 1975. The toxicity, absorption, metabolism and excretion of Irgasan DP 300 by goldfish. Final report on Project No. CW 27160. [Place of Publication unknown]: Unilever Research Colworth. [Restricted Accesss]

Newton APN, Cadena SMSC, Rocha MEM, Carnieri EGS, de Oliveira MBM. 2005. Effects of triclosan (TRN) on energy-linked functions of rat liver mitochondria. Toxicol. Lett. 160:49-59.

[NHPID] Natural Health Products Ingredients Database [database on the Internet]. 2015. Ottawa (ON): Health Canada. [cited 2015]. Available from: http://webprod.hc-sc.gc.ca/nhpid-bdipsn/search-rechercheReq.do

[NICNAS] National Industrial Chemicals Notification and Assessment Scheme. 2009. Triclosan (Priority existing chemical assessment report No. 30) [Internet]. Sydney (AU): Australian Government, Department of Health and Ageing, National Industrial Chemicals Notification and Assessment Scheme. Available from: www.nicnas.gov.au/publications/car/pec/pec30/pec_30_full_report_pdf.pdf

Nieuwkoop PD, Faber J. 1994. Normal table of *Xenopus laevis* (Daudin). London (GB): Garland Publishing.

[NITE] National Institute of Technology and Evaluation (JP). 2002. Biodegradation and bioconcentration of the existing chemical substances under the Chemical Substances Control Law [Internet]. Tokyo (JP): National Institute of Technology and Evaluation. [cited 2007 Nov 9]. Available from: www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html

[NITE] National Institute of Technology and Evaluation (JP). 2006. Japan chemicals collaborative knowledge database (J-CHECK) [Internet]. Tokyo (JP): Ministry of Health, Labour and Welfare, Ministry of the Environment and National Institute of Technology and Evaluation. [cited 2011 Oct 27]. Available from: www.safe.nite.go.jp/jcheck/direct.do?table_name=bunchiku&k_no=0592

Novo A, André S, Viana P, Nunes OC, Manaia CM. 2013. Antibiotic resistance, antimicrobial residues and bacterial community composition in urban wastewater. Water Res. 47(5):1875-1887.

[NLM] U.S. National Library of Medicine. 2014. Amniotic fluid – Medline Plus: Trusted Health Information for You [Internet]. Bethesda (MD): U.S. National Library of Medicine. [last updated 9 July 2014; cited May 2014]. Available from: http://www.nlm.nih.gov/medlineplus/ency/article/002220.htm

[OECD] Organisation for Economic Co-operation and Development. 2007. SIDS initial assessment report for 2,4-dichlorophenol [Internet]. Paris (FR): Organisation for Economic Co-operation and Development, Environment Directorate. [cited 2009 Aug 31]. Available from: http://webnet.oecd.org/HPV/UI/handler.axd?id=cc8440ef-aa6e-48d5-9d87-71fa94966486 [see also OECD website at: http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?Key=30051e47-7cdb-4d1e-b684-f49704750f55&idx=0]

[OECD] Organisation for Economic Co-operation and Development. 2011. SIDS initial assessment profile. 3380-34-5. Triclosan; Phenol, 5 chloro-2-(2,4-dichlorophenoxy)-. SIAM 30, 20–22 April 2010. Available from: http://webnet.oecd.org/Hpv/UI/handler.axd?id=a867909a-abee-46c9-b45a-11edd069697e [see also OECD website at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=F7CECB3D-096C-4F92-AFBB-F2039BE080EF]

[OECD] Organisation for Economic Co-operation and Development. 2012. Fish toxicity testing framework. Series on testing and assessment. No. 171. ENV/JM/MONO(2012)16. [Internet]. Paris (FR): Organisation for Economic Co-operation and Development, Environment Directorate. [cited 2014 May 23]. Available from: http://www.oecd.org/chemicalsafety/testing/seriesontestingandassessmentpublicationsbynumber.htm

Okumura T, Nishikawa Y. 1996. Gas chromatography–mass spectrometry determination of triclosans in water, sediment and fish samples via methylation with diazomethane. Anal Chim Acta 325(3):175–184.

Oliveira R, Domingues I, Grosolia CK, Soares AMVM. 2009. Effects of triclosan on zebrafish early-life stages and adults. Environ Sci Pollut Res. 16:679–688.

O'Neil MJ, editor. 2001. The Merck Index—An encyclopedia of chemicals, drugs, and biologicals. 13th ed. Whitehouse Station (NJ): Merck and Co., Inc. p. 1447. [cited in HSDB 2007].

Orvos DR, Versteeg DJ, Inauen J, Capdevielle M, Rothenstein A, Cunningham V. 2002. Aquatic toxicity of triclosan. Environ Toxicol Chem. 21(7):1338–1349.

Ostrea EM, Bielawski DM, Posecion Jr NC. 2006. Meconium analysis to detect fetal exposure to neurotoxicants. Arch Dis Child. 91:628-629.

Özkaynak H, Xue J, Zartarian V, Glen G, Smith L. 2011. Modeled estimates of soil and dust ingestion rates for children. Risk Anal. 31(4):592–608.

Palenske NM, Nallani GC, Dzialowski EM. 2010. Physiological effects and bioconcentration of triclosan on amphibian larvae. Comp Biochem Physiol C Toxicol Pharmacol 152(2):232–240.

Palmer RK, Hutchinson LM, Burpee BT, Tupper EJ, Pelletier JH, Kormendy Z, Hopke AR, Malay ET, Evans BL, Velez A et al. 2012. Antibacterial agent triclosan suppresses RBL-2H3 mast cell function. Toxicol Appl Pharmacol. 258:99-108.

Pannu MW, Toor GS, O'Connor GA, Wilson PC. 2012a. Toxicity and bioaccumulation of biosolids-borne triclosan in food crops. Environ Toxicol Chem. 31(9):2130-2137.

Pannu MW, O'Connor GA, Toor GS. 2012b. Toxicity and bioaccumulation of biosolids-borne triclosan in terrestrial organisms. Environ Toxicol Chem 31(3):646-653.

Parboosingh J, Doig A. 1973. Studies of nocturia in normal pregnancy. J Obstet Gynaecol Br Commonw. 80:888-895.

Parsons JR. 1992. Influence of suspended sediment on the biodegradation of chlorinated dibenzo-*p*-dioxins. Chemosphere 25:1973–1980.

Parsons JR, Storms MCM. 1989. Biodegradation of chlorinated dibenzo-*p*-dioxins in batch and continuous cultures of strain JB1. Chemosphere 19:1297–1308.

Paul KB, Hedge JM, Devito MJ, Crofton KM. 2010a. Short-term exposure to triclosan decreases thyroxine *in vivo* via upregulation of hepatic catabolism in young Long-Evans rats. Toxicol Sci 113(2):367–379.

Paul KB, Hedge JM, Devito MJ, Crofton KM. 2010b. Developmental triclosan exposure decreases maternal and neonatal thyroxine in rats. Environ Toxicol Chem 29(12):2840–2844.

Paul KB, Hedge JM, Bansal R, Zoeller RT, Peter R, DeVito MJ, Crofton KM. 2012. Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 300(1-2):31-45.

Paul KB, Hedge JM, Macherla C, Filer DL, Burgess E, Simmons SO, Crofton KM, Hornung MW. 2013a. Cross-species analysis of thyroperoxidase inhibition by xenobiotics demonstrates conservation of response between pig and rat. Toxicology. 312:97-107.

Paul KB, Thompson JT, Simmons SO, Vanden Heuvel JP, Crofton KM. 2013b. Evidence for triclosan-induced activation of human and rodent xenobiotic nuclear receptors. Toxicol In Vitro. 27:2049-2060.

Paul KB, Hedge JM, Rotroff DM, Hornung MW, Crofton KM, Simmons SO. 2014. Development of a thyroperoxidase assay for high-thoughput screening. Chem Res Toxicol. 27:387-399.

Paxéus N. 1996. Organic pollutants in the effluents of large wastewater treatment plants in Sweden. Water Res. 30(5):1115–1122.

Pearson MA, Lu C, Schmotzer BJ, Waller LA, Riederer AM. 2009. Evaluation of physiological measures for correcting variation in urinary output: Implications for assessing environmental chemical exposure in children. J Exposure Sci and Environ Epi. 19:336-342.

Pedersen BM, Nielsen U. 2003. Monitoring programme for wastewater treatement plant Lynetten, household chemicals and endocrine disrupting substances. Report to Lynettefaellesskabet I/S [in Danish]. [cited in Samsoe-Petersen et al. 2003].

Perucca J, Bouby N, Valeix P, Bankir L. 2007. Sex difference in urine concentration across differing ages, sodium intake, and level of kidney disease. Am J Physiol Regul Integr Comp Physiol. 292:R700-R705.

Peters JM. 2008. Mechanistic evaluation of PPAR-alpha-mediated hepatocarcinogenesis: Are we there yet? Toxicol Sci 101(1):1–3.

Philippat C, Wolff MS, Calafat AM, Ye X, Bausell R, Meadows M, Stone J, Slama R, Engel SM. 2013. Prenatal exposure to environmental phenols: Concentrations in amniotic fluid and variability in urinary concentrations during pregnancy. Environ Health Perspect. 121(10):1225-1231.

Pirard C, Sagot C, Deville M, Dubois N, Charlier C. 2012. Urinary levels of bisphenol A, triclosan and 4-nonylphenol in a general Belgian population. Environ Int. 48:78-83.

[PMRA] Pest Management Regulatory Agency. 1999. The Pest Management Regulatory Agency's strategy for implementing the Toxic Substances Management Policy. Ottawa (ON): Pest Management Regulatory Agency. Available from: www.hc-sc.gc.ca/cps-spc/pubs/pest/_pol-guide/dir99-03/index-eng.php

Prentice A. 1987. Breast feeding increases concentrations of IgA in infants' urine. Arch Dis Child 62(8):792–795. Available from: www.ncbi.nlm.nih.gov/pmc/articles/PMC1778476/pdf/archdisch00695-0034.pdf

Price OR, Williams RJ, van Egmond R, Wilkinson MJ, Whelan MJ. 2010. Predicting accurate and ecologically relevant regional scale concentrations of triclosan in rivers for use in higher-tier risk assessments. Environ Int. 36:521–526.

Prosser RS, Lissemore L, Solomon KR, Sibley PK. 2014. Toxicity of biosolids-derived triclosan and triclocarban to six crop species. Environ Toxicol Chem. 33:1840-1848.

[QSAR] QSAR Toolbox. 2008. Version 2.2. Paris (FR): Organisation for Economic Co-operation and Development, Environment Directorate. Available from: www.oecd.org/document/23/0,3343,en_2649_34379_33957015_1_1_1_1,00.html

Queckenberg C, Meins J, Wachall B, Doroshyenko O, Tomalik-Scharte D, Bastian B, Abdel-Tawab M, Fuhr U. 2010. Absorption, pharmacokinetics, and safety of triclosan after dermal administration. Antimicrob Agents Chemother 54(1):570–572.

Quigley R. 2012. Developmental changes in renal function. Current Opinion in Pediatrics. 24(2): 184-190.

Raut SA, Angus RA. 2010. Triclosan has endocrine-disrupting effects in male western mosquitofish, *Gambusia affinis*. Environ Toxicol Chem 29(6):1287–1291.

Reiss R, Lewis G, Griffin J. 2009. An ecological risk assessment for triclosan in the terrestrial environment. Environ Toxicol Chem 28(7):1546–1556.

Remberger M, Sternbeck J, Strömberg K. 2002. Screening of triclosan and some brominated phenolic substances in Sweden. IVL Svenska Miljöinstitutet AB. [in Swedish]. [cited in Samsoe-Petersen et al. 2003].

Remer T, Fonteyn N, Alexy U, Berkemeyer S. 2006. Longitudinal examination of 24-h urinary iodine excretion in schoolchildren as a sensitive, hydration status-independent research tool for studying iodine status. Am J Clin Nutr. 83:639-646.

Revúsová V, Zvara V, Gratzlová J. 1971. Some Laboratory Findings in Patients with Urolithiasis. Int Urol Nephrol 3(3), 251-258.

Roberts J, Price O, Bettles N, Rendal C, van Egmond R. 2014. Accounting for dissociation and photolysis: a review of the algal toxicity of triclosan. Environ Toxicol Chem. 33(11): 2551–2559

Rouaze-Romet M, Vranckx R, Savu L, Nunez EA. 1992. Structural and functional microheterogeneity of rat thyroxine-binding globulin during ontogenesis. Biochem J. 286(Pt 1):125–130.

Rule KL, Ebbett VR, Vikesland PJ. 2005. Formation of chloroform and chlorinated organics by free-chlorine-mediated oxidation of triclosan. Environ Sci Technol. 39:3176–3185.

Rydberg P, Gloriam DE, Zaretzki J, Breneman C, Olsen L. 2010a. SMARTCyp: a 2D method for prediction of cytrochrom P450-mediated drug metabolism. ACS Med Chem Lett. 1(3):96-100.

Rydberg P, Gloriam DE, Olsen L. 2010b. The SMARTCyp cytochrome P450 metabolism prediction server. Bioinformatics. 26(23):2988-2989.

Rydberg P, Olsen L. 2012a. Ligand-based site of metabolism prediction for cytochrome P450 2D6. ACS Med Chem Lett. 3(1):69-73.

Rydberg P, Olsen L. 2012b. Predicting drug metabolism by cytochrome P450 2C0: comparison with the 2D6 and 3A4 isoforms. ChemMedChem. 7(7):1202-1209.

Rydberg, P, Jørgensen MS, Jacobsen TA, Jacobsen A-M, Madsen KG, Olsen L. 2013a. Nitrogen inversion barriers affect the N-oxidation of tertiary alkylamines by cytochromes P450. Angew Chem Int Ed Engl. 52(3):993-997.

Rydberg P, Rostkowski M, Gloriam DE, Olsen L. 2013b. The contribution of atom accessibility to site of metabolism models for cytochromes P450. Mol Pharm. 10(4):1216-1223.

Sabaliunas D, Webb SF, Hauk A, Jacob M, Eckhoff MS. 2003. Environmental fate of triclosan in the River Aire Basin, UK. Water Res. 37(13):3145–3154.

Sabourin L, Beck A, Duenk PW, Kleywegt S, Lapen DR, Li H, Metcalfe CD, Payne M, Topp E. 2009. Runoff of pharmaceuticals and personal care products following application of dewatered municipal biosolids to an agricultural field. Sci Total Environ. 407:4596–4604.

Sabourin L, Duenk P, Bonte-Gelok S, Payne M, Lapen DR, Topp E. 2012. Uptake of pharmaceuticals, hormones and parabens into vegetables grown in soil fertilized with municipal biosolids. Sci Total Environ. 431:233-236.

Sakuratani Y, Noguchi Y, Kobayashi K, Yamada J, Nishihara T. 2008. Molecular size as a limiting characteristic for bioconcentration in fish. J Environ Biol. 29(1):89–92.

Saleh S, Haddadin RN, Baillie S, Collier PJ. 2011. Triclosan - an update. Lett Appl Microbiol. 52(2):87–95.

Samsoe-Petersen L, Winther-Wilson M, Madsen T. 2003. Fate and effects of triclosan. Environmental Project No. 861. Copenhagen (DK): Danish Ministry of the Environment, Danish Environmental Protection Agency, DHI Water & Environment. Available from: www2.mst.dk/udgiv/publications/2003/87-7972-984-3/pdf/87-7972-985-1.pdf

Sánchez-Brunete C, Miguel E, Albero B, Tadeo JL. 2010. Determination of triclosan and methyl triclosan in environmental solid samples by matrix solid-phase dispersion and gas chromatography–mass spectrometry. J Sep Sci. 33:2768–2775.

Sanchez-Prado L, Llompart M, Lores M, Garcia-Jares C, Bayona JM, Cela R. 2006. Monitoring the photochemical degradation of triclosan in wastewater by UV light and sunlight using solid-phase microextraction. Chemosphere. 65:1338–1347.

Sandborgh-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. 2006. Pharmacokinetics of triclosan following oral ingestion in humans. J Toxicol Environ Health 69:1861–1873.

[SAP] Science Advisory Panel. 2004. Transmittal of meeting minutes of the FIFRA Scientific Advisory Panel meeting held December 9, 2003. Memorandum to Office of Pesticide Programs and Office of Pollution Prevention and Toxics from Office of Science Coordination and Policy, US Environmental Protection Agency. Available from: www.epa.gov/scipoly/sap/meetings/2003/december9/meetingminutes.pdf

Savage JH, Matsui EC, Wood RA, Keet CA. 2012. Urinary levels of triclosan and parabens are associated with aeroallergen and food sensitization. J Allergy Clin Immunol. 130:453-460.

Savu L, Vranckx R, Maya M, Nunez EA. 1987. A thyroxine binding globulin (TBG)-like protein in the sera of developing and adult rats. Biochem Biophys Res Commun 148(3):1165–1173.

Sax NI, Lewis R. 2000. Sax's dangerous properties of industrial materials. 10th ed. New York (NY): Reinhold Publishing Corp. p. 3529–3530.

[SCCP] Scientific Committee on Consumer Products. 2009. Opinion on triclosan (COLIPA No. P32). European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Products. Available from: http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_166.pdf

[SCCS] Scientific Committee on Consumer Safety. 2010. Opinion on triclosan: Antimicrobial resistance. European Commission, Directorate-General for Health & Consumers, Scientific Committee on Consumer Safety. Available from: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_023.pdf

[SCCS] Scientific Committee on Consumer Safety. 2011. Opinion on triclosan (COLIPA No. P32). Addendum to the SCCP opinion on triclosan (SCCP/1192/08) from January 2011. European Commission, Directorate-General for Health & Consumers, Scientific Committee on Consumer Safety. Available from: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_054.pdf

[SCENIHR] Scientific Committee on Emerging and Newly Identified Health Risks. 2009. Assessment of the antibiotic resistance effects of biocides. European Commission, Directorate-General for Health & Consumers, Scientific Committee on Emerging and

Newly Identified Health Risks. Available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_021.pdf

[SCENIHR] Scientific Committee on Emerging and Newly Identified Health Risks. 2010. Research strategy to address the knowledge gaps on the antimicrobial resistance effects of biocides. European Commission, Directorate-General for Health & Consumers, Scientific Committee on Emerging and Newly Identified Health Risks. Available from: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_028.pdf

Schettgen C, Schmidt A, Butte W. 1999. Variation of accumulation and clearance of the predioxin 5-chloro-2-(2,4-dichlorophenoxy)-phenol (Irgasan DP 300, triclosan) with the pH of water. Organohalogen Compds. 43:49–52.

Schettgen C. 2000. Bioakkumulation von Triclosan bei verschiedenen pH-Werten des Wassers und der Pyrethroide Cyfluthrin, Cypermethrin, Deltamethrin und Permethrin. Dissertation Universität Oldenburg.

Schultz MM, Bartell SE, Schoenfuss HL. 2012. Effects of triclosan and triclocarban, two ubiquitous environmental contaminants, on anatomy, physiology, and behaviour of the fathead minnow (*Pimephales promelas*). Arch Environ Contam Toxicol. 63:114-124.

Serrano M, Robatzek S, Torres M, Kombrink E, Somssich IE, Robinson M, Schulze-Lefert P. 2007. Chemical interference of pathogen-associated molecular pattern-triggered immune responses in *Arabidopsis* reveals a potential role for fatty-acid synthase type II complex-derived lipid signals. J Biol Chem. 282(9):6803–6811.

Shah YM, Morimura K, Yang Q, Tanabe T, Takagi M, Gonzalez FJ. 2007. Peroxisome proliferator-activated receptor regulates a microRNA-mediated signaling cascade responsible for hepatocellular proliferation. Mol Cell Biol. 27(12):4238–4247.

Singer H, Muller S, Tixier C, Pillonel L. 2002. Triclosan: occurrence and fate of widely used biocide in the aquatic environment: field measurements in wastewater treatment plants, surface water and lake sediments. Environ Sci Technol. 36:4998–5004.

Skovgaard S, Nielsen LN, Larsen MH, Skov RL, Ingmer H, Westh H. 2013. *Staphylococcus epidermidis* isolated in 1965 are more susceptible to triclosan than current isolates. PLoS One 8(4):e62197.

Smith GR, Burgett AA. 2005. Effects of three organic wastewater contaminants on American toad, *Bufo americanus*, tadpoles. Ecotoxicology. 14:477–482.

Son A, Kennedy IM, Scow KM, Hristova KR. 2010. Quantitative gene monitoring of microbial tetracycline resistance using magnetic luminescent nanoparticles. J Environ Monit 12(6): 1362–1367.

Stasinakis AS, Mamais D, ThomaidisNS, Danika E, Gatidou G, Lekkas TD. 2008a. Inhibitory effect of triclosan and nonylphenol on respiration rates and ammonia removal in activated sludge systems. Environ Pollut. 159(6):1599-1605.

Stasinakis AS, Petalas AV, Mamais D, Thomaidis NS. 2008b. Application of the OECD 301F respirometric test for the biodegradability assessment of various potential endocrine disrupting chemicals. Bioresour Technol. 99:3458–3467.

Statistics Canada. 2013a. Add title. Custom data tables created for the Existing Substances Risk Assessment Bureau. Created in September 2013.

Statistics Canada. 2013b. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 2. Ottawa (ON): Statistics Canada. Available from: http://www23.statcan.gc.ca/imdb-bmdi/document/5071_D4_T9_V1-eng.htm

Stevens KJ, Kim S-Y, Adhikari S, Vadapalli V, Venables BJ. 2009. Effects of triclosan on seed germination and seedling development of three wetland plants: *Sesbania herbacea*, *Eclipta prostrata* and *Bidens frondosa*. Environ Toxicol Chem. 28(12):2598–2609.

Stierlin H. 1972. GP 41 353: Scouting studies to ascertain the cutaneous resorption of GP 41 353 in humans after topical application in a crème excipient. Basel (CH): Ciba Geigy Ltd. [cited in SCCP 2009].

Stoker TE, Gibson EK, Zorrilla LM. 2010. Triclosan exposure modulates estrogen-dependent responses in the female Wistar rat. Toxicol Sci .177(1):45–53.

Study Submissions. 2009. Unpublished confidential studies submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division

Study Submission 2013. Unpublished confidential studies submitted to Environment Canada under the Chemicals Management Plan initiative. Gatineau (QC): Environment Canada, Program Development and Engagement Division

Suller MT, Russell AD. 2000. Triclosan and antibiotic resistance in *Staphylococcus aureus*. J Antimicrob Chemother. 46(1):11-18.

Summit Toxicology. 2013. Relationship between concentrations of short-lived analytes in spot and 24-hour urine voids. Contract No.:4500306874. Unpublished report prepared for Health Canada, Nov 8, 2013.

Svensson A. 2002. Ecotoxic substances in sewage sludge—a study of nineteen WWTPs in Västra Götaland, Sweden [in Swedish]. Länsstyrelsen Västra Götaland, Report 2002:39. [cited in Samsoe-Petersen et al. 2003].

Tamura I, Kagota KI, Yasuda Y, Yoneda S, Morita J, Nakada N, Kameda Y, Kimura K, Tatarazako N, Yamamoto H. 2012. Ecotoxicity and screening level ecotoxicological risk assessment of five antimicrobial agents: triclosan, triclocarban, resorcinol, phenoxyethanol and p-thymol. J Appl Toxicol. 33: 1222-1229.

Tatarazako N, Ishibashi H, Teshima K, Kishi K, Arizono K. 2004. Effects of triclosan on various organisms. Environ Sci. 11(2):133-140.

Tefre de Renzy-Martin K, Frederiksen H, Christensen JS, Boye Kyhl H, Andersson AM, Husby S, Barington T, Main KM, Jensen TK. 2014. Current exposure of 200 pregnant Danish women to phthalates, parabens and phenols. Reproduction. 147:443-453.

Tetra Tech. 2014. Report to Health Canada on Synthesis and Interpretation of New Information on Triclosan and Antimicrobial Resistance. Contract No.: 4600000340. Unpublished report prepared for Health Canada, February 10, 2014.

Thomas PM, Foster GD. 2005. Tracking acidic pharmaceuticals, caffeine, and triclosan through the wastewater treatment process. Environ Toxicol Chem. 24(1):25–30.

Thompson TA, Borman CH, Goodblatt RS. 1975. Triclosan (report 2): Concentration of human plasma and urinary excretion after dermal application of GP 41353 patient skin prep. Drug Metabolism Report 1975-18. [cited in SCCP 2009].

Thorp JM, Norton PA, Lewis Wall L, Kuller JA, Eucker B, Wells E. 1999. Urinary incontinence in pregnancy and the puerperium: A prospective study. Am J Obstet Gynecol. 181:266-273.

Tixier C, Singer HP, Canonica S, Muller SR. 2002. Phototransformation of triclosan in surface waters: a relevant elimination process for this widely used biocide—laboratory studies, field measurements, and modeling. Environ Sci Technol. 36(16):3482–3489.

Toms L-ML, Allmyr M, Mueller JF, Adolfsson-Erici M, McLachlan M, Murby J, Harden FA. 2011. Triclosan in individual human milk samples from Australia. Chemosphere. 85:1682-1686.

Topp E, Monteiro SC, Beck A, Coelho BB, Boxall ABA, Duenk PW, Kleywegt S, Lapen DR, Payne M, Sabourin L, et al. 2008. Runoff of pharmaceuticals and personal care products following application of biosolids to an agricultural field. Sci Total Environ. 396:52–59.

Trimmer GW. 1994. 90-day subchronic dermal toxicity study in the rat with satellite group with Irgasan DP300. Study No. 139910B. East Millstone (NJ): Exxon Biomedical Sciences, Inc., Toxicology Laboratory.

Trutter JA. 1993. 13-week subchronic oral toxicity study of triclosan in CD-1R mice. Vienna (VA): Hazleton Washington, Inc.

Udoji F, Martin T, Etherton R, Whalen MM. 2010. Immunosuppressive effects of triclosan, nonylphenol, and DDT on human natural killer cells *in vitro.* J Immunotoxicol. 7(3):205–212.

[US EPA] US Environmental Protection Agency. 2008a. Triclosan reregistration eligibility decision (RED) document. List B Case No. 2340. Washington (DC): US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available from: www.epa.gov/oppsrrd1/REDs/2340red.pdf

[US EPA] US Environmental Protection Agency. 2008b. 5-Chloro-2-(2,4-dichlorophenoxy)phenol (triclosan): toxicology chapter for the reregistration eligibility decision (RED) document. Washington (DC): US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available from: www.regulations.gov/#!searchResults;rpp=10;po=10;s=EPA-HQ-OPP-2007-0513

[US EPA] US Environmental Protection Agency. 2008c. Cancer assessment document: evaluation of the carcinogenic potential of triclosan. Final, January 4, 2008. Washington (DC): US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Available from: www.regulations.gov/#!searchResults;rpp=10;po=10;s=EPA-HQ-OPP-2007-0513

[US EPA] US Environmental Protection Agency. 2008d. Triclosan: Occupational and residential exposure assessment. Washington (DC): US Environmental Protection Agency, Office of Pesticide Programs, Antimicrobials Division. Available from: www.regulations.gov/#!searchResults;rpp=10;po=10;s=EPA-HQ-OPP-2007-0513

[US EPA] US Environmental Protection Agency. 2008e. Revised environmental fate science chapter for the triclosan reregistration eligibility decision (RED) document. Reregistration Case No.: 2340. Washington (DC): US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. 42 p. Available from: www.regulations.gov/#!searchResults;rpp=10;po=10;s=EPA-HQ-OPP-2007-0513

[US EPA] US Environmental Protection Agency. 2008f. Revised ecological hazard and environmental risk assessment science chapter for the triclosan reregistration eligibility decision (RED) document. Reregistration Case No.: 2340. Washington (DC): US Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. 33 p. Available from: www.regulations.gov/#!searchResults;rpp=10;po=10;s=EPA-HQ-OPP-2007-0513

[US EPA] US Environmental Protection Agency. 2011a. Integrated approaches to testing and assessment strategy: use of new computational and molecular tools. FIFRA Scientific Advisory Panel Consultation, May 24–26, 2011. Arlington (VA): FIFRA Scientific Advisory Panel Meeting. Available from: www.epa.gov/scipoly/sap/meetings/2011/may/052411minutes.pdf

[US EPA] US Environmental Protection Agency. 2011b. Draft triclosan residential exposure and illustrative risk assessment. May 4, 2011. Washington (DC): US Environmental Protection Agency, Office of Pesticides Programs, Antimicrobials Division.

[US EPA] US Environmental Protection Agency. 2011c. Exposure factors handbook [Internet]. Washington (DC): US Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252#Download

[US EPA] US Environmental Protection Agency. 2014. US EPA Triclosan final work plan. Registration Review Case#2340. March 2014. Washington, D.C. 20460. Available from: www.regulations.gov

[USP] United States Pharmacopeia and National Formulary. 2009. Official Monographs (triclosan). USP 32-NF 27. Rockville (MD): US Pharmacopeia Convention.

Valters K, Li H, Alaee M, D'Sa I, Marsh G, Bergman A, Letcher R. 2005. Polybrominated diphenyl ethers and hydroxylated and methoxylated brominated and chlorinated analogues in the plasma of fish from the Detroit River. Environ Sci Technol 39:5612–5619.

Van Hoogen G, Opperhuizen A. 1988. Toxicokinetics of chlorobenzenes in fish. Environ Toxicol Chem 7:213-219.

Veldhoen N, Skirrow RC, Osachoff H, Wigmore H, Clapson DJ, Gunderson MP, van Aggelen G, Helbing CC. 2006. The bactericidal agent triclosan modulates thyroid hormone–associated gene expression and disrupts postembryonic anuran development. Aquat Toxicol 80(3):217–227.

Vélez MP, Arbuckle TE, Fraser WD. Female exposure to phenols and phthalates and time to pregnancy: the Maternal-Infant Research on Environmental Chemicals (MIREC) study. 2015. Fertil Steril. 103(4): 1011-1020.

Voets JB, Pipyn P, Van Lanker P, Verstraete W. 1976. Degradation of microbicides under different environmental conditions. J Appl Bacteriol. 40:67–72.

Waiser MJ, Humphries D, Tumber V, Holm J. 2011. Effluent-dominated streams. Part 2: Presence and possible effects of pharmaceuticals and personal care products in Wascana Creek, Saskatchewan, Canada. Environ Toxicol Chem. 30:508–519.

Walker M. 2011. Breastfeeding management for the clinician. 2nd ed. Sudbury (MA): Jonees and Bartlett Publishers, LLC. p. 220–221.

Waller NJ, Kookana RS. 2009. Effect of triclosan on microbial activity in Australian soils. Environ Toxicol Chem. 28(1):65–70.

Walser T, Demou E, Lang DJ, Hellweg S. 2011. Prospective environmental life cycle assessment of nanosilver T-shirts. Environ Sci Technol. 45(10):4570–4578.

Waltman EL, Venables BJ, Waller WT. 2006. Triclosan in a North Texas wastewater treatment plant and the influent and effluent of an experimental constructed wetland. Environ Toxicol Chem 25(2):367–372.

Wang H, Zhang J, Gao F, Yang Y, Duan H, Wu Y, Berset J-D, Shao B. 2011. Simultaneous analysis of synthetic musks and triclosan in human breast milk by gas chromatography tandem mass spectrometry. J Chromatogr B. 879:1861–1869.

Wang X, Liu Z, Wang W, Yan Z, Zhang C, Wang W, Chen L. 2014. Assessment of toxic effects of triclosan on the terrestrial snail (*Achatina fulica*). Chemosphere. 108:225-230.

Wang X, Zhang C, Liu Z, Wang W, Chen L. 2015. Development of predicted no effect concentration (PNEC) of for TCS to terrestrial species. Chemosphere. 139:428-433.

Water UK. 2006. Ask about: Children [Internet]. London (GB): Water UK. [cited 2011 Sep]. Available from: www.water.org.uk/home/water-for-health/medical-facts/children

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 Heal Persp. 111(8): 994–1006.

Weiss L, Arbuckle TE, Fisher M, Ramsay T, Mallick R, Hauser R, LeBlanc A, Walker M, Dumas P, Lang C. 2015. Temporal variability and sources of triclosan exposure in pregnancy. Int J Hyg Environ Heal. doi:10.1016/j.ijheh.2015.04.003

Wignall GR, Goneau LW, Chew BH, Denstedt JD, Cadieux PA. 2008. The effects of triclosan on uropathogen susceptibility to clinically relevant antibiotics. J Endourol. 22(10):2349-2356.

Wilson BA, Smith VH, deNoyelles F, Larive CK. 2003. Effects of three pharmaceutical and personal care products on natural freshwater algal assemblages. Environ Sci Technol. 37(9):1713–1719.

Wilson R , Jones-Otazo H, Petrovic S, Mitchell I, Bonvalot Y, Williams D, Richardson GM. 2013 Revisiting Dust and Soil Ingestion Rates Based on Hand-to-Mouth Transfer, Human and Ecological Risk Assessment: An International Journal, 19:1,158-188, DOI: 10.1080/10807039.2012.685807

Wisk JD, Cooper KR. 1990. Comparison of the toxicity of several polychlorinated dibenzo-*p*-dioxins and 2,3,7,8-tetrachlorodibenzofuran in embryos of the Japanese medaka (*Oryzias latipes*). Chemosphere 20:361–377.

Witorsch RJ. 2014. Critical analysis of endocrine disruptive activity of triclosan and its relevance to human exposure through the use of personal care products. Crit Rev Toxicol. 44(6):535-555.

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, Wetmur J, Calafat AM. 2008. Prenatal phenol and phthalate exposures and birth outcomes. Environ Heal Persp. 116:1092–1097.

Wu AHB. 2006. Tietz clinical guide to laboratory tests. 4th ed. St. Louis (MO): Saunders Elsevier. p. 1102–1104.

Wu C, Spongberg AL, Witter JD. 2009. Adsorption and degradation of triclosan and triclocarban in soils and biosolids-amended soils. J Agric Food Chem 57:4900–4905.

Wu C, Spongberg AL, Witter JD, Fang M, Czajkowski KP. 2010a. Uptake of pharmaceuticals and personal care products by soybean plants from soils applied with biosolids and irrigated with contaminated water. Environ Sci Technol 44:6157–6161.

Wu C, Spongberg AL, Witter JD, Fang M, Ames A, Czajkowski KP. 2010b. Detection of pharmaceuticals and personal care products in agricultural soils receiving biosolids application. Clean Soil Air Water 38(3):230–237.

Xu J, Wu L, Chang AC. 2009. Degradation and adsorption of selected pharmaceuticals and personal care products (PPCPs) in agricultural soils. Chemosphere 77:1299–1305.

Yalkowsky SH, He Y. 2003. Handbook of aqueous solubility data: an extensive compilation of aqueous solubility data for organic compounds extracted from the AQUASOL database. CRC Press LLC. p. 813. [cited in HSDB 2007].

Yang L-H, Ying G-G, Su H-C, Stauber JL, Adams MA, Binet MT. 2008. Growth-inhibiting effect of 12 antibacterial agents and their mixtures on the freshwater microalga *Pseudokirchneriella subcapitata*. Environ Toxicol Chem 27(5):1201–1208.

Ye X, Bishop A, Needham L, Calafat A. 2008. Automated on-line column-switching HPLC-MS/MS method with peak focusing for measuring parabens, triclosan, and other environmental phenols in human milk. Anal Chim Acta. 622:150–156.

Ying G-G, Yu X-Y, Kookana RS. 2007. Biological degradation of triclocarban and triclosan in a soil under aerobic and anaerobic conditions and comparison with environmental fate modeling. Environ Pollut. 150:300–305.

Zhang H, Huang CH. 2003. Oxidative transformation of triclosan and chlorophene by manganese oxides. Environ Sci Technol. 37(11):2421–2430.

Zhang Y-M, White SW, Rock CO. 2006. Inhibiting bacterial fatty acid synthesis. The J of Biol Chem 281(26):17541-17544.

Zhao J-L, Ying G-G, Liu Y-S, Chen F, Yang J-F, Wang L. 2010. Occurrence and risks of triclosan and triclocarban in the Pearl River system, South China: from source to the receiving environment. J Hazard Mater 179:215–222.

Zorrilla LM, Gibson EK, Jeffay SC, Crofton KM, Setzer WR, Cooper RL, Stoker TE. 2009. The effects of triclosan on puberty and thyroid hormones in male Wistar rats. Toxicol Sci 107(1):56–64.

List of Abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
AUC	area under the plasma concentration versus time curve
BAF	bioaccumulation factor
BASL4	Biosolids-Amended Soil Level 4
BCF	bioconcentration factor
BMDL	lower 95% confidence limit on the benchmark dose
bw	body weight
CAF	composite assessment factor
CAR	constitutive androstane receptor
CAS	Chemical Abstracts Service
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CMA	Chemical Manufacturers' Association
C_{max}	maximum concentration in plasma
CTV	critical toxicity value
CYP	cytochrome P450
DCDD	dichlorodibenzo-*p*-dioxin
DCP	dichlorophenol
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DSL	Domestic Substances List
DT_{50}	median dissipation time
dw	dry weight
EC	effective concentration
EU	European Union
FIFRA	*Federal Insecticide, Fungicide, and Rodenticide Act*
GUS	groundwater ubiquity score
HC_5	hazardous concentration to 5% of species
HPV	high production volume
IC	inhibitory concentration
IUPAC	International Union of Pure and Applied Chemistry
K_d	soil/water partition coefficient
K_{oa}	octanol/air partition coefficient
K_{oc}	soil organic carbon partition coefficient
K_{ow}	*n*-octanol/water partition coefficient
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOEC	lowest-observed-effect concentration
LOEL	lowest-observed-effect level
LOQ	limit of quantification
MATC	maximum allowable toxicant concentration

MDL	method detection limit
MITI	Ministry of International Trade and Industry (Japan)
MOA	mode of action
MOE	margin of exposure
MQL	method quantification limit
NHANES	National Health and Nutrition Examination Survey (United States)
NICNAS (Australia)	National Industrial Chemicals Notification and Assessment Scheme
NITE	National Institute of Technology and Evaluation (Japan)
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
P4	Plastic and Personal-Care Product Use in Pregnancy
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCPA	*Pest Control Products Act*
PEC	predicted environmental concentration
pK_a	$-\log_{10}$ acid dissociation constant
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PNEC	predicted no-effect concentration
PPAR	peroxisome proliferator-activated receptor
ppb	parts per billion
ppm	parts per million
PXR	pregnane X receptor
QSAR	quantitative structure–activity relationship
RED	Reregistration Eligibility Decision
RN	registry number
RNA	ribonucleic acid
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SIDS	Screening Information Data Set
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SSD	species sensitivity distribution
$t_{½}$	half-life
T_3	triiodothyronine
T_4	thyroxine
TCDD	tetrachlorodibenzo-*p*-dioxin
TR	thyroid receptor
TriCDD	trichlorodibenzo-*p*-dioxin
TSH	thyroid-stimulating hormone
TSMP	Toxic Substances Management Policy
US EPA	United States Environmental Protection Agency
ww	wet weight
WWTP	wastewater treatment plant

Appendices

Appendix A. Toxicological Endpoints for Triclosan Health Risk Assessments

Appendix A-1. Toxicological Endpoints for Triclosan Health Risk Assessments

Exposure scenario	Dose (mg/kg bw per day)	Study	Toxicological effects	Database UF	PCPA factor	CAF or target MOE
ADI / aggregate All populations	NOAEL = 25 ADI = 0.08	90-day toxicity study in mice	Increased liver weights and liver pathology, decrease in hematology parameters (red blood cells, hemoglobin and hematocrit) and cholesterol at 75 mg/kg bw per day	3 (lack of DNT study)	1	300[a]
Short-term incidental oral (direct exposure of children)	NOAEL = 25	As per ADI (above)	As above			
Dermal (all durations)	NOAEL = 40	90-day dermal toxicity study in rats	Based on increased incidence of occult blood in the urine, minor decrease in hematology parameters (red blood cells, hemoglobin, hematocrit), decrease in triglyceride (males) and			

Exposure scenario	Dose (mg/kg bw per day)	Study	Toxicological effects	Database UF	PCPA factor	CAF or target MOE
			cholesterol levels (males and females) and a slight focal degeneration of cortical tubules in males at 80 mg/kg bw per day			
Acute, short-term, intermediate-term and long-term inhalation	NOAEL = 3.21	21-day inhalation toxicity study in rats	Based on decreased thrombocytes and total serum proteins, increased alkaline phosphatase in male rats at 3.21 mg/kg bw per day			

Abbreviations used: ADI, acceptable daily intake; CAF, composite assessment factor; DNT, developmental neurotoxicity; NOAEL, no-observed-adverse-effect level; PCPA, *Pest Control Products Act*; target MOE, target margin of exposure for occupational and residential assessments; UF, uncertainty factor

[a]CAF/target MOE of 300 based on the application of a 10-fold uncertainty factor to account for interspecies extrapolation and a 10-fold uncertainty factor for intraspecies variation, as well as a 3-fold database deficiency factor (for lack of a DNT study). The PCPA factor was reduced to 1-fold, since uncertainties with respect to the completeness of the data were accounted for through application of the database deficiency factor, and there was a low level of concern for prenatal and postnatal toxicity given the endpoints and uncertainty factors selected for risk assessment.

Appendix B. Unadjusted, Specific Gravity and Creatinine Adjusted Urinary Triclosan Concentrations per Unit Body Weight (ug/L/kg)

In order to estimate daily intakes from the spot urinary triclosan concentrations, the body weight of each individual was incorporated to give urinary triclosan concentrations in units of µg/L/kg. This was done by dividing the concentration by each individual's body weight.

Table B-1. Unadjusted urinary triclosan concentrations (µg/L/kg) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)

Gender	Age	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	0.22 (0.17–0.28)	11 (7.3–14)
Males and Females	3–5	0.45 (0.36–0.55)	6.4 (4.2–8.7)
Males and Females	6–11	0.24 (0.18–0.31)	8.5[E] (4.1–13)
Males and Females	12–19	0.30 (0.22–0.42)	12[E] (7.2–17)
Males and Females	20–59	0.24[E] (0.16–0.36)	12 (7.4–16)
Males and Females	60–79	--	8.0 (5.7–10)
Males	3–79	0.24[E] (0.16–0.35)	11[E] (5.2–17)
Males	6 –11	0.23[E] (0.15–0.36)	F
Males	12–19	0.30[E] (0.20–0.45)	F
Males	20–59	0.25[E] (0.14–0.45)	12[E] (4.6–20)
Males	60–79	0.15[E] (0.083–0.27)	X
Females	3–79	0.20 (0.16–0.27)	10 (7.0–14)
Females	6–11	0.24[E] (0.15–0.36)	F
Females	12–19	0.31[E] (0.20–0.49)	13[E] (8.0–18)
Females	20–59	0.23[E] (0.15–0.35)	11[E] (6.4–16)
Females	60–79	--	X
Females	13–49	0.28[E] (0.18–0.42)	12 (8.2–16)

(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table B-2. Specific gravity adjusted urinary triclosan concentrations (µg/L/kg) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)

Gender	Age	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	0.33 (0.26–0.43)	14 (10–17)
Males and Females	3–5	0.57 (0.47–0.69)	7.2 (4.9–9.5)
Males and Females	6–11	0.29 (0.21–0.39)	9.6[E] (2.8–16)
Males and Females	12–19	0.38 (0.29–0.52)	12[E] (5.7–19)
Males and Females	20–59	0.37[E] (0.24–0.55)	15 (10–19)
Males and Females	60–79	--	10[E] (4.4–16)
Males	3–79	0.33[E] (0.22–0.48)	14 (9.8–18)
Males	6–11	0.27[E] (0.17–0.42)	F
Males	12–19	0.35[E] (0.23–0.54)	F
Males	20–59	0.35[E] (0.19–0.65)	16 (11–21)
Males	60–79	0.22[E] (0.14–0.36)	X
Females	3–79	0.34 (0.26–0.44)	12[E] (7.2–17)
Females	6–11	0.31[E] (0.20–0.48)	F
Females	12–19	0.42[E] (0.27–0.64)	14[E] (7.7–21)
Females	20–59	0.38[E] (0.25–0.58)	13[E] (7.8–19)
Females	60–79	--	X
Females	13–49	0.43[E] (0.28–0.65)	16[E] (9.5–22)

(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table B-3. Creatinine adjusted urinary triclosan concentrations (µg/g creatinine/kg) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)

Gender	Age	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	0.22 (0.17–0.28)	8.8[E] (5.5–12)
Males and Females	3–5	0.78 (0.65–0.92)	10 (8.3–12)
Males and Females	6–11	0.27 (0.19–0.37)	8.0[E] (3.1–13)
Males and Females	12–19	0.23 (0.17–0.32)	7.9[E] (4.4–11)
Males and Females	20–59	0.23[E] (0.15–0.34)	10[E] (5.3–15)

Males and Females	60–79	--	6.9[E] (3.2–10)
Males	3–79	0.21 (0.14–0.30)	9.8[E] (3.9–16)
Males	6–11	0.27[E] (0.16–0.44)	9.7[E] (2.9–17)
Males	12–19	0.21[E] (0.14–0.33)	F
Males	20–59	0.21[E] (0.12–0.37)	12[E] (3.5–19)
Males	60–79	0.14[E] (0.088–0.22)	X
Females	3–79	0.24 (0.18–0.31)	8.7[E] (5.5–12)
Females	6–11	0.27[E] (0.18–0.42)	F
Females	12–19	0.26[E] (0.17–0.38)	7.9[E] (2.6–13)
Females	20–59	0.25[E] (0.17–0.38)	8.8[E] (4.7–13)
Females	60–79	--	X
Females	13–49	0.27[E] (0.18–0.40)	9.9[E] (5.5–14)

(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table B-4. Unadjusted and specific gravity (SG) adjusted urinary triclosan concentrations (µg/L/kg) for Canadian pregnant women from the P4 and MIREC Studies and for infants from the P4 Study (Arbuckle et al. 2015a, 2015b)

Study	Type	Age	N[a]	Geometric Mean (95% CI)	95th Percentile (95% CI)
P4	Unadjusted	<25–40+	1096	0.29 (0.24–0.35)	11.70 (10.6–13.27)
P4	SG-Adjusted	<25–40+	1096	0.32 (0.27–0.38)	11.42 (1.00–13.09)
P4	Unadjusted	0–3 months old	95	0.72 (0.42–1.23)	12.62 (5.83–27.87)
P4	SG-Adjusted	0–3 months old	95	0.64 (0.38–1.10)	12.17 (5.97–18.53)
MIREC	Unadjusted	<25– ≥35	1755	0.19 (0.17–0.21)	10.79
MIREC	SG-Adjusted	<25– ≥35	1753	0.21 (0.19–0.23)	8.50

[a]For P4 Study, “N” refers to number of urine samples. For MIREC Study, “N” refers to number of individual participant.

Appendix C. Range of Typical Daily Urine Volumes

Table C-1. Range of typical daily urine volumes

Gender	Age (years)	Daily Mean Urine Volumes (L/day)	Reference
Males and Females	0–3 months	0.015–0.580	Aggarwal et al [date not specified]; Ingelfinger 1991; Lentner 1981; Prentice 1987; Walker 2011; Wu 2006; Water UK 2006
Males and Females	1–3 years	0.4–0.6	ICRP 2003 and Wu 2006
Males and Females	3–5	0.449 – 0.7	ICRP 2003; Lakind and Naiman 2008; Lentner 1981; Wu 2006
Males and Females	6–11	0.274–1.14	ICRP 2003; Lakind and Naiman 2008; Lentner 1981; Remer et al. 2006; Wu 2006
Males and Females	12–19	0.441–1.4	ICRP 2003; Lentner 1981; Wu 2006
Males and Females	20–59	0.6–2.03	Addis and Watanabe 1961; Davison and Nobel 1981; Francis 1960; ICRP 2003; Lakind and Naiman 2008; Lentner 1981; Parboosingh and Doig 1973; Perucca et al. 2007; Revúsová 1971; Wu 2006
Males	20–59	0.8–1.8	Addis and Watanabe 1961; ICRP 2003; Lentner 1981; Perucca et al. 2007; Revúsová 1971; Wu 2006
Females	20–59	0.6–2.03	Addis and Watanabe 1961; Davison and Nobel 1981; Francis 1960; ICRP 2003; Lakind and Naiman 2008; Lentner 1981; Parboosingh and Doig 1973; Perucca et al. 2007; Revúsová 1971; Wu 2006
Pregnant Females	NA	0.8–2.7	Davison and Nobel 1981; Francis 1960; Higby et al. 1994; Neithardt et al. 2002; Parboosingh and Doig 1973; Thorp et al. 1999;
Males and Females	60–79	0.25–2.4	ICRP 2003; Lentner 1981; Wu 2006

Abbreviation: NA, not applicable.

Appendix D. Estimated Daily Doses

Table D-1. Estimated daily dose (µg/kg bw per day) for Canadians aged 0 to 79 years of age using the unadjusted urinary concentrations (ug/L) per kg body weight (Statistics Canada 2013a, Arbuckle et al. 2014a,b)[a]

Gender	Age	Geometric Mean	95th Percentile
Males and Females	3–5	0.37–0.58	5.32–8.30
Males and Females	6–11	0.12–0.51	4.31–17.94
Males and Females	12–19	0.25–0.78	9.80–31.11
Males and Females	20–59	0.27–0.90	13.33–45.11
Males and Females	60–79	--	3.70–35.56
Males	6–11	0.12–0.49	F
Males	12–19	0.25–0.78	F
Males	20–59	0.37–0.83	17.78–40.00
Males	60–79	0.07–0.67	X
Females	6–11	0.12–0.51	F
Females	12–19	0.25–0.80	10.62–33.70
Females	20–59	0.26–0.86	12.22–41.35
Females	60–79	--	X
Females	13–49	0.31–1.05	13.33–45.11
Pregnant Women (P4)	<25–40+	0.43–1.45	17.33–58.50
Pregnant Women (MIREC)	<25– ≥35	0.28–0.93	15.98–53.92
Infants (P4)	0–3 months old	0.02–0.77	0.35–13.55

[a]Daily Dose = Unadjusted Urine Concentration (µg/L/kg) x Daily Urine Volume (L/day) / Urinary Excretion Fraction (FUE = 0.54)
(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table D-2. Estimated daily dose (µg/kg bw per day) for Canadians aged 0 to 79 years of age using the specific gravity adjusted urinary concentrations (ug/L) per kg body weight (Statistics Canada 2013a, Arbuckle et al. 2014a,b, Personal Communication September 2014, Health Canada)[a]

Gender	Age	Geometric Mean	95th Percentile
Males and Females	3–5	0.47–0.74	5.99–9.33
Males and Females	6–11	0.15–0.61	4.87–20.27
Males and Females	12–19	0.31–0.99	9.80–31.11
Males and Females	20–59	0.41–1.39	16.67–56.39
Males and Females	60–79	--	4.63–44.44
Males	6–11	0.14–0.57	F
Males	12–19	0.29–0.91	F
Males	20–59	0.52–1.17	23.70–53.33
Males	60–79	0.10–0.98	X
Females	6–11	0.16–0.65	F
Females	12–19	0.34–1.09	11.43–36.30
Females	20–59	0.42–1.43	14.44–48.87
Females	60–79	--	X
Females	13–49	0.48–1.62	17.78–60.15
Pregnant Women (P4)	<25–40+	0.47–1.60	16.92–57.10
Pregnant Women (MIREC)	<25– ≥35	0.31–1.06	12.59–42.47
Children (MIREC CD Plus)[b]	23–36 months	0.22–0.34	7.11–10.67
Infants (P4)	0–3 months old	0.0178–0.687	0.338–13.07

[a]Daily Dose = Specific Gravity Adjusted Urine Concentration (µg/L/kg) x Daily Urine Volume (L/day) / Urinary Excretion Fraction (FUE = 0.54).
[b]Preliminary results.
(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table D-3. Estimated daily dose (µg/kg bw) for Canadians aged 3 to 79 years of age using the Mage equations described in Huber et al. (2011) to predict the creatinine excretion rate (CER) for each CHMS participant, then using the CER to compute the daily dose[1] (2014 personal communication from Environmental and Radiation Health Sciences Directorate, Health Canada, to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).[a]

Gender	Age	Geometric Mean (95% confidence intervals)	95th Percentile (95% confidence intervals)

Males and Females	3–5	0.47 (0.39, 0.56)	6.3 (4.3, 8.3)
Males and Females	6–11	0.32 (0.23, 0.44)	11[E] (3.9, 17)
Males and Females	12–19	0.55 (0.41, 0.74)	18[E] (9, 26)
Males and Females	20–59	0.61[E] (0.42, 0.89)	25[E] (15, 35)
Males and Females	60–79	0.26 (0.21, 0.32)	15[E] (6.8, 24)
Males	3–5	0.47 (0.38, 0.59)	7.4[E] (3.9, 11)
Males	6–11	0.34[E] (0.22, 0.53)	F
Males	12–19	0.6[E] (0.4, 0.91)	F
Males	20–59	0.68[E] (0.41, 1.1)	30[E] (15, 46)
Males	60–79	0.33[E] (0.22, 0.49)	X
Females	3–5	0.46 (0.35, 0.61)	4.8[E] (2.2, 7.5)
Females	6–11	0.29[E] (0.2, 0.44)	F
Females	12–19	0.51[E] (0.35, 0.73)	F
Females	20–59	0.55[E] (0.37, 0.81)	20E (9.1, 31)
Females	60–79	0.21[E] (0.14, 0.32)	X
Females	13–49	0.6[E] (0.4, 0.88)	25[E] (11, 39)

[a]Daily Dose = [Creatinine Adjusted Urine Concentration (µg/g Cr) x CER (g/day)]/ [Body Weight (kg) x Urinary Excretion Fraction (FUE = 0.54)].
[E]Use data with caution
[F]Data is too unreliable to be published
[X]Suppressed to meet the confidentiality.

Appendix E. Unadjusted, Specific Gravity and Creatinine Adjusted Urinary Triclosan Concentrations

Statistics Canada (2013a) analysed the urinary triclosan data from the CHMS Cycle 2 (2009-2011). In order to perform these analyses, the CHMS Data Users Guide was used (Statistics Canada 2013b). Values below the limit of detection (LOD) were assumed to be LOD/2. The age categories were changed from what is presented in the Second Report on Biomonitoring (Health Canada 2013).

Adults aged 20-59 were combined and an additional group of females aged 13-49, representing females of child-bearing age, was created similar to the approach taken in the preliminary assessment with the NHANES data. The P4 and MIREC data were analyzed by those involved in each project (refer to Arbuckle et al. 2015a, 2015b).

Table E-1. Unadjusted urinary triclosan concentrations (µg/L) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)

Gender	Age	N	Percent < LOD[a]	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	2550	28.20	15 (12–19)	710 (540–880)
Males and Females	3–5	523	29.45	8 (7–10)	120[E] (68–160)
Males and Females	6–11	515	33.98	8 (6–10)	250[E] (82–410)
Males and Females	12–19	510	19.02	19 (14–26)	640E (400–870)
Males and Females	20–59	712	24.16	18[E] (12–27)	770[E] (440–1100)
Males and Females	60–79	290	41.72	--	590 (430–750)
Males	3–79	1274	26.77	17 (12–25)	790[E] (350–1200)
Males	6–11	262	34.35	8[E] (5–12)	F
Males	12–19	254	18.11	19[E] (13–30)	F
Males	20–59	358	22.35	21[E] (12–36)	960[E] (370–1600)
Males	60–79	141	36.88	12[E] (7–22)	X
Females	3–79	1276	29.62	13 (10–17)	680[E] (410–960)
Females	6–11	253	33.60	7[E] (5–11)	F
Females	12– 9	256	19.92	18[E] (12–27)	620[E] (370–870)
Females	20–59	354	25.99	16[E] (10–25)	710[E] (430–990)
Females	60–79	149	46.31	No data	X
Females	13–49	499	23.68	18[E] (12–29)	720[E] (410–1000)

(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table E-2. Specific gravity adjusted urinary triclosan concentrations (µg/L) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)[a]

Gender	Age	N	Percent < LOD	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	2550	28.20	22 (17–28)	990 (790–1200)
Males and Females	3–5	523	29.45	10 (8.5–13)	120[E] (49–190)

Males and Females	6–11	515	33.98	9.2 (6.9–12)	F
Males and Females	12–19	510	19.02	24 (17– 32)	840[E] (440–1200)
Males and Females	2059	712	24.16	28[E] (18–42)	1000 (870–1200)
Males and Females	60–79	290	41.72	--	760[E] (460–1100)
Males	3–79	1274	26.77	23[E] (16–34)	1100 (910–1200)
Males	6–11	262	34.35	8.8[E] (5.7–14)	450[E] (140–760)
Males	12–19	254	18.11	23[E] (15–35)	790[E] (26–1300)
Males	20–59	358	22.35	29[E] (16–53)	1100 (820–1400)
Males	60–79	141	36.88	19[E] (12–30)	X
Females	3 –79	1276	29.62	21 (16–27)	760 (550 – 970)
Females	6–11	253	33.60	9.7[E] (6.5–15)	F
Females	12–19	256	19.92	24[E] (16–36)	940[E] (450–1400)
Females	20–59	354	25.99	27[E] (17–41)	790[E] (400–1200)
Females	60–79	149	46.31	--	X
Females	13–49	499	23.68	19[E] (19–44)	980[E] (480–1500)

[a]The approach used to adjust the urinary concentrations using specific gravity was taken from Miller et al. (2004). SG Adjusted = Unadjusted x (SGref-1/SGsample-1) where SGref was assumed to be 1.024 for the CHMS data.
(--) If >40% of samples were below the limit of detection (LOD), the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table E-3. Creatinine adjusted urinary triclosan concentrations (µg/g creatinine) for Canadians aged 3 to 79 years of age (Statistics Canada 2013a)

Gender	Age	N	Percent < LOD	Geometric Mean (95% CI)	95th Percentile (95% CI)
Males and Females	3–79	2540	28.20	15 (12–19)	620 (400–830)
Males and Females	3–5	522	29.45	14 (12–17)	190 (140–250)
Males and Females	6–11	513	33.98	8.7 (6.4–12)	270[E] (79–470)
Males and Females	12–19	508	19.02	14 (11–19)	500[E] (290–710)
Males and Females	20–59	708	24.16	17[E] (12–26)	720[E] (400–1000)
Males and Females	60–79	289	41.72	--	600[E] (290–910)
Males	3–79	1270	26.77	15 (11–21)	700[E] (360–1000)
Males	6 – 11	261	34.35	8.8[E] (5.6–14)	F
Males	12–19	253	18.11	14[E] (9.0–21)	450[E] (220–690)
Males	20–59	357	22.35	17[E] (9.6 - 30)	880[E] (390–1400)
Males	60–79	141	36.88	12[E] (7.5–18)	X
Females	3–79	1270	29.62	15 (11–19)	570[E] (340–800)
Females	6–11	252	33.60	8.5[E] (5.6–13)	F
Females	12–19	255	19.92	15[E] (10–22)	610[E] (280–950)
Females	20–59	351	25.99	18[E] (12–27)	660[E] (340–980)
Females	60–79	148	46.31	--	X
Females	13–49	495	23.68	18[E] (12–28)	710[E] (370–1100)

(--) If >40% of samples were below the LOD, the percentile distribution is reported but means were not calculated.
[E]Use data with caution.
[F]Data is too unreliable to be published.
[X]Supressed to meet the confidentiality requirements of the *Statistics Act*.

Table E-4. Unadjusted and specific-gravity (SG) adjusted urinary triclosan concentrations (µg/L) for Canadian pregnant women from the P4 and MIREC studies and infants (0 to 3 months old) (Arbuckle et al. 2015a, 2015b)

Study	Population	Type	Age	N[a]	Percent < LOD	Geometric Mean (95% CI)	95th Percentile
P4	Pregnant Women	Unadjusted	<25–40+	1247	16.4	21.61 (18.17–25.71)	833.4 (740.7 – 918.1)
P4	Pregnant Women	SG-Adjusted[b]	<25–40+	1247	13.2	22.9 (19.2–27.2)	774.9 (673.6–880.8)
P4	Infants	Unadjusted	0–3 months	100	39.0	2.8 (1.6–4.9)	52.0 (22.7–100.0)
P4	Infants	SG-Adjusted	0–3 months	98	24	2.5 (1.5–4.4)	53.4 (35.2–229.8)
MIREC	Pregnant Women	Unadjusted	<25–≥35	1861	0.6	12.64 (11.38–14.03)	697.58
MIREC	Pregnant Women	SG-Adjusted	<25–≥35	1858	0.6	14.36 (13.01–15.85)	571.10

[a]For P4 Study, "N" refers to number of urine samples. For MIREC Study, "N" refers to number of individual participant.
[b]The approach used to adjust the urinary concentrations using specific gravity was SG Adjusted = Unadjusted x (SGref-1/SGsample-1) where SGref was equal to the median of the cohort.