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CHALLENGES IN MANAGING AND RISK ASSESSMENT OF EMERGING ENVIRONMENTAL POLLUTANTS

Comprehensive insight into triclosan—from widespread occurrence to health outcomes

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Abstract
Humans are exposed to the variety of emerging environmental pollutant in everyday life. The special concern is paid to endocrine disrupting chemicals especially to triclosan which could interfere with normal hormonal functions. Triclosan could be found in numerous commercial products such as mouthwashes, toothpastes and disinfectants due to its antibacterial and antifungal effects. Considering the excessive use and disposal, wastewaters are recognized as the main source of triclosan in the aquatic environment. As a result of the incomplete removal, triclosan residues reach surface water and even groundwater. Triclosan has potential to accumulate in sediment and aquatic organisms. Therefore, the detectable concentrations of triclosan in various environmental and biological matrices emerged concerns about the potential toxicity. Triclosan impairs thyroid homeostasis and could be associated with neurodevelopment impairment, metabolic disorders, cardiotoxicity and the increased cancer risk. The growing resistance of the vast groups of bacteria, the evidenced toxicity on different aquatic organisms, its adverse health effects observed in vitro, in vivo as well as the available epidemiological studies suggest that further efforts to monitor triclosan toxicity at environmental levels are necessary. The safety precaution measures and full commitment to proper legislation in compliance with the environmental protection are needed in order to obtain triclosan good ecological status. This paper is an overview of the possible negative triclosan effects on human health. Sources of exposure to triclosan, methods and levels of detection in aquatic environment are also discussed.

Keywords Triclosan · Antimicrobial agent · Personal care product · Endocrine disrupting chemical · Emerging environmental pollutant · Environmental pollution · Adverse health effects

Introduction

Humans are exposed to the vast range of chemicals in everyday life, and the major issue nowadays presents substances that could interfere with endocrine system through alteration of receptor expression and/or hormone synthesis, metabolism, transport, distribution and clearance (Milanović et al. 2016; Gao et al. 2021; La Merrill et al. 2020). Endocrine disrupting chemicals (EDCs) are defined as 'an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations' (European Commission 2020).

EDCs are all around us, in food, food contact materials, textile, electronics, plastic, medical devices, cosmetics, personal care products, etc. Although the impact of chronic EDC exposure on human health represents relatively new toxicological and eco-toxicological issue, the concerns of the various scientific institutions and regulatory bodies worldwide are rapidly growing. The reasons are reflected in the increased trends of endocrine-related diseases and their evidence-based association with EDCs (Milić et al. 2015; Milošević et al. 2017, 2018, 2020; Milanović et al. 2020). However, EDCs are a heterogeneous set of chemical compounds, and the information about the relationship between exposure to an EDC and a certain disorder are mostly incomplete. Consequently, there are still inconsistencies in the regulation of EDCs.

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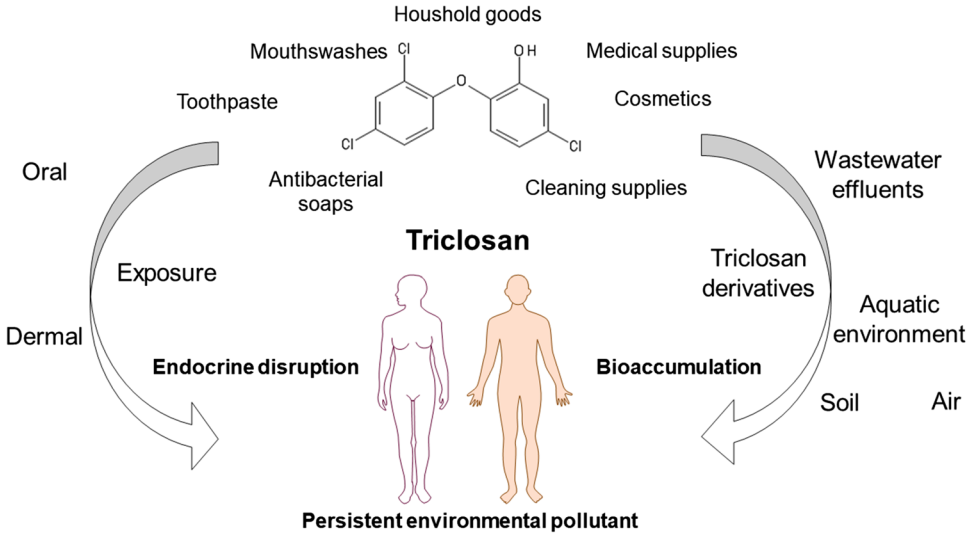

Fig. 1 Sources and pathways of human exposure to triclosan

Triclosan (TCS, 5-chloro-2-(2,4-dichlorophenoxy) phenol) is a synthetic, multi-purpose antimicrobial agent which could be found as an ingredient in mouthwashes, toothpastes, soaps, disinfectants, deodorants, clothing textiles, furniture and other materials (Dhillon et al. 2015). TCS in commercial products could also be named Irgasan (Lee et al. 2019). It has been estimated that 1500 tons of TCS is globally produced per year, and 132 million liters of TCS-containing products are used annually only in the USA (Alfhili and Lee 2019). Probably, the production rates have changed since the outbreak of coronavirus disease 2019 (COVID-19) due to the high demand for disinfection (Chu et al. 2020; Ejtahed et al. 2020; Usman et al. 2020).

Halogenated biphenyl ether structure of TCS is stable to hydrolysis (in the pH range 4–9) and is related to other EDCs such as bisphenol A (BPA) and dioxins (Montaseri and Forbes 2016). The US National Institute of Environmental Health Sciences (NIEHS) and Environmental Protection Agency (EPA) declare TCS as an EDC (NIEHS 2020), while according to the European Food Safety Authority (EFSA) and European Chemical Agency (ECHA), it is still under assessment as EDCs (ECHA 2020). The environmental and human toxicology data about TCS suggest the acute toxicity to aquatic organisms and potential human carcinogenicity, mild genotoxicity, endocrine disruption and induction of antimicrobial resistance (Huang et al. 2014a; Li 2021). However, the adequate regulatory evaluation of TCS usage and exposure limits are still incomplete.

The TCS use in the over-the-counter antiseptic wash products (liquid, foam, soaps and body washes) has been banned by the United States Food and Drug Administration (FDA) since 2016. However, the hand sanitizers, wipes and other TCS-containing products are not yet regulated by FDA (FDA 2016). On the contrary, the use of TCS as biocide as well as in food contact materials has been banned in the European Union, while its application in personal care products is still allowed (European Commission 2020). According to the European Commission as well as the national standards set by Canada, the USA and China, the maximum allowed TCS concentration in soaps, deodorants and mouth products should not exceed 0.3% (w/w) (Wang and Liang 2021). Japan decided to decrease the allowable TCS limits in cosmetic products (0.1%), while there is still no rule in Norway regarding TCS maximum allowable concentration (Cosmetic Ingredient Review (CIR) 2010). Besides the differences in regulations of some cases, it presents a real challenge to ensure compliance and additional efforts that could be required. Today, disinfectants and antiseptic wash products are essential in the control and prevention of devastating spread of SARS-CoV-2 virus (Dhama et al. 2021). However, the excessive use and disposal of TCS containing disinfectants and antiseptics raise concerns to the negative effects on the human health and the environment (Mukherjee et al. 2021). Therefore, further efforts regarding the monitoring of possible related TCS health effects and safety precaution measures are necessary in order to achieve not only the harmonization of the global legislation regarding TCS but also the long-term health and environmental benefits.

This paper aims to provide an overview of the potential sources of TCS exposure with the detected concentrations in the environment and biological matrices, methods of analyses and its removal. The special attention is paid to the TCS-associated risk to human health.

Sources of TCS exposure

Possible sources of human exposure to triclosan are presented in Fig. 1. Over 80% of TCS usage is contributed to cosmetics, various personal care products and household cleaning products which contain mostly between 0.1 and 0.3% of TCS (Gao et al. 2018). However, TCS-containing personal care products

are recognized as the primary source of TCS, although the maximum allowed concentration of TCS in different products varies worldwide. Besides toothpastes, antibacterial and deodorant soaps, dishwashing liquids and antiperspirants/deodorants, TCS is found in a wide range of consumer products as a material preservative (kitchen utensils, toys, clothes, fabrics, etc.) (Dhillon et al. 2015; Zhu et al. 2020).

Based on the TCS exposure study conducted in Korea, the systemic exposure dosage (SED) was 0.4952 μmol/kg of body weight per day depending on the sum of representative cosmetic and oral care products. If only the rinse-off cosmetics, deodorants, color cosmetics as well as oral care products were considered, SED would be 0.1635 μmol/kg of body weight per day (Lee et al. 2019; Park et al. 2019). According to the Scientific Committee on Consumer Safety (SCCS) no-observed-adverse-effect level (NOAEL) of TCS is 41.44 μmol/kg of body weight per day based on the established chronic hematoxicity and the decreased spleen mass in rats, whereas exposure to TCS through inhalation was not considered. However, EPA calculated NOAEL remained almost three times higher, 103.61 μmol/kg of body weight (Scientific Committee on Consumer Safety (SCCS) 2011).

Besides the direct use of TCS products, the exposure to TCS via air, surface water, drinking water and soil is also possible and could lead to the long-term exposure to TCS. It has been estimated that more than a half of the amount of the total TCS consumed is directly discharged into the environment (Huang et al. 2014a).

Occurrence of TCS in different environmental matrices

Air

Considering the low volatility of TCS, the TCS mass distribution in air is less than 1%, and it is believed that air is the least migration pathway for TCS (Zhang et al. 2021). Therefore, the limited number of studies has been available in the literature up to now. Regarding the frequent usage of TCS as a material preservative, it was detected in 100% of the indoor dust samples (Zhu et al. 2020). Interestingly, based on the study conducted in France, TCS concentrations varied between the observed locations (house, apartment, day nursery and office), and the office was identified as the most contaminated site (0.794 pmol/m^3) (Laborie et al. 2016). The TCS was also measured in 100% of indoor dust from Beijing at the levels up to 4075.4 nmol/kg (Wang et al. 2021). However, TCS was found in much lower concentrations (up to 759.8 nmol/kg) in indoor dust samples in Belgium (Geens et al. 2009a).

In the recently published study, the positive correlations were found between urinary TCS levels and indoor dust samples (Zhang et al. 2021). Based on the paired human urine and indoor dust samples, the addition of indoor dust ingestion to the total TCS exposure was minor (Zhang et al. 2021; Wang et al. 2021). However, the obtained findings imply that indoor dust is also an important source of human exposure to TCS.

Occurrence and removal of TCS from wastewater

TCS-containing personal care products are recognized as the primary source of TCS in wastewater. It is supposed that TCS reaches surface water, ground water, soil and ultimately drinking water via municipal and industrial wastewater effluent, due to the incomplete removal and/or lack of wastewater treatment plants (WWTPs) (Huang et al. 2014a).

Although, the highest TCS concentration was measured in raw wastewater in the USA (297.7 nM), TCS was detected at high level in both raw and treated wastewater in South Africa (60.8 nM versus 44.9 nM, Table 1) (Kumar et al. 2010; Lehutso et al. 2017). The available wastewater treatment technologies vary among the countries, and the differences are more pronounced between developing and developed countries. Advanced treatment methods are relatively scarce in the developing world (Wee et al. 2020). Some cities, even in Europe, are still without an urban waste water treatment plant (Milanović et al. 2016).

The increased TCS concentrations in influent were followed with the decreased in effluent in Australia (Ying and Kookana 2007), Thailand (Juksu et al. 2019) and UK (Petrie et al. 2016) (Table 1). The TCS removal from wastewater depends strongly on its physicochemical properties (Lee 2015). The lipophilic character of TCS is related to the high sorption potential. TCS is mostly removed via biodegradation or adsorption, and WWTP removal efficiency could be up to 99% (Olaniyan et al. 2016). Some of the commonly applied biological treatment methods are activated sludge process, trickling filters, oxidation ditches and rotating biological contactors (Jagini et al. 2019). It was observed that the removal efficiency was more than three times higher during the aerobic conditions compared with anaerobic (97% versus 30%) (Gangadharan et al. 2012). Additionally, the removal efficiency could be affected by temperature, pH value as well as by the lipid, protein and carbohydrate contents (Winkler et al. 2007).

Activated carbon, carbon nanotubes, zeolite, clay and the adsorption with biochar were also tested for the removal of TCS (Kaur et al. 2018). Additionally, polymeric resins showed high adsorption of TCS (99%) (Solak et al. 2014), and among different types of membrane technologies, ultrafiltration was observed as the highly efficient method (Sheng et al. 2016). Although the adsorption is efficient (˃ 80%) in TCS removal, the large quantity of the solid residue

Table 1 The occurrence of triclosan in different environmental matrices

Matrix	Method	Method detection limit	TCS concentration (range)	Country	Reference
Indoor air	ASE, LC–MS/MS	LOD Gaseous phase $4{\cdot}10^{-4}$ pmol/m^3	Mean by location:	France	Laborie et al. (2016)
		LOD Particulate phase $3{\cdot}10^{-4}$ pmol/m^3	Office 0.794 pmol/m^3		
		LOQ Gaseous phase $1{\cdot}10^{-4}$ pmol/m^3	Apartment 0.528 pmol/m^3		
			House 0.359 pmol/m^3		
		LOQ Particulate phase $9{\cdot}10^{-4}$ pmol/m^3	Day nursery 0.235 pmol/m^3		
Indoor dust	LLE with SPE, UPLC-MS/MS	LOD 0.794 nmol/kg	Mean 127.1 nmol/kg	China	Wang et al. (2021)
		LOQ 2.763 nmol/kg	Median 138.5 nmol/kg		
			(n.d.–4075.4 nmol/kg)		
Raw wastewater	SPE, GC–MS	LOQ 0.01 nM	1.98–2.92 nM	Australia	Ying and Kookana (2007)
Treated wastewater	SPE, GC–MS	LOQ 0.01 nM	Median 0.373 nM	Australia	Ying and Kookana (2007)
			Mean 0.490 nM		
			(0.08–1.50 nM)		
Treated wastewater	SPE, GC–MS	LOQ $5{\cdot}10^{-3}$ nM	0.045–0.375 nM	New Zealand	Emnet et al. (2020)
Raw wastewater	SPE, UHPLC-MS/MS	LOD $9{\cdot}10^{-4}$ nM	Mean 1.69 ± 1.23 nM	Thailand	Juksu et al. (2019)
		LOQ $3{\cdot}10^{-3}$ nM			
Treated wastewater	SPE, UHPLC-MS/MS	LOD $2{\cdot}10^{-4}$ nM	Mean 0.281 ± 0.111 nM	Thailand	Juksu et al. (2019)
		LOQ $9{\cdot}10^{-4}$ nM			
Raw wastewater	LLE, LC–MS	LOD 0.07 nM	6.94–60.8 nM	South Africa	Lehutso et al. (2017)
Treated wastewater	LLE, LC–MS	LOD 0.07 nM	3.42–44.9 nM	South Africa	Lehutso et al. (2017)
Raw wastewater	LLE, LC–MS/MS	/	n.d.–297.7 nM	USA	Kumar et al. (2010)
Treated wastewater	LLE, LC–MS/MS	/	n.d.–18.6 nM	USA	Kumar et al. (2010)
Raw wastewater	SPE, UHPLC-MS/MS	LOD 0.02 nM	3.64 ± 0.363 nM	UK	Petrie et al. (2016)
		LOQ 0.06 nM			
Treated wastewater	SPE, UHPLC-MS/MS	LOD 0.02 nM	0.687 ± 0.071 nM	UK	Petrie et al. (2016)
		LOQ 0.05 nM			
River water	Direct injection, LC–MS/MS	LOQ 0.02 nM	Mean 0.06 nM	Canada	Lalonde et al. (2019)
			(n.d.–3.02* nM)		
River water	SPE, UHPLC-MS/MS	LOQ $3{\cdot}10^{-4}$ nM	Mean 0.02 nM	China	Ma et al. (2018)
			Median $6.4{\cdot}10^{-3}$ nM		
			(n.d.–0.227* nM)		
River water	SPE, LC-LC–MS/MS	LOD $6{\cdot}10^{-4}$ nM	n.d.–0.770* nM	Spain	Esteban et al. (2014)
		LOQ $2{\cdot}10^{-3}$ nM			
River water	LLE, HPLC–UV/VIS	LOQ 0.01 nM	n.d.–0.107* nM	Japan	Nishi et al. (2008)

Table 1 (Continued)

Matrix	Method	Method detection limit	TCS concentration (range)	Country	Reference
River water	SPE, HPLC–PDA	LOD 0.03 nM LOQ 1.17 nM	n.d.–3.87* nM	South Africa	Madikizela et al. (2014)
River water	SPE, GC–MS	LOQ 0.01 nM	Mean 0.114* nM (0.03–0.259* nM)	Australia	Ying and Kookana (2007)
River water	SPE, UHPLC-MS/MS	LOD 0.01 nM LOQ 0.03 nM	0.349 ± 0.032* nM	UK	Petrie et al. (2016)
River water	SPE, UHPLC-MS/MS	/	0.023–0.075* nM	China	Yao et al. (2019)
River water	LLE, GC–MS	LOD 0.01 nM	Median 0.490* nM Mean 3.26* nM Max. 17.82* nM	India	Ramaswamya et al. (2011)
River water	SPE, UHPLC-MS/MS	LOD $7{\cdot}10^{-5}$ nM LOQ $2{\cdot}10^{-4}$ nM	Upstream mean 0.587 ± 0.604* nM Discharged point mean 0.184 ± 0.642* nM Downstream mean 0.414 ± 0.337* nM	Thailand	Juksu et al. (2019)
River water	SPE, GC–MS	LOD $7{\cdot}10^{-3}$ nM	0.01–0.207* nM	Denmark	Matamoros et al. (2012)
Lake water	/	/	0.02–1.07* nM	USA	Lyndall et al. (2017)
Lake water	SPE, LC–MS/MS	LOD $4{\cdot}10^{-3}$ nM	$8.3{\cdot}10^{-3}$–0.021 nM	USA	Bai and Acharya (2019)
Lake water	SPE, GC–MS	LOD $7{\cdot}10^{-3}$ nM LOQ 0.014 nM	Mean 0.03 nM	Denmark	Matamoros et al. (2012)
Wetland	SPE, GC–MS	LOD $7{\cdot}10^{-3}$ nM LOQ 0.014 nM	Mean 0.08* nM	Denmark	Matamoros et al. (2012)
Channel	SPE, GC–MS	LOD $7{\cdot}10^{-3}$ nM LOQ 0.014 nM	Mean 0.03 nM (0.014–0.055 nM)	Denmark	Matamoros et al. (2012)
Sediment	Microwave-assisted extraction with SPE, GC–MS	LOD $2{\cdot}10^{-3}$ nmol/kg LOQ $7{\cdot}10^{-3}$ nmol/kg	0–0.18 nmol/kg	Spain	Azzouz and Ballesteros (2016)
Sediment	Ultrasonic extraction, UHPLC-MS/MS	LOD 0.1 nmol/kg LOQ 0.3 nmol/kg	Upstream mean 150 ± 197 nmol/kg Discharged point mean 156 ± 142 nmol/kg Downstream mean 176 ± 209 nmol/kg	Thailand	Juksu et al. (2019)
Sediment	Ultrasonic extraction—SPE, HPLC–MS/MS	LOD 0.2 nmol/kg LOQ 0.7 nmol/kg	Mean 24.2 nmol/kg Median 5.63 nmol/kg (n.d.–224.1 nmol/kg)	China	Chen et al. (2020)

Table 1 (Continued)

Matrix	Method	Method detection limit	TCS concentration (range)	Country	Reference
Wild fish plasma	SPE, UHPLC-MS/MS	With enzyme hydrolysis: LOD 10 nM LOQ 33.7 nM Without enzyme hydrolysis: LOD 6.3 nM LOQ 20.9 nM	Wet With enzyme hydrolysis: Median 0 (0–33.7 nM) Dry With enzyme hydrolysis: Median 0 (0–60.8 nM)	China	Yao et al. (2019) Without enzyme hydrolysis: Median 0 (0–20.9 nM) Without enzyme hydrolysis: Median 0 (0–27.1 nM)
Quagga mussels	SPE, LC–MS/MS	LOD 0.035 nmol/g	0.083–0.097 nmol/g	United States	Bai and Acharya (2019)
Fish	QuEChERS, UHPLC-MS/MS		Muscle 0 nmol/g Blood mean 0.189 ± 0.093 nM Liver mean 0.172 ± 0.084 nmol/g Bile mean 2.39 ± 1.04 nM	Thailand	Juksu et al. (2019)
Fish	Soxhlet extraction, HPLC–PDA	LOQ 3.45 nmol/kg	314.6–2034.3 nmol/kg	India	Das Sarkar et al. (2020)
Groundwater	SBSE, atmospheric pressure GC–TOF–MS	LOD < 0.003 nM	0.235* nM	Spain	Pintado-Herrera et al. (2014)
Groundwater	LLE, GC–MS	LOD $3 \cdot 10^{-5}$ nM	0–$1 \cdot 10^{-4}$ nM	Zambia	Sorensen et al. (2015)
Groundwater	SPE, HPLC–UV, GC–MS	LOD 0.05 nM	n.d.–0.183* nM	USA	Karnjanapiboonwong et al. (2011)
Drinking water	SPE, LC–MS/MS	LOD 4 $\cdot 10^{-3}$ nM LOQ 0.01 nM	Mean 9 $\cdot 10^{-3}$ nM (n.d.–0.034 nM)	Malaysia	Wee et al. (2020)
Drinking water	SPE, GC–MS	LOD 0.432 nM	Mean 2.54 nM	United States	Loraine and Pettigrove (2006)
Drinking water	SPE, GC–MS	LOD $7 \cdot 10^{-4}$ nM LOQ $2 \cdot 10^{-3}$ nM	Median 0.033 nM (n.d.–0.050 nM)	China	Li et al. (2010)
Bottled water	SPE, GC–MS	LOD $7 \cdot 10^{-4}$ nM LOQ $2 \cdot 10^{-3}$ nM	Median 0.012 nM ($2 \cdot 10^{-3}$–0.033 nM)	China	Li et al. (2010)
Sludge	Ultrasonic extraction, UHPLC-MS/MS	LOD $2 \cdot 10^{-4}$ nmol/g LOQ $7 \cdot 10^{-4}$ nmol/g	Mean 2.09 ± 1.39 nmol/g	Thailand	Juksu et al. (2019)
Biosolid	LLE, SPE, GC–MS	LOQ 0.017 nmol/g	Mean 19.27 nmol/g Median 8.01 nmol /g (0.3–58 nmol/g)	Australia	Ying and Kookana (2007)
Biosolid	PLE, LC–MS/MS	LOD $4 \cdot 10^{-4}$ nmol/g	0.311–24.38 ng/g	USA	Cha and Cupples (2009)
Soil	PLE, LC–MS/MS	LOD $2 \cdot 10^{-4}$ nmol/g	n.d.–3.52 nmol/kg	USA	Cha and Cupples (2009)
Soil	ASE, LC–MS	LOD 171.3 nmol/kg	331.6–552.6 nmol/kg	USA	Kinney et al. (2008)

* PNEC value is exceeded (0.069 nM)

requires the further treatment (Luo et al. 2019). The efficient removal from the sludge could be met by trickling filters (˃ 90%) (Winkler et al. 2007). However, in the sewage sludge, the microbial activity transforms TCS to methyl triclosan (MTCS). After biological treatment, MTCS was detected in wastewater (mean 0.037 nM), treated sludge (mean 0.446 nmol/g) as well as in surface water in the concentrations up to 0.02 nM (Tohidi and Cai 2015; Wang and Kelly 2017).

Nevertheless, the main removal TCS pathway from water sources is still oxidation. Particularly, photocatalysis is more appropriate for TCS removal from wastewater (Hippargi et al. 2021; Kaur et al. 2020). TCS is identified as biodegradable, photo-unstable, and chlorine and ozone readily reactive. Although oxidation techniques (such as chlorination, ozonation, Fenton processes, photolysis/photocatalysis and electrochemical oxidation) demonstrated the high TCS removal efficiency, chlorination and photooxidation can result in the formation of hazardous compounds (Bedoux et al. 2012; Luo et al. 2019). Chlorinated TCS derivatives and dioxins such as 2,8-dichlorodibenzo-P-dioxin (2,8-DCDD), 2,4-dichlorophenol and 2,4,6-trichlorophenol are more toxic than the parent TCS (Aranami and Readman 2007; Olaniyan et al. 2016; Reiss et al. 2002). These compounds are associated with serious effects such as genotoxicity, mutagenicity and carcinogenicity (Adithya et al. 2021). It is worth noting that chlorination triggers the endocrine disruption and results in 30-fold higher TCS anti-estrogenic activity (Li 2021). The TCS degradation products seem to be more persistent with higher bioaccumulation potential, due to its increased lipophilicity and volatility (Tohidi and Cai 2015). Considering all the facts mentioned above, the regular monitoring programs and the comprehensive risk assessment of TCS and TCS degradation products in the surface water are needed in order to protect better both environment and health.

Surface water

Besides the accomplished advances in WWTPs, the complete removal of TCS is still hard to achieve. Therefore, in several studies conducted worldwide, TCS was detected in surface water despite the lipophilic nature and easy absorption into the sediment and sewage sludge (Table 1).

As a part of the priority list review process within the Water Frame Directive, the Joint Research Centre conducted a large survey in 10 countries at 686 sampling sites, and TCS was quantified in more than 40% inland whole water samples (in total 5430 analyzed samples) with the maximum detected concentration of 96.7 nM (Carvalho et al. 2016). It is worth noting that TCS was prioritized as one of the top ten specific pollutants among 500 pollutants in the Elbe River basin (von der Ohe et al. 2011). In Europe, the detected TCS concentrations in different river bodies significantly varied from 0.207 nM in Denmark to 0.770 nM in Spain (Esteban et al. 2014; Matamoros et al. 2012). The measured concentrations of TCS were significantly higher in India (up to 17.8 nM), South Africa (up to 3.1 nM) and Canada (3 nM) compared to Japan (0.107 nM), China (0.227 nM) and the USA (1.1 nM) (Lalonde et al. 2019; Ma et al. 2018; Madikizela et al. 2014; Nishi et al. 2008; Ramaswamya et al. 2011).

Owing to the bioaccumulation potential (von der Ohe et al. 2012), TCS presence was detected in sediment and aquatic organisms such as wild fish plasma, quagga mussels and fish (Bai and Acharya 2019; Das Sarkar et al. 2020; Juksu et al. 2019; Yao et al. 2019). TCS was even found in the 30-year-old sediment cores (Singer et al. 2002). Hence, TCS is proposed as a contaminant that is mainly associated with the acute and genetic toxicity in the sediment (Chen et al. 2015).

Based on the reported values given in Table 1, TCS concentrations in surface water were several times higher than the predicted no observed effect concentration (PNEC) of TCS set by European Commission (0.069 nM). Hence, the current prioritization methodology of TCS is questionable due to the growing resistance of the vast groups of bacteria and the demonstrated TCS toxicity toward different aquatic organisms at the environmental levels (Khatikarn et al. 2018; Lydon et al. 2018; Westfall et al. 2019).

Groundwater

Due to the widespread exposure, TCS could be even found in groundwater samples. Despite the limited number of studies, TCS levels in groundwater ranged from 0.0001 nM in Zambia, 0.183 nM in the USA to even 0.235 nM in Spain (Karnjanapiboonwong et al. 2011; Pintado-Herrera et al. 2014; Sorensen et al. 2015).

Drinking water

Regarding the drinking water samples, TCS was measured in the USA in the extremely high concentrations up to 2.54 nM (Perez et al. 2013). TCS was also detected in drinking water samples in Malaysia (up to 0.034 nM), China (0.05 nM) and Taiwan (up to 0.356 nM) (Yang et al. 2014; Wee et al. 2020). In bottled water, TCS was detected with high frequency (in 18 out of 21 samples in China), but in lower concentration (0.033 nM in bottled water versus 0.05 nM in tap water) (Li et al. 2010).

Soil

Due to the high lipophilicity, TCS is easily adsorbed into sewage sludge and can be found in the biosolids and agricultural soils, presenting a high risk for entering the food chain

via agricultural products. The application of recycled water for irrigation purposes is also associated with the occurrence of TCS in soils (Mendez et al. 2016). Although about 50% of biosolids are land applied in the USA, the available data about the TCS concentration in soil are still limited. TCS levels in soil samples, after the application of biosolids, ranged from 0.562 to 3.52 nmol/kg (Cha and Cupples 2009). In another study, TCS was measured in much higher concentration (331.6–552.6 nmol/kg) after the land application of biosolids (Kinney et al. 2008). In sludge, detected levels of TCS were 3.48 nmol/g in Thailand, whereas in biosolids 32.05 nmol/g in the USA and even 57.9 nmol/g in Australia (Cha and Cupples 2009; Juksu et al. 2019; Ying and Kookana 2007).

The half-life of TCS in aerobic soil was 18 days (Dhillon et al. 2015), and the bioaccumulation potential of triclosan was observed in different fruits, root crops, radish, soybean plants, lettuce and pinto beans (Karnjanapiboonwong.et al. 2011; Calderon-Preciado et al. 2012). TCS was found in edible parts of onions (up to 1.5 nmol/g) when the plant was cultivated in irrigated soil with TCS environmental concentrations (0–5 nM) (Mendez et al. 2016). In radish almost the same TCS concentration was obtained as in the cultivated soil (31.8 µmol/kg versus 34.2 µmol/kg) (Pannu et al. 2012). Nevertheless, it was found that biosolid amendment of soils resulted in the increased persistence, plant accumulation and overall ecotoxicological risk of TCS (Fu et al. 2016).

TCS pharmacokinetics

Considering the fact that TCS was measured in various types of environmental compartments, it can be considered as a ubiquitous pollutant. Hence, oral ingestion can be identified as the main source of TCS uptake (Lu et al. 2018). The ingestion of TCS is followed by a rapid gastrointestinal absorption and median urinary excretion of 54%, within 4 days (Sandborgh-Englund et al. 2006). On the contrary, after dermal exposure, which is identified as the second main exposure route, less than 10% of TCS is absorbed (Queckenberg et al. 2010). Additionally, TCS can be absorbed through the oral mucous membrane (Weatherly and Gosse 2017).

Owing to the lipophilic properties, TCS is mainly distributed in liver and adipose tissue. During the metabolism mostly performed in liver, more polar TCS metabolites are formed (Moss et al. 2000). In an in vitro study, using human and rat liver fractions, it was found that in phase I, glutathione adducts and aromatic hydroxylation products were formed followed by sulphation and glucuronidation in the phase II (Guesmi and Sleno 2020). The cleavage process resulted in the formation of 2,4-dichlorophenol and 4-chlorocatechol that were detected in rat urine and feces (Fang et al. 2010). However, TCS can also be directly conjugated and is mainly excreted in urine as TCS-glucuronide and TCS-sulphate (Sandborgh-Englund et al. 2006).

Regardless the route of exposure, TCS is primary excreted via urine, with the elimination half-life around 11 h (Queckenberg et al. 2010; Sandborgh-Englund et al. 2006). Therefore, urinary TCS is predominantly used as a biomarker of TCS exposure.

Methods of TCS analysis

Extraction methods

The analysis of environmental pollutants at trace and ultra-trace levels is a complex task and presents a real challenge (Wise et al. 2006). The protocols for TCS analysis in various matrices involve different sample preparation methods (Table 1). One of the key challenges in the development of reliable preconcentration step is the hydrophobic nature of TCS and the fact that TCS is usually present in a complex mixture with a great number of pollutants and degradation products.

A rapid and economic enzyme-linked immunosorbent assay (ELISA) together with the different types of eco-friendly microextraction techniques has been developed in recent years for monitoring of TCS exposure such as air-assisted liquid–liquid microextraction (AALLME), microextraction by packed sorbent (MEPS), stir bar sorptive extraction (SBSE) and vortex assisted-supramolecular solvent-based microextraction (VA-SSME) (Ahn et al. 2012; González-Mariño et al. 2011; Mpupa et al. 2017; Rocha et al. 2019).

However, liquid/liquid extraction (LLE) and solid-phase extraction (SPE) are still the most popular methods for the separation and enrichment of TCS before further analysis. High TCS recoveries at low concentrations can still be met for surface water, groundwater and even drinking water (Table 1). LLE involves large quantities of organic solvents (hexane, dichloromethane, etc.), whereas C18 and HLB cartridges are needed for the SPE technique (González-Mariño et al. 2011). Both extraction methods can cause loss of trace-level analyte due to the multi-step procedure (Arditsoglou and Voutsa 2008; Gatidou et al. 2007; Li et al. 2010, 2013; Pirard et al. 2012; Schebb et al. 2011).

To tackle TCS in air and soil samples, pressure liquid extraction (PLE) and accelerated solvent extraction (ASE) can be used (Cha and Cupples 2009; Laborie et al. 2016; Kinney et al. 2008). Ultrasonic extraction and the combination of microwave-assisted extraction with SPE are reliable techniques in TCS sediment analysis (Azzouz and Ballesteros 2016; Juksu et al. 2019; Chen et al. 2020). Soxhlet

extraction and SPE (QuEChERS) can also be applied for TCS extraction from biota (Bai and Acharya 2019; Das Sarkar et al. 2020; Juksu et al. 2019; Yao et al. 2019).

In order to determine the total TCS (free and conjugated) in urine samples, the incubation with β-glucuronidase and sulfatase enzymes must be performed, prior to the extraction process (Moos et al. 2014; Sandborgh-Englund et al. 2006). Again, SPE is mostly used as preconcentration step prior the further chromatographic analysis. Urine is generally accepted as the matrix of choice for biomonitoring to the TCS exposure, while other biological fluids, such as blood, breast milk and amniotic fluid, are rarely used (Azzouz et al. 2016; Iyer et al. 2018; Shekhar et al. 2017). The cumulative exposure to TCS could be evaluated by analysis of human nails (Shi et al. 2013).

Analytical methods

In last decade, owing to the great improvements in instrumentalization, the detection of TCS in water samples is even possible in 10^{-4} nM concentrations (Table 1). Classical high-performance liquid chromatography (HPLC) coupled with visible (VIS), ultraviolet (UV) or diode array detector can be unable to fulfill the required limit of the detection (LOD) and quantification (LOQ) both in environmental and biological samples.

Actually, chromatography coupled with mass spectrometry (GC–MS) allows the routine detection of TCS in different samples (Table 1). After the extraction, a derivatization step is required for GC–MS analysis due to the TCS low volatility. The substances like 2,3,4,5,6-pentafluorobenzyl bromide, pentafluorobenzoyl chloride (PFBCl), N,O-bis (trimethylsilyl) trifluoroacetamide (BSTFA), trimethylchlorosilane (TMCS) and pyridine are commonly used as derivatization agents (Azzouz et al. 2016; Gatidou et al. 2007; Geens et al. 2009b; Provencher et al. 2014).

Liquid chromatography coupled with mass spectrometry (LC–MS) or tandem mass spectrometry (LC–MS/MS) equipped with C8 or C18 column are commonly applied for the development of rapid and sensitive analytical methods (Table 1). Particularly, the tandem MS ensures selective TCS detection and high sensitivity even at pM level. Considering the fact that TCS levels in groundwater are expected to be low, time of flight (TOF–MS) detector can meet fM level sensitivity (Table 1) (Pintado-Herrera et al. 2014). Although current analytical method is reliable and sensitive, the overall processes are still complex and expensive.

In spite of the significant improvement in the TCS analysis, the development of an appropriate, simple and inexpensive technique to monitor TCS regularly still presents a real analytical challenge due to the high lipophilicity of TCS, complexity of matrices and low concentrations.

Possible adverse effects of TCS

In vitro *analyses*

Bearing in mind the TCS properties, the exposure routes and ubiquitous occurrence in the environment, several in vitro toxicity screenings were conducted. The summarized findings are presented in Table 2.

The TCS exposure caused a significant hippocampal neuronal function damage and was related to the decreased long-term memory formation (Arias-Cavieres et al. 2018), while based on murine cardiac skeletal muscle cell experiments TCS led to the dysregulation of excitation–contraction coupling, which could result in serious complications such as heart failure and arrhythmias (Cherednichenko et al. 2012).

TCS acts as estrogenic agonist and antagonist based on the experiments conducted on various breast cancer cells (Huang et al. 2014b; Henry and Fair 2013). Thus, antagonist effects of TCS were also observed on glucocorticoid, androgenic and thyroid receptors (Kenda et al. 2020). Different mechanisms of in vitro disruption of thyroid homeostasis were suggested such as dose–response inhibition of T4 to T3 conversion (Butt et al. 2011) as well as a non-competitive inhibition of iodide uptake in rat thyroid follicular cells and thyroid peroxidase activity in rat microsomes (Wu et al. 2016).

TCS impact on early embryonic development (Kim et al. 2020), particularly on rodent neurons, was recently studied (Szychowski et al. 2015, 2019; Tran et al. 2020). The disturbed differentiation and development of various stem cells were observed (Cheng et al. 2019; Guo et al. 2012; Park et al. 2016). The observed developmental toxicity was the consequence of different apoptotic processes. The mechanisms include morphological and functional changes of mitochondria with the increased production of reactive oxygen species (ROS). Oxidative stress was also related to the human thyroid follicular epithelial cell toxicity (Zhang et al. 2018) and to the observed effects on primary human keratinocytes, NIH-3T3 mouse fibroblasts and RBL-2H3 mast cells (Weatherly et al. 2018).

Today, there is a rising concern that the everyday exposure to TCS and related compounds in personal care products potentially increase the risk of cancer incidence. In this regard, TCS could increase proliferation, migration and invasion of human prostate cancer cells (Kim et al. 2015), human lung carcinoma cells (Winitthana et al. 2014) and both estrogen positive and estrogen negative human breast cancer cells (Farasani and Darbre 2020; Lee et al. 2014). Wu et al. (2015) also observed the proliferation of mouse epidermis-derived cells. These findings are worrying since the consumption of certain hygiene products leads to the

Table 2 In vitro triclosan toxicity

Experimental model	TCS dose	Effects	Reference
Hippocampal slices from male rats, hippocampal cell cultures from the rat embryos	1, 5 and 10 µM	↓ Hippocampal neuronal functions	Arias-Cavieres et al. (2018)
Neural stem cells from Sprague Dawley rat embryos	1 to 50 µM	↑ Neurodegenerative effects ↑ ROS activation ↑ Apoptosis	Park et al. (2016)
Cortical neurons from mouse embryos	1 nM to 100 µM	↑ Apoptosis	Szychowski et al. (2015)
	0.01 µM and 1 µM	↓ Proliferation ↑ Apoptosis	Tran et al. (2020)
Mouse neocortical neurons from fetuses of pregnant female Swiss mice	10 µM	↑ Neurotoxicity via NMDAR activation ↑ ROS production ↑ LDH release ↑ Apoptosis	Szychowski et al. (2019)
Murine cardiac and skeletal muscle cells	0.5, 1 and 10 µM	↓ Excitation–contraction coupling	Cherednichenko et al. (2012)
Human liver microsomes	400 µM (IC_{50})	↓ T4 to T3 conversion	Butt et al. (2011)
FRTL-5 rat thyroid follicular cells, rat thyroid microsomes	21.3 µM (inhibition constant K_i), 165.8 µM (IC_{50})	↓ Sodium/iodide symporter-mediated iodide uptake ↓ Thyroid peroxidase activity	Wu et al. (2016)
Nthy-ori 3–1 human thyroid follicular epithelial cells	10 µM	↑ Oxidative stress and ROS production ↓ Viability ↑ p38 pathway	Zhang et al. (2018)
GH3.TRE-Luc thyroid-responsive rat pituitary tumor cells	5 and 10 µM	Thyroid receptor antagonist	Kenda et al. (2020)
GH3 rat pituitary somatolactotrophic cell line	10^{-3}, 0.1 and 10 µM	↑ CaBP-9 k mRNA and protein estrogenic activity via ER-dependent pathway	Jung et al. (2012)
MCF-7	0.1 µM	↑ Migration and invasion	Farasani and Darbre (2020)
	0.1 to 10 µM	↑ Cell growth via ER-mediated signaling pathway ↑ Cyclin D1 expression ↓ p21 expression	Lee et al. (2014)
	10^{-3} to 1 µM	Estrogenic effect	Huang et al. (2014b)
MCF-7 BOS	0.007 to 691 mM	Estrogenic and anti-estrogenic	Henry and Fair (2013)
MCF-10F, MDA-MB-231	0.1 µM	↑ Migration and invasion	Farasani and Darbre (2020)
MDA-kb2	5 and 10 µM	Glucocorticoid, estrogenic, androgenic, thyroid receptor antagonist	Kenda et al. (2020)
AR-EcoScreen hamster ovary cell line cells, hERa-HeLa-9903	5 and 10 µM	Androgen receptor antagonist Estrogen receptor antagonist	Kenda et al. (2020)
CV-1 African green monkey kidney cells	10^{-3} to 1 µM	Weak estrogenic effect	Huang et al. (2014b)
Primary human keratinocytes, NIH-3T3 mouse fibroblasts, RBL-2H3 mast cells	1 to 20 µM	↑ Morphological changes and ↓ Membrane potential of mitochondria ↑ ROS production Endoplasmic reticulum and mitochondrial Ca^{2+} levels alteration	Weatherly et al. (2018)
JB6 Cl 41-5a mouse epidermis-derived cells	0.01 to 100 µM	↑ Proliferation	Wu et al. (2015)
Human mesenchymal stem cells	0.156 to 2.5 µM	↓ Adipocyte differentiation	Guo et al. (2012)
Porcine oocytes	1, 10 and 100 µM	↓ Meiotic maturation and cumulus cell expansion ↑ Mitochondrial superoxide levels and mediated apoptosis	Park et al. (2020)
Porcine parthenogenetic embryos	50 and 100 µM	↓ Early embryonic development ↑ ROD-related oxidative stress ↑ Mitochondrial dysfunction	Kim et al. (2020)

Table 2 (continued)

Experimental model	TCS dose	Effects	Reference
Mouse embryonic stem cells (ESCs)	1.7 to 138.1 μM—cardiac differentiation, 0.01 to 8.6 μM—osteogenic differentiation	↓ Cardiac and osteogenic differentiation	Cheng et al. (2019)
LNCaP	0.01 to 10 μM	↑ Proliferation and migration	Kim et al. (2015)
NCI-H460	2.5, 5 and 7.5 μM	↑ Growth, migration, invasion and survival via the epithelial-to-mesenchymal transition process	Winitthana et al. (2014)

chronic daily exposure to TCS through the dermal route. However, it remains unanswered if the studied effect is relevant to humans (Wu et al. 2015).

In vivo *analyses*

Some of the toxicity mechanisms of TCS were confirmed in the in vivo studies on rodents (Table 3). Multiple neurodegenerative TCS effects were determined in mice and rats, including reduced spatial memory performance, anxiety-related behavior and reduced neuromuscular functions (Arias-Cavieres et al. 2018; Tabari et al. 2019). Neurobehavioral toxicity was also observed in the mice offspring after subcutaneous treatment with TCS (Tran et al. 2020).

Additionally, cardiovascular and skeletal muscle toxicity was also confirmed in vivo in mice (Cherednichenko et al. 2012). Regarding reproductive health, the placenta might be particularly susceptible to TCS accumulation and TCS-induced dysregulation of endocrine function (Feng et al. 2016). Endocrine disrupting properties of TCS were also examined in various animal models within a wide range of doses and dosing regimens, which makes the obtained results difficult to compare. For instance, administration of TCS in concentration up to 0.345 mmol/kg/day resulted in a decrease of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in female mice (Cao et al. 2018), while at the higher oral dose (0.639 mmol/kg/day), increased both FSH and LH were measured in Sprague Dawley rats (Abd-Elhakim et al. 2018). However, a comparable reduction in thyroid hormones, T3 and T4, was observed in male Wistar albino rats (Taha et al. 2020), female Sprague Dawley rats (Abd-Elhakim et al. 2018) and female mice (Cao et al. 2018). The findings are in agreement with the in vitro data suggesting TCS hypothyroidism-inducing effects (Butt et al. 2011). The parameters of metabolic disorders, such as increased serum glucose and lipid levels, as well as morphological and functional liver changes were measured in TCS-treated rodents (Huang et al. 2020; Ma et al. 2020; Yang et al. 2015; Yueh et al. 2020). The conducted animal studies revealed that TCS possessed a certain hormonal activity, especially on female sex hormones. Furthermore, an endocrine receptor (ER)-dependent signaling pathway of breast tumor growth in mice was proposed (Lee et al. 2014).

Considering the antimicrobial activity, TCS was also associated with the decreased gut microbiota diversity in treated animals (Yang et al. 2018; Yueh et al. 2020). Besides this fact, proinflammatory TCS potential was responsible for the adverse effects noticed on the pulmonary and digestive systems, liver and spleen (Mohammed et al. 2017; Yang et al. 2018). TCS impact on the immune system was recently studied by Shane and co-authors (Shane et al. 2020).

Although animal studies suggest that TCS represents a hazardous substance for different body systems and biochemical processes, epidemiological studies are needed to test the hypotheses.

Epidemiological studies

Most of the available epidemiological studies regarding the adverse effects of TCS are focused on developmental toxicity and involve women, or women-children's pairs (Table 4). This is reasonable due to the estrogen-dependent toxicity pathways observed in vitro and in vivo. In a prospective cohort study, gestational and childhood TCS concentrations were positively associated with hyperactivity, attention and behavior disorders (Jackson-Browne et al. 2019). Moreover, it was concluded that TCS prenatal exposure might affect the intelligence and academic performance of children of the ages 7 and 8 (Jackson-Browne et al. 2020; Tanner et al. 2020). Although ROS activation and apoptosis induction were observed in vitro in undeveloped neurons (Park et al. 2016), the mechanisms of this neurodevelopmental impairment related to TCS exposure were not clarified. The potential relationship between TCS exposure and the decreased cognitive functioning and induced hypothyroidism was suggested (Jackson-Browne et al. 2019), both in the in vivo and in vitro studies (Butt et al. 2011; Zhang et al. 2018). The thyroid hormone homeostasis could be particularly vulnerable to EDCs in pregnancy, and accordingly, an association

Table 3 In vivo triclosan toxicity

Experimental model	TCS dose	Effects	Reference
Male Sprague Dawley rats	10 µM in hippocampus	↓ Spatial memory performance	Arias-Cavieres et al. (2018)
C57BL/6 J male and female mice	0, 0.03 and 0.345 mmol/kg subcutaneous	Offspring ↓ spatial memory performance, ↑ Cognitive dysfunction, ↑ Social deficiency, ↑ Anxiety-like behavior, ↓ Nesting-behavior	Tran et al. (2020)
Adult male NMRI mice	3.45, 7 and 13.81 mmol/kg oral	↑ Anxiety-related behavior ↓ Motor coordination, muscle strength, neuromuscular function ↑ Morphological changes ↓ Neuronal count	Tabari et al. (2019)
Mice	0.02, 0.04 and 0.09 mmol/kg intraperitoneal, 0.138 mmol/kg intraperitoneal	↓ Cardiovascular functions ↓ Skeletal muscle contractility	Cherednichenko et al. (2012)
Pregnant Sprague Dawley rats	0.1, 0.35, 1 and 2.1 mmol/kg/day	Placental bioaccumulation ↓ Serum progesterone, estradiol, testosterone, human chorionic gonadotropin, prolactin ↑ Placental steroid metabolism enzymes ↑ Progesterone, estrogen and androgen receptor expression Abortion induction ↓ Gravid uterine weight	Feng et al. (2016)
Female Sprague Dawley immature rats	0.03, 0.13 and 0.65 mmol/kg	↑ Uterine weight ↑ CaBP-9 k and C3 mRNA expression Estrogenic activity via ER-dependent pathway	Jung et al. (2012)
Female mice	0.002, 0.0035 and 0.007 mmol subcutaneous injection	↑ Endogenous and exogenous 17-β estradiol	Pollock et al. (2016)
	0.034 and 0.345 mmol/kg/day oral	↓ LH, FSH, progesterone, GnRH ↓ Hypothalamic kisspeptin expression ↓ T3, T4 ↑ TSH and TRH	Cao et al. (2018)
Female Sprague Dawley rats	0.639 mmol/kg/day oral	↓ T3, T4 ↑ Estradiol, FSH, LH	Abd-Elhakim et al. (2018)
Male Wistar albino rats	0.034 and 0.173 mmol/kg	↓ T3, T4, norepinephrine, dopamine, serotonin, and 5-hydroxyndoleacetic acid	Taha et al. (2020)
Male Sprague Dawley rats	0.173, 0.345 and 0.691 mmol/kg/day oral	Hypothyroidism induction ↑ Liver weight ↓ T3, T4 ↑ Deiodinase 3 protein and hepatic enzyme expression ↓ Thyroid peroxidase protein expression Histopathologic changes in rat thyroids ↑ p38 and JNK pathway	Zhang et al. (2018)
Female BALB/c nude mice with transplanted MCF-7 cells	0.345 mmol/kg	↑ Tumor mass via ER-dependent signaling pathway	Lee et al. (2014)
Female PPARα-humanized and wild-type mice	0, 0.2 and 0.432 mmol/kg dermal	↑ Liver increase and PPARα activation ↑ Production of hepatocyte peroxisomes	Tang et al. (2018)
Pregnant mice	0.03 mmol/kg/day oral	Offspring: ↑ Food intake, body weight gain, visceral fat and adipocyte size ↓ Glucose clearance and insulin sensitivity ↑ Fasting plasma glucose	Hua et al. (2019)
Sprague Dawley rats	0.034 and 0.173 mmol/kg oral	↑ Blood glucose, HDL-C, LDL-C, TG, leptin ↑ Hepatic TG ↓ Hepatic glycogen ↓ Diversity of gut microbiota	Ma et al. (2020)

Table 3 (continued)

Experimental model	TCS dose	Effects	Reference
Male C57BL/6 mice (knockout $Atf4^{\Delta Hep}$ and control $Atf4^{F/F}$, $Ppar\alpha$-null)	0.35 mM/day oral + high fat diet (HFD)	↑ Protein deficiency ↑ Accumulation of lipid droplets and ALT levels ↑ Dysregulation of lipid metabolic genes ↓ Cholesterol levels ↑ Abdominal adipose tissue fat ↑ Development of nonalcoholic steatohepatitis and toxicant-associated steatohepatitis ↓ Gut microbiota diversity	Yueh et al. (2020)
Pathogen-free SD rats	0.14, 0.45 or 1.4 µM, inhalation	↑ Postdosing salivation ↑ Serum glucose (females) Histopathological changes in kidneys, liver, lung, trachea, larynx, nasal cavity and epididymides	Yang et al. (2015)
Male C57BL/6 mice	0.034 and 0.345 mmol/kg/day oral	↑ Liver weight and hepatic lipid levels ↑ Genes related to synthesis, fatty acid oxidation and inflammation	Huang et al. (2020)
Male Sprague Dawley rats	0.034 µg/B.W. and 3.45 µg/B.W. intratracheal instillation	Acute pulmonary inflammation ↑ Total cell count, polymorphonuclear leukocytes, total protein, lactate acid dehydrogenase, TNFα, IL-6 Lung morphological changes	Kwon et al. (2013)
Mice	0.034 and 0.276 mM	↑ Spleen weight, IL-6 ↑ Inflammatory bowel disease ↑ Colitis-associated colon tumorigenesis ↓ Gut microbiota diversity	Yang et al. (2018)
Female BALB/c mice	25 µl/ear volume of 2% TCS, topical	↓ Total and activated CD4 + and CD8 + T cells at the infection site ↓ Th1 transcription factor T-bet	Shane et al. (2020)
Female Sprague Dawley rats	0.64 mmol/kg, oral	Lung tissue: ↓ SOD, CAT and GSH ↑ MDA and LDH ↑ BcL-2 and caspase-3 expression ↑ Morphological changes	Mohammed et al. (2017)

Table 4 Triclosan in human samples and related health disorders

Population (*n*), Age	Matrix	Method	Limit of the detection	TCS concentration (range)	Associated disorder	Country	Reference
Women-children pairs (202), ≥ 18 years women; 8 years children	Urine	Online SPE, isotope dilution LC–MS	7.9 nM	Mean gestational: 58.7 nM Childhood: 38 nM	Male children: ↑ Behavioral symptom index ↑ Externalizing and attention problems ↑ Hyperactivity ↑Somatization ↓ Academic achievements	USA	Jackson-Browne et al. (2019) Jackson-Browne et al. (2020)
Women-children pairs (718), 7 years children	Urine, serum, plasma	SPE, LC–MS/MS	0.345 nM	Mean 4.4 nM in maternal urine	Male children: ↓ Cognitive functioning	Sweden	Tanner et al. (2020)
Men and women (5990)	Urine	UPLC-MS	1.7 nM	75^{th} percentile: 4.2 nM 95^{th} percentile: 144.1 nM	↑ TSH in females	Korea	Ha et al. (2019)
Women-infants pairs (398), 22–42 years women	Urine	SPE, HPLC–MS/MS	0.345 nM	n.d.–308.6 nM	↓ Maternal T4 ↓ Neonatal T3	China	Wang et al. (2017)
Pregnant women (514), mean age 31.0 years	Urine	LC–MS/MS	0.207 nM	Median 3.0 nM	Male children: ↓ Head circumference ↓ Abdominal circumference ↓ Anogenital distance	UK	Lassen et al. (2016)
Pregnant women (620), mean age 30 years	Urine	SPE, HPLC–MS/MS	0.345 nM	2.6–46.1 nM	↑ Gestational diabetes mellitus risk ↑ Birthweight in female children	China	Ouyang et al. (2018)
Women (895), 18–45 years	Urine	NHANES: on-line SPE, HPLC–MS	5.9 nM	81.2 nM	↑ Infertility prevalence (when combined with other EDs)	USA	Arya et al. (2020)
Infertile women (296), 18–45 years	Urine	HPLC–MS	0.345 nM	Median 5.1 nmol/g creatinine (2.35–13.1 nmol/g creatinine)	↑ Polycystic ovary syndrome prevalence ↑ LH levels ↑ LH/FSH ratio	China	Ye et al. (2018)
Women (1848), ≥ 20 years	Urine	NHANES: automated SPE, isotope dilution HPLC–MS	7.9 nM	Mean 60.7 nmol/g creatinine (55.8–66.1—nmol/g creatinine)	↓ Bone mineral density ↑ Osteoporosis prevalence	USA	Cai et al. (2019)
Children (623, 294 girls and 329 boys), 8–12 years	Urine	Automated online SPE, HPLC–MS	7.9 nM	8–12,468 nM	↑ Allergic sensitization (inhalant allergens)	Norway	Bertelsen et al. (2013)

between lower maternal and neonatal thyroid hormones and maternal urinary TCS levels was also found in a prospective birth cohort study (Wang et al. 2017).

The increased TCS maternal urinary concentrations, as indicators of prenatal TCS exposure, were inversely associated with the anthropometric measures and anogenital distance in boys, with a borderline statistical significance, but not in girls waging to the anti-androgenic activity of TCS (Lassen et al. 2016). Another study, conducted on pregnant women of the Chinese urban cohort, observed the higher birth weight of female children, as well as the higher risk for development of gestation diabetes mellitus (GDM) (Ouyang et al. 2018). These effects could mainly be attributed to an increased maternal body mass index (BMI), but without statistical significance. Besides, insulin resistance and thyroid-mediated metabolic effects could cause elevated GDM risk (Ouyang et al. 2018).

On the contrary, Huo and co-authors (2018) found relatively low TCS concentrations in the urine samples of pregnant Chinese women, with no consistent associations with birth outcomes (Huo et al. 2018). No association was found between impaired glucose metabolism in pregnant women (Shapiro et al. 2018), nor in a cross-sectional study involving men and women (Ward et al. 2020). With regard to these results, it is worth noting that the data regarding the association of TCS exposure with metabolic disorders are inconsistent and should be further investigated.

The prevalence of other endocrine-related disorders, specific to the female population: osteoporosis (tightly related to thyroid hormones and estrogen activity) and polycystic ovary syndrome (associated with the impaired glucose metabolism and women infertility) were also found to be increased in women with elevated TCS urinary levels (Cai et al. 2019; Ye et al. 2018).

In children, both girls and boys, TCS urinary levels were associated with allergic sensitization to inhalant allergens (Bertelsen et al. 2013). However, the molecular basis of this adverse effect was not investigated despite the high incidence rate of allergic reactions.

Having in mind the widespread exposure to TCS on daily basis, more epidemiological studies on a large number of participants of different age and health status are necessary in order to understand the underlying mechanism and the health problems associated with TCS.

TCS and COVID-19

The outbreak of COVID-19 disease set an important requirement to achieve the highest levels of hygiene, particularly hand hygiene (Rundle et al. 2020). Therefore, the increased use of antibacterial soaps and disinfectants during the COVID-19 pandemic was followed with the increased exposure to TCS (Ejtahed et al. 2020; Usman et al. 2020). The non-alcohol-based sanitizers usually contain TCS instead of alcohol as antimicrobial or disinfecting agent (Atolani et al. 2020). TCS is a broad-spectrum antibacterial agent with antifungal effects. Interestingly, during the outbreak of severe acute respiratory syndrome (SARS) in 2003, it was determined that only 0.05% of TCS ensures 'at least a 3-log reduction of the virus from the surface without any virus recovered in any of the wells within a 30-s contact time' (Dellanno et al. 2009). Consequently, it was believed that TCS poses virucidal efficacy also against SARS-CoV-2 strain (Ejtahed et al. 2020).

Full commitment to the principles of personal hygiene remains a major action for the prevention of transmission of SARS-CoV-2 virus. Apart from the fact that TCS induces *Staphylococcus aureus* and *Escherichia coli* resistance to antibiotics, the repeated exposure to TCS can also result in skin and gut microbiome alterations followed with the development of chronic disease (Ejtahed et al. 2020; Subramanya et al. 2021). In this context, if the harmful compound as TCS is present in personal care products, compliance with health recommendations can have negative impact to both human health and environment.

Conclusion

On the basis of the available literature data, it is high time to consider TCS as a rapidly growing environmental issue, especially now during the COVID-19 pandemic when the high level of sanitation and personal hygiene is constantly required. Despite the TCS antibacterial and antifungal effects as well as suggested virucidal efficacy against SARS-CoV-2 strain, the alarming results about the negative consequences of the permanent exposure to low TCS levels should strengthen the critical revision of current international standards regarding TCS and necessitate the establishment of the stricter measures at worldwide scale. However, the awareness among the policy-makers and stakeholders is still lacking. Further follow-up studies conducted on a large number of participants will expand the current knowledge about the TCS-induced health effects. The reevaluation and harmonization of current legislation regarding the utilization of TCS in different products are of high demand together with the new prioritization methodology which will consider TCS as a priority substance included in the regular monitoring programs worldwide. Both environmental and health risks associated with TCS cannot be reduced without proper management and full commitment to adequate legislation in compliance with the environmental protection in order to obtain a good ecological status.

Author contribution MM: conceptualization, visualization, resources, writing original draft preparation; LĐ: resources, writing original draft preparation; NM: visualization, writing-reviewing and editing; NM: conceptualization, writing—reviewing and editing, supervision.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

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