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Source, bioaccumulation, degradability and toxicity of triclosan in aquatic environments: A review

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ABSTRACT

Triclosan (TCS), a lipophilic broad-spectrum biocide is widely used in personal care, acrylic, veterinary, medical and household products. It has been observed to be present in aquatic environments, animal and plant tissues around the world, and even in human blood, urine and breast milk. Under natural conditions, TCS degrades photolytically as well as through microbial action into more persistent and toxic byproducts like dioxins. Moreover, accumulation in deep water bodies or soil strata where light is not adequately available makes its degradation even more prolonged. Present review has been undertaken with an objective to highlight the concerns surrounding TCS exposure to aquatic organisms, the infiltration routes into the food chain, its persistence and accumulation, teratogenic, biochemical and cytogenic effects on a wide range of aquatic species. The widespread use of products containing TCS and potential toxicity at lethal concentrations makes it a compound of utmost concern worldwide and hence its use under permissible levels, proper disposal needs to be regulated.

Contents

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1. Introduction

A large variety of pharmaceutical and personal care products (PPCPs) and metabolites thereof are continuously introduced into the environment through human activities (excretion, washing, manufacturing etc.) and have thus become the most widely detected contaminants in the aquatic ecosystems (Zhao et al., 2010; Faggio et al., 2016; Pagano et al., 2016). TCS [5-chloro-2-(2,4-dichlorophenoxy)phenol)-TCS] an ionizable chlorinated biphenyl ether, widely used as an antimicrobial and antifungal agent in various products of domestic importance (Dann and Hontela, 2011). TCS is hydrolytically stable, nonvolatile (vapour pressure [Pvp] $= 40 \times 10^{-6}$ mm Hg at 20 °C) and has a moderate water solubility (12 mg/L) with a pKa of 8.1 at 20 °C (McAvoy et al., 2002; Reiss et al., 2002). It has a half-life ranging from 1.3–1.4 d in water and 53.7–60.3 d in sediments (SCCS, 2010). Being an organochloride, TCS is susceptible to photo degradation and its photolytic half-life has been reported to vary from 41 min in sunlight to 39.8–55.99 d in darkness (Bester, 2005). Wide use and persistence of TCS have contributed to its presence in aquatic ecosystems all over the world, TCS has been detected in 57.6% of the water bodies (139 streams) across 30 states of USA, with a maximum level of 2.3 μg/L and a median level of 0.14 μg/L during the early years of the 21st century (Kolpin et al., 2002). TCS has high lipophilicity with octanol water partition coefficient (log K_{ow}) of 4.8, which makes it readily available to aquatic organisms (Shanmugam et al., 2014) inducing adverse effects in them due to bioaccumulation (Dann and Hontela, 2011). TCS is widely used as an active ingredient in products like soaps, toothpastes, detergents, sponges, deodorants, kitchenware, clothes, toys etc. which have witnessed significant increase in consumption over the recent years (Perez et al., 2013). Most of these products are intended for a daily use and as a result, its concentration in aquatic ecosystems has been constantly on the rise making it a subject of serious environmental concern worldwide.

Ecotoxicology studies have revealed that TCS exhibits toxicity to several aquatic organisms (Weatherly and Gosse, 2017); plants (Prosser et al., 2014); fish (Dar et al., 2019); algae (Bi et al., 2018); arthropods (Peng et al., 2013); molluscs (Geiß et al., 2016); nematodes (Vingskes and Spann, 2018) among others. The index of LC_{50} or least concentration which results in mortality of 50% of test organisms, is often used to demonstrate the acute toxicity of TCS (Dar et al., 2019). Consequently, it has been observed that fish species were more sensitive to TCS toxicity having LC_{50} values ranging from 0.26 to 0.45 mg/L (Orvos et al., 2002). The toxic effects of TCS were observed in terms of biochemical alterations, endocrine disruption, and delay in embryonic development in several fish species including, Japanese medaka, *Oryzias latipes* (Ishibashi et al., 2004), zebrafish, *Danio rerio* (Oliveira et al., 2009) and major carps like *Labeo rohita*, *Cirrhinus mrigala*, *Ctenopharyngodon idella* and *Cyprinus carpio* (Dar et al., 2019, 2020a). Orvos et al. (2002) reported loss of equilibrium, fish jaw locked open, erratic swimming, spinal curvature, and quiescence in rainbow trout, *Oncorhynchus mykiss* at 80 mg/L TCS. It has been observed to be androgenic (Foran et al., 2000) or estrogenic (Ishibashi et al., 2004) in nature. In *Mytilus galloprovincials*, Canesi et al. (2007) observed that TCS induced increase in lysosomal membrane destabilization, phagocytotic activity and phosphorylation of PKCα and PKCβII isoform both *in vitro* and *in vivo*, they also reported that it stimulated the activity of glutathione transferase (GST) and catalase (CAT) but did not induce changes in total glutathione in the digestive gland. In the zebra mussel, *Dreissena polymorpha*, TCS has been observed to cause cytotoxic (apoptosis of hemocytes due to destabilization of lysosomal membrane) and genotoxic (DNA damage) effects after *in vitro* and *in vivo* experiments (Binelli et al., 2009a). In mature male western mosquitofish, *Gambusia affinis*, exposure to 0.101 mg/L of TCS for 35 d decreased sperm counts but increased liver size and vitellogenin mRNA (Raut and Angus, 2010). It also alters the structure and composition of microbes present in the environment thereby disturbing local ecosystem functions (Richmond et al., 2017; Bever et al., 2018).

The toxic interactions of TCS in living tissues has put its use under the scanner and attracted severe regulations by law enforcing or policy-making agencies like the United States Food & Drug Administration (USFDA), Environmental Protection Agency (EPA), Centers for Disease Control & Prevention and EU directives. Following a comprehensive review of scientific reports, USFDA in 2016 imposed a ban on the use of TCS in soaps (Weatherly and Gosse, 2017). The decision was seen as a remarkable one due to the fact that household soaps containing TCS as antimicrobial additive did not offer significant benefits as compared to plain soaps that did not contain TCS (Mahalak et al., 2020). However, it is still allowed in many other personal care products like toothpastes, mouthwashes and hand sanitizers (Kux, 2016). Following a similar suite, the European Commission in January 2017, stopped the use of TCS in products intended for general hygiene and regulated its concentration as a preservative in some cosmetics (0.3%) and mouthwashes (0.2%) (EU directive, 2021). Strict regulations like the ones in United States and European Union might have resulted in low concentrations of TCS released in the environment in the recent past. However, in rest parts of the world like India and several African nations, TCS continues to be used unabatedly having serious implications for the global natural resources. The concentration of TCS, for instance in surface waters of Gomti River in India and Buffalo River in South Africa was observed to be as high as 9.65 μg/L (Nag et al., 2018) and 1.26 μg/L (Olaniyan and Okoh, 2020) respectively, underlining the importance of global regulations on its

Table 1
Common products having TCS as an active ingredient.

Category	Products	References
Personal care products	Soaps, detergents, shave gels, face washes, sponges and wipes, skin cleaners, toothbrushes, toothpastes, mouthwashes, cosmetics, deodorants	Weatherly and Gosse (2017)
Household goods	Kitchenware, dish washes, toys, computer equipment, furniture, humidifiers, helmets, wall coverings, air filters, blankets, mops, handrails, paint, ear plugs, coolers, waterers, feeders, vacuum food sealers	Dhillon et al. (2015)
Textile	Clothes, shoes, sandals, towels	Zhao et al. (2016)
First aid	Antiseptics, Burn creams, Night splints, Medicated sprays	Dhillon et al. (2015)
Office and school products	Calculators, scissors, paper, adhesives, cutting instruments, view binders, pencils	Dhillon et al. (2015)
Food packaging	Active food packages, plastic crates	Espitia et al. (2016)

use and disposal. Present review is an attempt to highlight the eco-toxicity of TCS, its impacts on the aquatic environment, the source of its origination, accumulation and interactions with biomolecules in aquatic systems based on an updated literature.

2. Occurrence and bioaccumulation

The worldwide production of TCS increased from 1500 tons per year in 1998 (Bester, 2005) to 4762 tons per year in 2015 with a maximum production of 6350 tons per year in 2011 (Weatherly and Gosse, 2017). During 1992 to 1999, about 70% antibacterial marketing products contained TCS as an active ingredient (Schweizer, 2001). Perencevich et al. (2001) reported that, 75% of the liquid and 30% of bar soaps from 1999 to 2000 contained TCS. Report of USFDA (2013) shows that in 93% of liquid, gels or foam soaps sampled from 2008 to 2010, TCS was found as an active ingredient. Adolfsson-Erici et al. (2002) reported that in Sweden, 25% of toothpaste brands used 2 tons of TCS and other personal care products like soaps, deodorants etc. accounted for another 300 kg of TCS yearly. A summary of common products having TCS as an active ingredient is given in Table 1.

TCS ends up in water after being disposed down the drain through consumer products of daily use and is finally washed out into the wastewater treatment plants in urban municipalities (WWTPs) (Dann and Hontela, 2011). Removal of TCS from wastewater ranges between 58%–90%, which depends upon the removing potential of sewage treatment plants (Montaseri and Forbes, 2016). Approximately 50% of the TCS separated by activated sludge treatment and aerobic biosolid digestion in WWTPs is persistent and becomes available in biosolids (Ogunyoku and Young, 2014). Release of WWTPs effluent into the surface water and the use of TCS laden biosolids in agricultural land, lead to dispersal of TCS into the aquatic and terrestrial environments (Chalew and Halden, 2009).

Several studies have revealed the worldwide presence of TCS in the environment, mainly in wastewater effluent of WWTPs, surface waters and sediments. It has been observed in rivers, lakes and estuaries of America (Kolpin et al., 2002; Fair et al., 2009; Venkatesan et al., 2012), Europe (Lindström et al., 2002; Balmer et al., 2004; Xie et al., 2008), Africa (Lehutso et al., 2017; Olaniyan and Okoh, 2020), Australia (Ying and Kookana, 2007), and Asia (Lv et al., 2014; Wang and Kelly, 2017; Nag et al., 2018; Sarkar et al., 2020). In USA, it has been identified as one of the ten most prevalent contaminants of surface water (Kolpin et al., 2002). The worldwide concentration of TCS in water ranged from 0.001–40.000 μg/L in surface waters, 0.020–86.161 μg/L in wastewater influents, 0.023–5.370 μg/L in effluents from wastewater treatment plants, <0.100 μg/L in sea water, 0.201–328.8 μg/L in groundwater sources, <100–53,000 μg/kg dry weight (dw) in freshwater sediments, 0.02–35 μg/kg dw in marine water sediments, 20–133,000 μg/kg dw in WWTP biosolids and 580–15,600 μg/kg dw in sludge (SCCS, 2010; Montaseri and Forbes, 2016).

TCS levels in the surface waters show seasonal variations, lowest levels were observed during June and July in Tone Canal of Japan and Jiulong River of China as compared to other months. The seasonal variation in the TCS levels during these months may be attributed to the dilution of TCS due to the increase in water level in the water bodies (Nishi et al., 2008; Lv et al., 2014). TCS has also been detected in waters of 35 outdoor swimming pools in five districts in Changsha, China by Lu et al. (2017). The authors observed that TCS was the most frequently detected compound in swimming pool waters and ranged between 0.028 to 0.096 μg/L. They suggested that the increase in concentrations may be due to recreational activities involving the widespread use of sunscreens and other personal care products in swimming pools. Some studies have also reported the presence of TCS in drinking water (Kuster et al., 2008; Benotti et al., 2009). The highest-level ranging from 0.6 to 9.7 ng/L was detected in bottled and tap water in China (Li et al., 2010).

During bioaccumulation, concentration of a chemical in the tissues of an organism is much more compared to its concentration in the ambient environment that is water and/or sediment in case of aquatic organisms (Ruus et al., 2005; Pagano et al., 2020; Prokić et al., 2021; Shiry et al., 2021; Stara et al., 2021; Strungaru et al., 2021). High log Kow value (4.76) suggests high sorption potential of TCS and is also an indicator of its bioaccumulation potential. For aquatic organisms, the potential uptake mechanisms of lipophilic contaminants occurs predominantly via direct uptake from water through exposed surfaces, mainly gills (bioconcentration) and also through the consumption of contaminated food (biomagnification) (Dhillon et al., 2015; Sula et al., 2020; Stara et al., 2020a; Mohsenpour et al., 2020; Freitas et al., 2020;

Simionov et al., 2019; El Hajam et al., 2020). Incomplete removal of TCS during wastewater treatment processes leads to the continuous exposure of aquatic biota in receiving waters, which causes accumulation of TCS and its degradation products in the tissues of the organisms (Dann and Hontela, 2011).

Accumulation of TCS has been observed in the tissues of aquatic organisms captured form the natural water bodies. Adolfsson-Erici et al. (2002) measured TCS levels in rainbow trout (*Onchorhynchus mykiss*) caged in the WWTP effluent receiving water outside a small wastewater plant in Sweden, and compared it with the wild fish living downstream from the three plants and the fish exposed in tanks to treated water of two large plants. They reported that bile fluid from the fish contained TCS at concentrations ranging from <0.01–0.08 mg/kg fresh weight in controls and the fish sampled at the reference sites, but its range was 0.44–120 mg/kg fresh weight in the fish exposed to sewage water in tanks. Houtman et al. (2004) observed that TCS concentrations in the bile of male bream (*Abramis brama*) collected from River Dommel and North Sea canal of Netherlands were about 80 and 14 μg/mL bile, respectively. Fair et al. (2009) observed that concentration of TCS in the plasma of Atlantic bottlenose dolphins (*Tursiops truncates*) collected from Charleston, SC (CHS) of South Carolina, US and Indian river lagoon FL (IRL) of Florida, US, ranged from 0.12 to 0.27 ng/g wet weight. Shanmugam et al. (2014) collected *Gibelion catla* from nine locations of the Kaveri River and observed that TCS concentration in its tissues ranged from 0.73 to 50 ng/g wet weight with the mean concentration of 19.86 ng/g wet weight.

Experimental studies have shown that liver is one of the main target sites for TCS accumulation. Escarrone et al. (2016) exposed male and female guppy (*Poecilia vivipara*) to 0.2 mg/L TCS for 24, 96, 168, 336 h (uptake phase), and kept them for 24 h depuration period (clearance phase) and observed that its concentration increased over time till d 4 in muscle and till d 7 in liver and brain. They observed that TCS reached a steady state in all the tissues by d 7 except for gonads where its concentration increased continuously till the end of study. By the end of depuration period, they noticed that level of TCS declined by 15% in all the tissues except for liver (50% decline). They suggested that the experimental fish had high efficiency to get rid of this toxic agent. Accumulation of TCS also shows species specific variation in aquatic organisms. When Palenske et al. (2010) exposed North American amphibian larvae (*Xenopus laevis*, *Bufo woodhousii woodhousii* and *Rana sphenocephala*) to 0, 31, 94, 250 and 500 μg/L TCS for 96 h they noticed a concentration dependent increase in accumulation of TCS in the larval tissues. They observed that maximum uptake was found in *B. woodhousii woodhousii* (7600–370 000 ng/g) followed by *R. sphenocephala* (3700–88 000 ng/g) and *X. laevis* (11 500–57 000 ng/g). Dar et al. (2020b) noticed a concentration and time dependent increase in accumulation of TCS in the larvae of *Cyprinus carpio, Ctenopharyngodon idella, Labeo rohita and Cirhinnus mrigala* on exposure to 0.005, 0.01, 0.02 and 0.05 mg/L TCS for 7 and 14 d. They observed that accumulation was maximum between 7–14 d at 0.01 mg/L for *C. carpio* and *L. rohita* but at 0.005 mg/L for *C. idella* and *C. mrigala*.

3. Mechanism of antimicrobial action

TCS blocks lipid biosynthesis by targeting the synthesis of fatty acids as it inhibits the enzyme enoyl reductase (enoyl-acyl carrier protein reductase gene, *FabI*) (McMurry et al., 1998). TCS binds tightly but slowly with *FabI* and inhibits the enzyme which is a part of type 2 dissociated fatty acid synthase (Heath et al., 2002). The inhibition is expected to arise from a conformational change following *FabI*-TCS initiation complex formation. The structural disturbance arising as a consequence of TCS attachment may be due to reordering of substrate binding loop (Baldock et al., 1996; Levy, 2001). The reordering of the loop brings fused ring of the inhibitor and certain amino acids closer to each other and thus leads to establishment of newer contact with the cofactor (Roujeinikova et al., 1999). The pliability of loop (residues 192–198) plays salient role in inhibitor attachment and substrate identification (Sivaraman et al., 2004) while as the *FabI*-NAD^+-TCS ternary complex formation plays the potent role of inhibitor (Heath et al., 1999). TCS binds non-covalently to a place adjoining the nicotinamide part of NAD^+ (Heath et al., 1998). The residues leu-100, Tyr-146, Tyr-156, Met-159, Ala-196 and Ala-197 form a hydrophobic pocket in which TCS is positioned adjoining to NAD^+ (Stewart et al., 1999). TCS interaction with FabI is stabilized by π-π stacking interaction between nicotinamide ring portion of NAD^+ and 2-hydroxy-3-chlorophenyl ring. The hydrophobic side chains on the proteins such as Tyr-146 and Tyr-156 also surround the hydroxychlorophenol. The 2′-hydroxyl group of TCS forms two strong hydrogen bonds one with 2′-hydroxyl group of nicotinamide ribose and second with phenolic hydroxyl group of Tyr-156 (Heath et al., 1998). Tyr-156 has been suggested to work as a catalytic residue in substrate reduction (Baldock et al., 1998). The 90 degrees rotation of 2,4-dichlorophenyl ring occurs with respect to the plane of hydroxychlorophenyl group. Position of TCS adjoining to NAD^+ in the hydrophobic pocket of FabI enzyme results in hydrophobic contact between the backbone amide of Ala-95 and side chain of methionine-159 (Heath et al., 1998). Thus, formation of a firm *FabI*-NAD^+-TCS complex leads to efficacious inhibition of *FabI* by TCS. A schematic representation of the action of TCS on lipid biosynthesis in bacterial cells is provided in Fig. 2.

4. Degradation kinetics and half life

TCS has been observed to show variable half-life and degradation kinetics depending upon the nature of medium, availability of light, and initial concentration among other factors. The photolytic degradation of TCS is one of the most potent ways to reduce the concentration of TCS pollution in water. The degradation enhances with the increase in light intensity and it has been observed that TCS breaks down into degradation products as the intensity increases from

Table 2
Half-life of TCS in different media.

Source	Half-life	Reference(s)
Air	1 d	Halden and Paull (2005)
Fresh water	8 d	Aranami and Readman (2007)
Salt water	4 d	Aranami and Readman (2007)
Drinking water	41 min	Spare (1993)
Water sediment	540 d	Halden and Paull (2005)
Soil	120 d	Halden and Paull (2005)

1500 $\mu W/cm^2$ to 6000 $\mu W/cm^2$ (Zhang et al., 2020). The photolytic degradation half-life of un-dissociated TCS in surface water ranges roughly from 4 d in sea water, 8 d in fresh water (Aranami and Readman, 2007; Mezcua et al., 2004) and 41 min in drinking water (Spare, 1993). Its dissolution downstream can be evaluated through river die-away studies and the approximate half-life of TCS has been reported to be 11.3 h in Cibolo Creek, Texas following discharge from a waste water treatment plant, 3.3 h in the Aire River, the United Kingdom (Reiss et al., 2002) and 11 d in Ruhr River (Bester, 2005). Experiments of Huang et al. (2014) have shown that TCS is biologically as well as photolytically degraded and the degradation is faster in sediment systems as compared to unsterilized water with estimated half-life of 32 to 62 d and 89 to 161 d respectively. They also observed that photolytic degradation of TCS was mostly significant near the surface of water bodies in the euphotic zone as compared to parts of deep water where sunlight could not penetrate and could thus have potential implications on benthoic organisms. TCS degradation in water medium is significantly affected by presence of dissolved solids and as such the degradation has been observed to be rapid in wastewater as compared to pure water (Mezcua et al., 2004). This may be due to the presence of salinity, acidic pH and metal ions that enhance the degradation rate (Aranami and Readman, 2007). In terms of pH, TCS degradation has been observed to be highest under acidic conditions as compared to alkaline media (Chen et al., 2019). At lower pH, TCS could more readily take part in the polymerization reactions leading to the formation of its degradation products (Chen et al., 2008). Among other factors, microbial proliferation and presence has also been considered to positively affect TCS decay rate (Carr et al., 2011). Out of aerobic and anaerobic conditions of TCS containing media, it has been observed that the former conditions may have an enhancing effect on degradation rate and as such, proper ventilation of TCS media have favourable results on the degradation kinetics. This can be attributed to the availability of more oxygen for microbial growth that eventually increase the degradation rate (Yu et al., 2019). Estimated half-life of TCS in various media has been presented in Table 2.

Under certain conditions, it has been observed that TCS can transform to its degradation products such as dioxins, chlorophenols, chlorinated TCS and methylated TCS (Fig. 1). In aqueous environments it undergoes photochemical degradation by direct photolytic processes and is converted into potentially toxic dioxins (Sanchez-Prado et al., 2006; Buth et al., 2011). Kanetoshi et al. (1987, 1988) observed formation 2, 8-DCDD after 20 h in aqueous solution and after 18 h on glass slab. In several photo-transformation experiments on TCS in aqueous environments, 2,8-DCDD was recognized as one of the major photo-degradation products (Qiao et al., 2014; Tohidi and Cai, 2017; Yuval et al., 2017). In the presence of sunlight, TCS is transformed into four dioxin compounds 2, 8-DCDD, 2,3,7-TCDD, 1,2,8T, CDD and 1,2,3,8-TCDD (Buth et al., 2009). Dioxins and dibenzofurans also arise as unwanted by-products during the process of TCS manufacturing and find their way in aquatic bodies (Ni et al., 2005). In the experimental studies related to enhanced TCS degradation, the effect of light has been observed to be the most significant followed by the ozonolysis, chlorination, sonolysis etc. having pseudo-first order degradation kinetics (Bedoux et al., 2012). Ozone is a powerful oxidizing agent (Aslam et al., 2020, 2021a) and with chlorination it has shown the greatest degradation kinetics of TCS containing solutions, (half-life ranging from 0.9 ms to 2.2 min; (Canosa et al., 2005; Fiss et al., 2007; Suarez et al., 2007) followed by sonolysis (3–110 min; Sanchez-Prado et al., 2008), photo-solid phase micro-extraction (SPME) degradation (6.3–8.0 min; Sanchez-Prado et al., 2006), photocatalytic oxidation (15 min to 1 day; Jimmy et al., 2006) and finally photolysis (2.7 min to 8 days, Aranami and Readman, 2007; Sanchez-Prado et al., 2006; Tixier et al., 2002). Chlorine is one of the most used oxidants for water disinfection (Aslam et al., 2021b). For disinfecting (drinking water from various microbes) chlorination of drinking water is done by using active chlorine, however, TCS in the presence of active chlorine is transformed into dioxins which have been observed to be more toxic than parent TCS (Wu et al., 2019). Photo-degradation of TCS in the presence of free chlorine mediated oxidation products dioxins, chlorinated phenols, chlorinated phenoxy-phenols and trihalo methane (Onodera et al., 1987; Canosa et al., 2005; Rule et al., 2005; Li et al., 2018a). Some of these products like chloroform and 2,4,6-trichloro phenol are carcinogenic to humans as well as fishes (Golden et al., 1997; Toussaint et al., 2001; Zhang et al., 2018).

5. Exposure to aquatic organisms

5.1. Reproductive toxicity

TCS has been observed to exhibit reproductive toxicity and teratogenicity in organisms exposed to high concentrations with effects ranging from decrease in sperm viability, sperm count, fertilization rate, fertilization failure, delayed hatching and larval deformations. TCS interferes with stabilization and integrity of sperm membrane which could be the possible

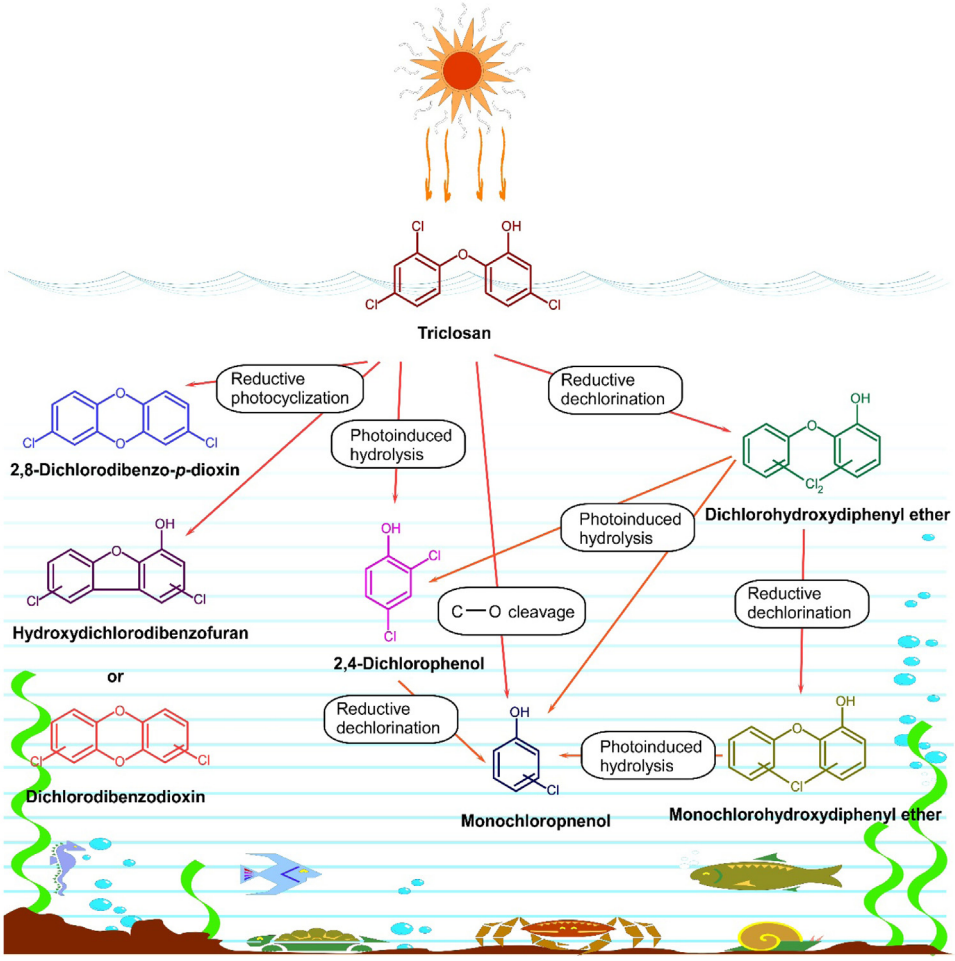

Fig. 1. Photodegradation products of triclosan (Sanchez-Prado et al., 2006).

reason for sperm mortality (Villalaín et al., 2001). Hwang et al. (2014) observed that 0.3 and 0.375 mg/L TCS significantly decreased sperm viability in sea urchin, (*Strongylocentrotus nudus*) by 13 and 22%, respectively. It also affected the rate of fertilization as exposure of 0.3 mg/L decreased fertilization rate by 82.7 ± 1.57% and fertilization failed (0%) at 0.375 mg/L.

5.2. Effects on hatching

Hatching is an important process in the life history of a fish. Generally, it involves softening or digestion of the chorion by the hatching enzymes that are secreted by hatching gland cells. Disintegration and degradation of the inner layer is caused by the synergistic action of proteases while the outer layer is broken by the movements of an embryo (Dar et al., 2019). However, inhibition of the hatching enzyme chorionase and osmotic disturbances interfering with the activity of the hatching enzyme and muscular action of the embryo have been reported to cause delayed hatching or hatching failure (Hallare et al., 2005). Ishibashi et al. (2004) exposed *Oryzias latipes* to 78, 156, 313, 625, 1250 and 2500 μg/L TCS for 14 d and noticed that at 313 μg/L, hatching declined to 70% and got delayed by 2 d, while at higher concentrations there was no hatching at all. In another study, Nassef et al. (2010) injected eggs of *O. latipes* 8 h post fertilization (hpf) with 1, 5 and 9 ng TCS egg^{-1} for 4 and 6 d and observed that hatchability decreased significantly over control at ≥ 5 ng TCS egg^{-1} at 1 day post fertilization (dpf) but there was 0% hatching at 9 ng TCS egg^{-1} as all the embryos died before hatching within 4 dpf. They observed that hatching time at 1 and 5 ng TCS egg^{-1} was significantly higher than the control groups. Schnitzler et al. (2016) reported that TCS at 20, 50 and 100 μg/L did not affect hatching success of *Cyprinodon variegatus* but delayed hatching by 6–13 h i.e. 4%–7% prolongation of developmental time compared to control embryos. They also noticed delayed metamorphosis and correlated it to the absence of T_3 peak at 12–15 dpf and suggested that the delayed metamorphosis could reduce juvenile fitness. When Wirt et al. (2018) exposed zebrafish eggs (2–4 hpf) to 0, 0.4, 4 and

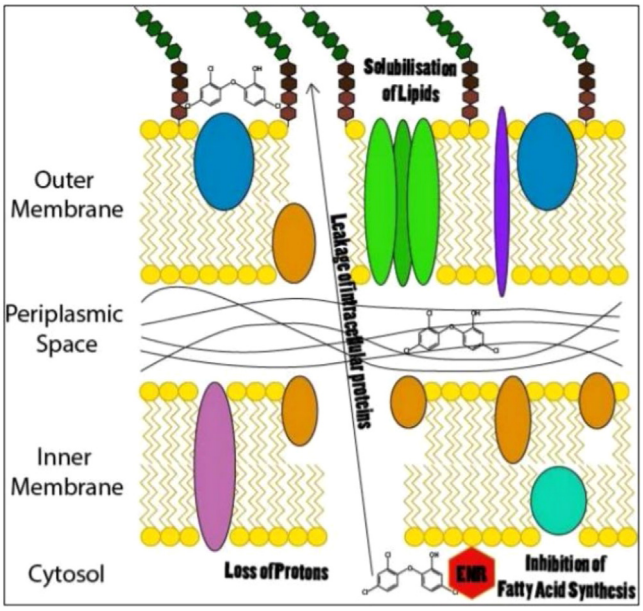

Fig. 2. Schematic representation of TCS action on lipid biosynthesis in bacterial cells.
Source: Adapted from Henly (2019).

40 μg/L TCS, all the eggs hatched 96 hpf at 0–4 μg/L TCS, but 20% eggs failed to hatch and died prior to 5 dpf at 40 μg/L TCS. They noticed that TCS did not impact growth or produce overt developmental malformations in significant number of eggs but there was a concentration dependent decrease in survival through 21 dpf. They also observed that reduction in survival was significant only in the highest treatment group (30% over control). Zhang et al. (2018) exposed zebrafish eggs to different concentrations (0, 0.21, 0.26, 0.32, 0.40, 0.50, and 0.63 mg/L) of TCS, 2,4-dichlorophenol (2,4-DCP), and 2,4,6-trichlorophenol (2,4,6-TCP) for 6 to 120 hpf and observed significant concentration-dependent decrease in hatching rate over controls at 72 hpf, on exposure to all three chemicals with a maximum decline of 93% at 0.63 mg/L TCS. They also observed delayed hatching in TCS and 2,4,6-TCP.

5.3. Developmental deformities

Stress of TCS has been observed to cause an increase in the incidence of deformities in developing fish. The deformations may be probably due to the lipophilic nature of TCS which enters into the lipid domains causing plasma membrane perturbations responsible for deformed tissues and organs (Coogan et al., 2007) or partly due to the TCS induced stress resulting in cell death that can alter tissue and organ development (Kong et al., 2016; Zhang et al., 2018). When Oliveira et al. (2009) exposed zebrafish embryos (0.5 hpf) for 144 h to 0.1, 0.3, 0.5, 0.7 and 0.9 mg/L TCS, they observed delay in otolith formation and appearance of eye and body pigmentation over control after 24 h exposure to 0.9 mg/L TCS, 0% hatching/100% mortality after 48 h exposure to higher concentrations. They also noted that after 96 h exposure, larvae exposed to 0.5 mg/L presented several developmental defects, including spine malformation, pericardial oedema and short sized body. Macedo et al. (2017) exposed zebrafish eggs to 1000, 400, 160, and 64 μg/L of TCS for 144 h and observed that TCS significantly increased percentage of pericardial oedema and yolk-sac abnormalities and also induced involuntary muscular contractions at 400 μg/L concentration at the end of the exposure. However, they noticed a significant increase in the percentage of pericardial oedema at 32 hpf at 1000 μg/L TCS and suggested that this could be a primary indicator of TCS toxicity since at 80 hpf there was 100% mortality at this concentration. A summary of experimental studies based on reproductive and teratogenic effects of TCS exposure to aquatic organisms is provided in Table 3.

5.4. Survival effects

In addition to the reproductive and teratogenic effects of TCS on aquatic organisms, it has also been observed to cause mortality of embryos, larvae, hatchlings and adults at different lethal concentrations depending upon the nature and type of species and water temperature (Paul et al., 2019) & pH (Paul et al., 2020). In one study, Nassef et al. (2009) exposed adult Japanese medaka (*O. latipes*) to 1, 2, 2.4 and 3 mg/L TCS for 96 h and observed 100%, 16.7%, 3.3% and 0% survival, respectively at the end of the bioassay. They calculated 96 h LC_{50} and no observed effect concentration (NOEC) of TCS

Table 3
Effect of TCS exposure on reproduction, hatching and development of aquatic organisms.

Organism	Scientific name	TCS parameters	Major findings	Reference(s)
Effects on reproduction				
Mosquitofish	*Gambusia affinis*	100–350 nM; 35 d	Vitellogenin gene expression ↑, Sperm count ↓	Raut and Angus (2010)
Sea urchin	*Strongylocentrotus nudus*	1.0 and 1.5 μM	Sperm viability ↓ by 13 & 22%. Rate of fertilization ↓ by 82.7 & 100%	Hwang et al. (2014)
Mud snail	*Potamopyrgus antipodarum*	0.660 μg/L	Fecundity ↑ by 40.6%	Geiß et al. (2016)
Common carp	*Cyprinus carpio*	0.04–0.16 mg/L; 42 d	Females carp: Testosterone ↑, Vitellogenin ↑, FSH ↑, LH ↑ Male carp: Vitellogenin ↑, FSH ↑, LH ↓, GnRH ↓	Wang et al. (2017, 2018b)
Japanese medaka	*Oryzias latipes*	174.1 and 345.7 μg/L	Hepatic vitellogenin ↑ in females and ↓ in males	Horie et al. (2018)
Effect on hatching				
Japanese medaka	*Oryzias latipes*	1000 and 500 μg/L; 24 h–3 d	100% mortality of the hatchlings	Foran et al. (2000)
Japanese medaka	*Oryzias latipes*	78–2500 μg/L; 14 d	Hatching ↓ by 70% at 313 μg/L No hatching at TCS > 313 μg/L	Ishibashi et al. (2004)
Zebrafish	*Danio rerio*	0.1–0.9 mg/L; 24–144 h	No hatching at 0.5, 0.7 and 0.9 mg/L TCS. 48% hatching in control.	Oliveira et al. (2009)
Japanese medaka	*Oryzias latipes*	1, 5 and 9 ng; 8 hpf	0% hatching at 9 ng	Nassef et al. (2010)
Sheephead minnow	*Cyprinodon variegatus*	20, 50 and 100 μg/L	4%–7% prolongation of developmental time compared to control embryos; delayed metamorphosis	Schnitzler et al. (2016)
Frog	*Peleophylax perezi*	0.25–2.5 mg/L; 72 h	Hatching rate ↓ by almost 70% after 72 h	Martins et al. (2017)
Zebrafish	*Danio rerio*	0.4–40 μg/L; 2–4 hpf	20% eggs failed to hatch and died prior to 5 dpf at 40 μg/L	Wirt et al. (2018)
Zebrafish	*Danio rerio*	0–0.63 mg/L; 6 to 120 hpf	93% ↓ in hatching at 0.63 mg/L	Zhang et al. (2018)

(*continued on next page*)

for this fish at 1.7 mg/L and 1.7 μg/L, respectively and noticed that NOEC value in their study was 12 times lower than the predicted environmental concentration (PEC) for the chemical. Oliveira et al. (2009), calculated 96 h LC_{50} of TCS at 0.42 mg/L for embryos/larvae of zebrafish and noticed that concentrations of TCS above 0.7 mg/L exhibited teratogenic effects, delayed development of embryo and resulted in 100% mortality within 48 h. In a similar study, Horie et al. (2018) noticed an increase in mortality of the embryonic and early larval stages of TCS exposed *O. latipes* with a steep increase in mortality soon after hatching. They reported that lowest observed effect concentrations of TCS for the embryos and larvae (276.3 μg/L), early life stage (134.4 μg/L) and adult stage (174.1 μg/L) were at least 55 times (compared with USA) and up to 13 400 times (compared with Germany) greater than the detected TCS levels in the aquatic environment. Wang et al. (2018a) exposed gold fish (*Carassius auratus*) to 0.6000, 0.6900, 0.7935, 0.9125, 1.0494 and 1.2068 mg/L TCS for 96 h and observed 60%, 50% and 10% mortality at 1.2068, 1.0496 and 0.9125 mg/L, respectively at the end of the bioassay. They calculated LC_{50} of TCS for this fish at 1.1119 mg/L. Zhang et al. (2018) exposed zebrafish eggs to different concentrations (0, 0.21, 0.26, 0.32, 0.40, 0.50, and 0.63 mg/L) of TCS, 2,4-dichlorophenol (2,4-DCP), and 2,4,6-trichlorophenol (2,4,6-TCP) for 6 to 120 hpf and calculated the respective LC_{50} values at 0.51, 1.11 and 2.45 mg/L. They observed a classical S type curve for lethal effect of TCS with a threshold dose 0.30 mg/L as there was a sharp increase in mortality at >3.0 mg/L. Table 4 summarizes the recent studies on lethal effects (LC_{50} values) of TCS exposure of aquatic organisms.

5.5. Biochemical toxicity

The effect of TCS on enzymes, non-enzymatic antioxidants and lipid peroxidation have been summarized in Table 5. TCS induces oxidative stress and causes alterations in the activities of antioxidative, detoxification, metabolic and neurological enzymes (Paul et al., 2020). Moreover, it affects the contents of non-enzymatic antioxidants and causes lipid peroxidation (Dar et al., 2020a). Exposure of organisms to contaminants often results in increased production of reactive oxygen species (ROS) like superoxide anion radical ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2) and reactive hydroxyl radical ($^{\cdot}OH$) (Samet and Wages, 2018). ROS have an important role in catalyzing diverse radical reactions in living systems (Valko et al., 2007)

Table 3 (*continued*).

Organism	Scientific name	TCS parameters	Major findings	Reference(s)
Deformities in embryos and larvae				
Japanese medaka	*Oryzias latipes*	1–100 μg/L; 60 d	Dorsal fin length ↑, Anal fin length ↑ in males, ↓ in females	Foran et al. (2000)
Zebrafish	*Danio rerio*	0.1–0.9 mg/L; 144 h; 0.5 hpf	Delay in otolith formation; Appearance of eye and body pigmentation (0.9 mg/L; 24 h); spine malformation, pericardial oedema and short sized body in larvae (0.5 mg/L; 96 h)	Oliveira et al. (2009)
Japanese medaka	*Oryzias latipes*	1, 5 and 9 ng; 4 and 6 d	Abnormal eye development (9 ng); Hemorrhage, shrunken yolk-sac and spinal curvature (at conc. ≥ 5 ng)	Nassef et al. (2010)
Zebrafish	*Danio rerio*	250 μg/L; 5 d	No effect on embryogenesis/organogenesis	Ho et al. (2016)
Zebrafish	*Danio rerio*	1000, 400, 160, and 64 μg/L; 144 h	Pericardial oedema, yolk-sac abnormalities; involuntary muscular contractions (400 μg/L)	Macedo et al. (2017)
Frog	*Peleophylax perezi*	0.25–2.5 mg/L; 72 h	Delay in eye and body development	Martins et al. (2017)
Zebrafish	*Danio rerio*	0.2–0.8 mg/L	Body length ↓, Head size ↓, Eye size ↓, Apopotosis in central nervous system ↑	Kim et al. (2018)
Zebrafish	*Danio rerio*	0.4, 4, and 40 μg/L	Larvae growth ↓, emaciation ↓	Wirt et al. (2018)
Zebrafish	*Danio rerio*	0.21–0.63 mg/L; 120 h	Narrow eyes, closure of swim bladder, pericardial and yolk cyst and crooked body	Zhang et al. (2018)
Zebrafish	*Danio rerio*	0.01, 0.1, 30, 300 and 500 μg/L; 96 hpf	Oedema in embryos, cardiac toxicity	Fu et al. (2019)
Common Carp	*Cyprinus carpio*	0.05–0.5 mg/L	Embryo deformities—cardiac and yolk sac oedema, bubbles in yolk, leaky yolk sac, dysregulation of yolk sac and aborted embryos Larvae deformities—curved tail, delayed otolith formation, deflated swim bladder and hemorrhage, paralytic larvae, pointed head, lean body, fused eyes (*C. carpio*), degenerated digestive tract (*L. rohita*), albinic hatchlings (*C. idella*), deformed caudal fin (*C. idella*), gas bubble disease (*C. mrigala, L. rohita*), hypopigmentation (*C. mrigala*), ruptured yolk sac (*C. mrigala*),	Dar et al. (2019, 2020b)
Rohu	*Labeo rohita*			
Grass carp	*Ctenpharyngodon idella*			
Mrigal	*Cirrhinus mrigala*			

Arrows indicate increase (↑) and decline (↓) in the respective parameters. Hpf: hours post fertilization.

and can attack various macromolecules such as DNA, proteins and lipids, leading to mutagenesis, cellular ageing, and carcinogenesis (Gniadecki et al., 2001). To minimize oxidative damage to cellular components, organisms have developed antioxidant defence system to manage increasing levels of ROS and consequently the oxidative stress (Peng et al., 2013; Stara et al., 2020b; Freitas et al., 2019; Vajargah et al., 2019; Burgos-Aceves et al., 2018; Hodkovicova et al., 2019). Generally, ROS generating contaminants result in either induction or inhibition of enzymes. Thus, the enzymes involved in the antioxidant system are used as biomarkers to indicate the stress of exposure to contaminants (Matozzo et al., 2012; Kaur and Kaur, 2015). An increased activity of Acetylcholine esterase (AChE), Glutathione S-transferase (GST) and Lactate dehydrogenase (LDH) in the larvae of zebrafish was observed on exposure to TCS (Oliveira et al., 2009). Falisse et al. (2017) exposed zebrafish (*D. rerio*) eggs to 50, and 100 μg/L TCS for 7 d and noticed that AChE and GPX showed a significant increase while GR showed a significant decline over control at both the concentrations.

An increased activity of Catalase (CAT), Superoxide dismutase (SOD) and GST in the gill and liver and inhibition of AChE activity in the brain of *Pangasianodon hypophthalmus* was noticed after exposure to sublethal concentrations of TCS (Sahu et al., 2018). The 30d exposure to low levels (84.83–271.39 μg/L) of TCS significantly altered the neurological, antioxidative, detoxification and metabolic enzyme activities in *P. hypophthalamus* (Paul et al., 2020). TCS significantly increased the activities of Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and GST in gill, liver and muscle tissues of *C. catla* fingerlings (Hemalatha et al., 2019a). Dar et al. (2020b) exposed the larvae of four food fishes viz. *C.carpio*, *C. idella*, *L. rohita* and *C. mrigala* to sublethal concentrations (0.005, 0.01, 0.02 and 0.05 mg/L) of TCS and observed that activity of AChE, and contents of GSH and GSSG declined while activities of GST, LDH, AST and ALT and content of Malondialdehyde (MDA) increased in a concentration dependent manner in all the fish. However, variation in these biomolecules was maximum in *L. rohita* and minimum in *C. mrigala.*. Therefore, it became clear that TCS caused species specific variation in biochemical responses. Even biomolecules of different sexes showed varied response to TCS, when Liang et al. (2013) exposed male and female sword tail fish (*Xiphophorus helleri*) to 0.002, 0.05 and 1.25 mg/L TCS for 24, 72 and 168 h. They observed that activity of GST increased in a dose dependent manner in females after 24 and

Table 4
Effect of TCS exposure on survival of aquatic organisms.

Organism	Scientific name	Exposure time (h)	Lethal Concentration (LC_{50}) value	Reference(s)
Japanese medaka (fry)	*Oryzias latipes*	48	352 μg/L	Foran et al. (2000)
Bluegill sunfish (adult)	*Lepomis macrochirus*	24, 48, 72, and 96	440 (24 h), 410 (48 h), and 370 (96 h) μg/L	Orvos et al. (2002)
Fathead minnows (adult)	*Pimephales promelas*	24, 48, 72, and 96	360 (24 h), 270 (48 h), 270 (72 h) and 260 (96 h) μg/L	Orvos et al. (2002)
Japanese medaka (embryos/larvae)	*Oryzias latipes*	24 and 96	602 (24 h) and 399 (96 h) μg/L	Ishibashi et al. (2004)
Japanese Medaka (larvae)	*Oryzias latipes*	96	0.60 mg/L	Kim et al. (2009)
Japanese Medaka (adult)	*Oryzias latipes*	96	1.7 mg/L	Nassef et al. (2009)
Zebrafish (embryos/larvae)	*Danio rerio*	96	0.42 mg/L	Oliveira et al. (2009)
Amphipod (adult) Mysids (adult)	*Annaphila abdita* *Bahia americamysis*	96 96	73.4 μg/L 74.3 μg/L	Perron et al. (2012)
Swordtail (adult)	*Xiphophorus helleri*	96	1.47 mg/L	Liang et al. (2013)
Guppy (adult)	*Poecilia vivipara*	96	0.6 mg/L	Escarrone et al. (2016)
Rotifer (adult)	*Plationus patulus* *Brachionus havanaensis*	24 24	300 μg/L 500 μg/L	González-Pérez et al. (2018)
Common carp (adult) Goldfish (adult) Zebrafish (embryos)	*Cyprinus carpio* *Carassius auratus* *Danio rerio*	96 96 120	0.80 mg/L 1.112 mg/L 0.51 mg/L	Wang et al. (2017) Wang et al. (2018a) Zhang et al. (2018)
Mayfly (adult) Fairy Shrimp (adult) Sludge worm (adult) Caddisflies (adult) Riceland prawn (adult)	*Baetis ephimeroptera* *Branchinella thailandensis* *Tubifex tubifex* *Leptocerus trichoptera* *Macrobrachium lanchesteri*	72 and 96 48 and 96 72 and 96 72 and 96 72 and 96	96 (72) and 72 μg/L (96 h) 130 (48 h) and 100 μg/L (96 h) 266 (72 h) and 259 μg/L (96 h) 866 (72 h) and 760 μg/L (96 h) 1005 (72 h) and 962 μg/L (96 h)	Khatikarn et al. (2018)
Catla (fingerlings)	*Catla catla*	96	0.36 mg/L	Hemalatha et al. (2019a)
Zebrafish (adult)	*Danio rerio*	96	0.29 (pH: 5.0), 0.41 (pH: 6.0), 0.50 (pH: 7.0) 0.55 (pH: 8.0), 0.70 (pH: 9.0) mg/L	Li et al. (2018b)
Water flea (adult)	*Daphnia magna*	24	0.15 (pH: 5.0), 0.17 (pH: 6.0), 0.22 (pH: 7.0) 0.36 (pH: 8.0), 0.56 (pH: 9.0) mg/L	
Red worm (adult)	*Limnodrilus hoffmeisteri*	24	1.57 (pH: 5.0), 1.61 (pH: 6.0), 1.62 (pH: 7.0) 1.66 (pH: 8.0), 1.86 (pH: 9.0) mg/L	
Striped catfish (juvenilies)	*Pangasionodon hypophthalamus*	96	848.33 (25 °C), 1181.94 (30 °C) and 1356.96 (35 °C) μg/L	Paul et al. (2019)
Common carp (embryos) Rohu (embryos) Grass carp (embryos) Mrigal (embryos)	*Cyprinus carpio* *Labeo rohita* *Ctenopharyngodon idella* *Cirrhinus mrigala*	96	0.315 mg/L 0.096 mg/L 0.116 mg/L 0.131 mg/L	Dar et al. (2019)
Striped catfish (juvenilies)	*Pangasionodon hypophthalamus*	96	910 (pH: 6.5), 110 (pH: 7.5), 1380 (pH: 8.5) μg/L	Paul et al. (2020)
Zebrafish (adult)	*Danio rerio*	96	398.9 μg/L	Gyimah et al. (2020)
Rohu (larvae)	*Labeo rohita*	96	126 μg/L	Sharma et al. (2021a)

168 h exposure. However, the dose-dependence was intangible for the females after 72 h exposure. They also noticed that GST activity in males increased gradually with the increase in exposure time and concentration of TCS.

5.6. Cytogeno toxicity

TCS due to its antiseptic nature disturbs the normal cell functioning which leads to cytotoxicity (Schweizer, 2001). TCS induces apoptosis or necrosis either directly by acting as an intercalating agent (through dioxins, the degraded product of TCS) or indirectly through oxidative stress (Aranami and Readman, 2007). TCS also affects the stability of DNA through ROS production and inhibition of DNA repair system (Binelli et al., 2009a,b). They observed that 3 nM concentration caused dose dependent increase in apoptotic cell frequency in zebra mussel hemocytes. Parenti et al. (2019) observed that 0.1 and 1 μg/L TCS significantly decreased cell viability and increased necrotic cell frequency in the embryos of *Danio rerio*.

The two main biomarkers used for genotoxic studies are single cell gel electrophoresis (SCGE) or Comet Assay and Micronuclei test (MN). The comet assay measures the extent of DNA damage on exposure of pollutant/toxicant and is

Table 5
Change in biochemical biomarkers on exposure to TCS.

Organism	Model organism	Tissue	Biochemical biomarkers	References
Zebra mussel	*Dreissena polymorpha*	Whole organism	GST ↑, CAT ↑, SOD ↑, GPx ↓	Binelli et al. (2011)
Venus clam	*Ruditapes philippinarum*	Gill Digestive glands	AChE ↓, SOD ↑ SOD ↓	Matozzo et al. (2012)
Zebrafish	*Danio rerio*	Whole Embryo	AChE ↑, LDH ↑	Oliveira et al. (2009)
Swordtail	*Xiphophorus helleri*	Liver	GST ↑	Liang et al. (2013)
Crustacean	*Daphina magna*	Whole organism	GST ↑, CAT ↑, SOD ↑, MDA ↑	Peng et al. (2013)
Yellow catfish	*Pelteobagrus fulvidraco*	Liver	GST ↓, CAT ↑, EROD ↓, ERND ↑, APND ↑, MDA ↑	Ku et al. (2014)
Rotifer	*Brachionus koreanus*	Whole organism	GST ↑	Han et al. (2016)
Frog	*Pelophylax ridibundus*	Liver Brain	GST ↑, LDH ↓, GSSG ↑ AChE ↓	Falfushynska et al. (2017)
Zebrafish	*Danio rerio*	Whole Embryo	AChE ↑, GST ↑, GPx ↑, GR ↓	Falisse et al. (2017)
Frog	*Pelophylax perezi*	Whole Embryo	AChE ↓	Martins et al. (2017)
Copepoda	*Tigriopus japonicus*	Whole organism	GST ↑, SOD ↑, GPx ↑, GSH ↑	Park et al. (2017)
Goldfish	*Carassius auratus*	Liver	CAT ↑, SOD ↑, GSH ↑, MDA ↑	Li et al. (2018b)
Striped catfish	*Pangasianodon hypophthal-mus*	Gill Liver Brain	GST ↑, CAT ↑, SOD ↑ GST ↑, CAT ↑, SOD ↑ AChE ↓	Sahu et al. (2018)
Catla	*Catla catla*	Gill Liver Muscle	GST ↑, AST ↑, ALT ↑ GST ↑, AST ↑, ALT ↑ GST ↑, AST ↑, ALT ↑	Hemalatha et al. (2019a)
Rohu	*Labeo rohita*	Gill Liver Kidney	GST ↑, CAT ↑, SOD ↑, GPx ↑, GSH ↑, MDA ↑ GST ↑, CAT ↑, SOD ↑, GPx ↑, GSH ↑, MDA ↑ GST ↑, CAT ↑, SOD ↑, GPx ↑, GSH ↑, MDA ↑	Hemalatha et al. (2019b)
Zebrafish	*Danio rerio*	Whole Embryo	GST ↑, CAT ↑, SOD ↑, GPx ↑	Parenti et al. (2019)
Striped catfish	*Pangasianodon hypophthalmus*	Gill Liver Brain Kidney Serum	GST ↑, CAT ↑, SOD ↑, LDH ↑, AST ↑, ALT ↑ GST ↑, CAT ↑, SOD ↑, LDH ↑, AST ↑, ALT ↑ AChE ↓, GST ↑, CAT ↑, SOD ↑ GST ↑, CAT ↑, SOD ↑ LDH ↑, AST ↑, ALT ↑	Paul et al. (2019)
Mosquitofish	*Gambusia affinis*	Liver	GST ↑, CAT ↑, SOD ↑, GPx ↑, GSH ↑, MDA ↑	Bao et al. (2021)
Common carp Grass carp Rohu Mrigal	*Cyprinus carpio* *Ctenopharyngodon idella* *Labeo rohita* *Cirrhinus mrigala*	Whole Embryos/larvae	AChE ↓, GST ↑, LDH ↑, AST ↑, ALT ↑, GSH ↓, GSSG ↓, MDA ↑	Dar et al. (2020a,b)
South American catfish	*Rhamdia quelen*	Whole Embryo	AChE ↑, SOD ↓	Gomes et al. (2021)
Zebrafish	*Danio rerio*	Liver	GST ↑, CAT ↓, SOD ↓, GPx ↓, GR ↓, GSH ↓, GSSG ↓, MDA ↑	Gyimah et al. (2020)
		Brain	CAT ↓, GPx ↑, CP ↑, 8-OHdG ↑	
	Danio rerio	Larvae	AChE ↓	Pullaguri et al. (2020)
Rohu	*Labeo rohita*	Larvae	Glucose ↓, Triglycerides ↓, Urea ↓, Uric acid ↓, ALP ↓, AST↓, ALT ↓	Sharma et al. (2021b)

Arrows indicate increase (↑) and decline (↓) over control.

commonly used in toxicological studies (Lin et al., 2010) while the clastogenic and aneugenic effects of xenobiotics have been monitored by MN (Wang et al., 2018a). The concentration dependent increase in Olive Tail Moment (OTM) was observed in *Tetrahymena thermophila* on exposure to TCS (Gao et al., 2015). Binelli et al. (2009a,b) reported the genotoxic effects of TCS on zebra mussel hemocytes in the form of elevated length/diameter ratios (LDR), Tail DNA (%) and MN frequency. An increase in temperature and pH dependent TCS toxicity were noticed in blood cells (comet assay and MN) and liver cells (comet assay) of *P. hypophthalmus* by Paul et al. (2019, 2020). They observed that TCS in combination with temperature and pH caused significant increase in DNA damage and MN frequency. Wang et al. (2018a) reported that TCS exposure increased MN frequency and tail moment (at highest dose) in blood and liver cells of gold fish, respectively. The TCS treatment caused significant DNA damage in red blood cells of rainbow trout (Capkin et al., 2017), liver cells of adult zebrafish (Gyimah et al., 2020) and fingerlings of *Labeo rohita* (Hemalatha et al., 2019b).

Table 6
Changes in the relative expression of genes after exposure to TCS.

Organism	Scientific name	Tissue	Relative expression	References
Mosquitofish	*Gambusia affinis*	Liver	Vitellogenin (VTG) ↑	Raut and Angus (2010)
Zebrafish	*Danio rerio*	Head	Thyroid stimulating hormone (TSH) ↑, sodium iodide symporter (NIS) ↑	Pinto et al. (2013)
Swordtail	*Xiphophorus helleri*	Liver	*CYP1A* ↑, *CYP3A* ↑, *GST* ↑, *P-gp* ↑	Liang et al. (2013)
Yellow Catfish	*Pelteobagrus fulvidraco*	Liver	*CYP1A* ↑, *CYP3A* ↑, *GST* ↑	Ku et al. (2014)
Zebrafish	*Danio rerio*	Whole Embryo	10 hpf: *Oct4* ↓, *Nanog* ↓	Chen et al. (2015)
			24 hpf: *Oct4* ↑, *Nanog* ↑, *Sox* ↑	
Rotifer	*Brachionus koreanus*	Whole organism	*CYP3024A2* ↑, *CYP3027C2* ↑, *GST-sigma* ↑, *CAT* ↑, *HSP* ↑	Han et al. (2016)
Sea urchin	*Strongylocentrotus nudus*	Whole Embryo	Bone morphogenic protein gene (BMPs) ↓, chromosomal binding protein gene (CBP) ↓, empty spiracles homeobox 1 (EMX-1) ↓	Hwang et al. (2017)
Rainbow trout	*Oncorhynchus mykiss*	Liver	*SOD* ↑, *GPX1* ↑, *GPX2* ↑, *GSTA* ↑, *CAT* ↑, *HSP90BB* ↑, *HSP90BA* ↑, *HSC70A* ↑	Capkin et al. (2017)
		Kidney	*SOD* ↑, *GPX1* ↑, *GPX2* ↑, *GSTA* ↑, *CAT* ↑, *HSP90BB* ↑, *HSP90BA* ↑, *HSC70A* ↑	
Harlequin fly	*Chironomus riparius*	larvae	*EcR* ↑, *usp* ↑, *E74* ↑, *ERR* ↑ *hsp70* ↑	Martínez-Paz et al. (2017)
Sea cucumbers	*Tigriopus japonicus*	Whole organism	*CYP326A3* ↑, *CYP3037A1* ↑, *GST-T* ↑	Park et al. (2017)
Common carp	*Cyprinus carpio*	Gonads	*CYP19A* ↑	Wang et al. (2017, 2018b)
		Hypothalamus	*CYP19B* ↑, *GnRHs* ↑, *CGnRH–ii–2* ↑, *SGnRH–1* ↑	
		Hepatopancreas	*Er mRNA* ↓ (male), *Er mRNA* ↑ (female)	
		Pituitary	*GtH–I–β* ↑, *GtH–II–β* ↑	
Zebrafish	*Danio rerio*	Whole Embryo	*p53* ↑, *Casp3* ↑, *Casp8* ↑, *Ngn1* ↑, *Nrd* ↑, *Elavl3* ↑, *α1-Tubulin* ↑, *Gap43* ↑, *Gfap* ↓, *Mbp* ↓	Kim et al. (2018)
Harlequin fly	*Chironomus riparius*	Larvae	*CYP4D2* ↑, *CYP6B7* ↑, *CYP9F2* ↑, *CYP12A2* ↑, *GSTd3* ↑, *GSTd6* ↓, *GSTe1* ↑, *GSTo1* ↑, *GSTt1* ↑	Martínez-Paz (2018)
Green alga	*Chlamydomonas reinhardtii*	Cells	*SOD* ↑, *GPx* ↓	Pan et al. (2018)
Zebrafish	*Danio rerio*	Larvae	*BCL-2* ↓, *Bax* ↑, *P53* ↑, *MAPK* ↑	Liu et al. (2019)
		Liver	*BCL-2* ↓, *Bax* ↑, *P53* ↑, *MAPK* ↑	
		Gill	*SOD* ↓, *GPx1a* ↓, *CAT* ↓, *sMT-B* ↓, *p53* ↓, *MDM-2* ↑, *Bax* ↓, *BCL-2/Bax* ↓	Wang et al. (2020a)
		Ovary	*SOD* ↓, *GPx1a* ↓, *CAT* ↓, *sMT-B* ↓, *BCL-2* ↓, *p53* ↑, *Bax* ↓, *BCL-2/Bax* ↓	
Mosquitofish	*Gambusia affinis*	Liver	*Nrf2* ↑, *NQO1* ↑, *GCLC* ↑, *GSTA* ↑, *GPx* ↑, *CAT* ↑, *SOD2* ↑, *Sirt1* ↑, *Sirt2* ↑, *Sirt3* ↓, *miR-34a* ↑, *miR34b* ↑, *miR-144* ↑, *miR-200b-5p* ↓, *miR-153a-5p* ↑, *ERK* ↓, *p38* ↓	Bao et al. (2021)
Zebrafish	*Danio rerio*	Whole Embryo	Urea transporter ↓, phenylalanine hydroxylase ↓, fatty acid synthase ↓, phosphoglucomutase ↓	Fu et al. (2020)
		Hepatocytes (ZF-L)	ATP binding proteins (ABCBs ↓, ABCC2 ↑)	Guidony et al. (2021)
		Skeletal muscles	*AChE* ↓, *mbp* ↓	Pullaguri et al. (2020)
Japanese medaka	*Oryzias latipes*	Whole Embryo	*dnmt1* ↓, *dnmt3aa* ↓, *dnmt3ba* ↓, *dnmt3bb* ↓	Song et al. (2020)
Zebrafish	*Danio rerio*	Whole Embryo	Pri-mir 125b1 ↑, Pri-*mir 125b3* ↑, *Nrf2* ↑, *C/EBPA* ↓, *PKCα* ↓, *ERα* ↓, *ERβ* ↓	Wang et al. (2020b)
Rohu	*Labeo rohita*	larvae	CYP1a ↓, CYP3a ↑, GST ↓, SOD ↓, CAT ↑, GR ↓, GPx ↓, LDH ↓, AST ↓, ALT ↑, AChE ↑, Trypsin ↓, Pancreatic amylase ↓, Creatinine kinase ↑	Sharma et al. (2021a,b)

Arrows indicate increase (↑) and decline (↓) over control.

5.7. Alteration in gene expression

In toxicological studies, alteration at molecular level is an effectively used tool/warning signal for assessment of pollution and effect of toxicants. Gene expression or mRNA copy number of a particular gene of interest is analysed by Real-Time Polymerase Chain Reaction (RT-PCR).

A number of studies have reported that TCS induced oxidative stress alters the expression of genes (Table 6). TCS has been found to cause developmental retardation in Zebrafish embryos by elevating the level of pluripotency factors (*Sox2, Nanog and Oct4*) (Chen et al., 2015). TCS mediated oxidative stress elevated the expression of antioxidant genes (*SOD, GPx1, GPx2, GSTA*) and heat shock proteins (*HSP90BB, HSP90BA, HSC70A*) in rainbow trout *Oncorhynchus mykiss* (Capkin et al., 2017). Wang et al. (2020a) noticed that TCS differentially regulated expression of apoptosis related genes in the gill and ovary of zebrafish. They reported that expression of antioxidant related genes was downregulated at 34 and 68 μg/L in the gill but at 68 μg/L in the ovary. Expression of Bax and p53 was downregulated at 68 μg/L in the gill while in the ovary both Bax (34 and 68 μg/L) and p53 (68 μg/L) were upregulated. Pullaguri et al. (2020) noticed that 48 h exposure to 0.6 mg/l TCS declined the mRNA level of *AChE* and *mbp* genes in the skeletal muscles of zebra fish which indicated that TCS might disrupt motor function and functioning of myelin sheath.

TCS induced phase I and phase II detoxification system differentially in male and female swordtail fish. Males had higher expression of antioxidant genes compared to females (Liang et al., 2013). Ku et al. (2014) noticed that the transcript level of *CYP1 A, CYP3A* and *GST* in yellow catfish showed marked induction and repression on exposure to TCS. AhR is a ligand activated transcription factor that controls the expression of diverse set of genes that are primarily activated by xenobiotics especially dioxins (Beischlag et al., 2008). TCS has similar structure to dioxins and in the presence of sunlight is converted to 4 types of dioxins. Activation of AhR results in transcription of CYP450 enzymes which are involved in metabolism of endogenous compounds and xenobiotics (Kawajiri and Fujii-Kuriyama, 2007). Taking into account the involvement of ROS in the mechanism of TCS action also can be related to the interaction between Nrf2/keap1 transcription factor with AhR signalling pathway as the cause of alteration in CYPs mRNA (Haarmann-Stemmann et al., 2012). Similarly the crosstalk of HIF-1α with AhR also affect transcription of AhR regulated genes including CYPs.

The report of Liu et al. (2019) suggests that TCS promotes apoptosis in embryos and liver of zebrafish as its exposure declined the expression of anti-apoptotic gene *Bcl-2* but elevated the expression of *Bax, P53* and *MAPK*. The study of Fu et al. (2020) on zebrafish embryos suggests that TCS decreases the expression of phosphoglucomutase (PGM), urea transporter (UT), fatty acid synthase (FASN) and phenylalanine hydroxylase (PAH). They concluded that TCS affected glucose metabolism, inhibited excretion of urea and led to urea accumulation and also inhibited fatty acid synthesis and caused abnormal development of central nervous system due to accumulation of phenylalanine and improper neurotransmitter levels.

Altered expression of differentially methylated fragments (DMFs) in zebrafish early developmental stages indicates that TCS affects DNA methylation during embryogenesis (Falisse et al., 2018). The elevated expression of vitellogenin mRNA in male mosquitofish *Gambusia affinis* demonstrates the endocrine disrupting nature of TCS (Raut and Angus, 2010). TCS affects thyroid functioning as it upregulated thyroid stimulating hormone (TSH) and Sodium Iodide Symporter (NIS) mRNA level in zebrafish (Pinto et al., 2013). Hwang et al. (2017) related the abnormal embryonic development in TCS exposed sea urchin *Strongylocentrotus nudus* to the significant decline in the expression of genes like *EMX-1* (Empty spiracles homeobox), Bone morphogenetic protein and chromosomal binding protein. Fritsch et al. (2013) related the alteration in swimming behaviour of TCS exposed fathead minnow *Pimephales promelas* to the disruption of signalling and transcription of genes related with excitation–contraction of muscles.

Conclusion

Triclosan is an antimicrobial additive and is present in a wide range of products of day-to-day importance. It is disposed down the drain and accumulates in natural environments exposing aquatic and terrestrial life to its potential toxic effects. TCS degrades into more toxic and persistent byproducts necessitating strict regulatory legislations and proper disposal methods. The potential toxicity and accumulation in biological tissues in addition to the effects at molecular levels have been made abundantly clear from the present review. It is clear that TCS causes teratogenicity, cytogenotoxicity and induces alterations in detoxification and metabolic enzymes in aquatic animals and also causes resistance in bacteria leading to selection of pathogenic bacteria in the ecosystems. Further research should be focused on finding rapid and sensitive biomarkers for evaluating toxicity mechanism of this emerging contaminant in aquatic organisms. This would present a better understanding of mechanisms related to teratogenic effects at a molecular level. Moreover, species specific studies encompassing the organisms of lesser economic importance need to be encouraged in order to present a wider perspective of its effects on aquatic biota. From an environmental conservation parlance, studies related to standardization of improved disposal methods in order to restrict it from contaminating the natural environment would also add value. Hence it can be concluded that presence of such emerging contaminants in the aquatic environments is a matter of great concern, and there is a need to regulate the use and disposal of TCS into the aquatic environments.

CRediT authorship contribution statement

Owias Iqbal Dar: Conceptualization, Writing – original draft, Writing – review & editing. **Raouf Aslam:** Writing – review & editing. **Deng Pan:** Writing – review & editing. **Sunil Sharma:** Writing – review & editing. **Megha Andotra:** Writing – review & editing. **Arvinder Kaur:** Supervision, Writing – review & editing. **Ai-Qun Jia:** Supervision, Writing – review & editing. **Caterina Faggio:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data analysed during this study are included in this article.

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Appendix A. Supplementary data

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