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Review article

Toxicity evolution of triclosan during environmental transformation and human metabolism: Misgivings in the post-pandemic era

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ABSTRACT

In the context of pandemic viruses and pathogenic bacteria, triclosan (TCS), as a typical antibacterial agent, is widely used around the world. However, the health risks from TCS increase with exposure, and it is widespread in environmental and human samples. Notably, environmental transformation and human metabolism could induce potentially undesirable risks to humans, rather than simple decontamination or detoxification. This review summarizes the environmental and human exposure to TCS covering from 2004 to 2023. Particularly, health impacts from the environmental and metabolic transformation of TCS are emphasized. Environmental transformations aimed at decontamination are recognized to form carcinogenic products such as dioxins, and ultraviolet light and excessive active chlorine can promote the formation of these dioxin congeners, potentially threatening environmental and human health. Although TCS can be rapidly metabolized for detoxification, these processes can induce the formation of lipophilic ether metabolic analogs via cytochrome P450 catalysis, causing possible adverse cross-talk reactions in human metabolic disorders. Accordingly, TCS may be more harmful in environmental transformation and human metabolism. In particular, TCS can stimulate the transmission of antibiotic resistance even at trace levels, threatening public health. Considering these accruing epidemiological and toxicological studies indicating the multiple adverse health outcomes of TCS, we call on environmental toxicologists to pay more attention to the toxicity evolution of TCS during environmental transformation and human metabolism.

1. Introduction

There is a global increase in the production and utilization of antibacterial agents, especially in the context of pandemic viruses and pathogenic bacteria (Amigun Taiwo et al. 2022; Dhama et al. 2021). Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol], (TCS), as a representative broad-spectrum antimicrobial agent, can effectively inhibit the activity of bacteria, fungi, and viruses. TCS has been used for about 55 years and added to over 2,000 products, such as personal care products, medical supplies, and household goods (Halden Rolf et al. 2017; Rodricks et al. 2010). Global annual TCS production increased from 1,500 tons in 1998 to 4,762 tons in 2015 (Dar et al. 2022), with the USA consuming 132 million liters of TCS-containing products annually (Alfhili and Lee 2019). Humans are continuously exposed to TCS, primarily through skin/oral pathways (Rodrickset al. 2010), and the per capita consumption is approximately 1.3 mg/person/day (Zhao et al. 2013). In particular, the use of TCS increased significantly through the widespread use of hand sanitizer following the COVID-19 pandemic outbreak (Wang et al. 2022). Accordingly, the estimated maximum TCS intake in children increased to 2.791 mg/kg/day, significantly higher than the 0.3 mg/kg/day permitted daily dosage for adults from the United States Environmental Protection Agency (US EPA) (Wanget al. 2022). Alarmingly, increasing amounts of TCS are released into the environment, potentially causing harm to both the environment and

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human health (Capdevielle et al. 2008; Milanović et al. 2023).

Although TCS-containing toothpaste can reduce plaque and gingivitis, the scientists have voiced concerns about the potential hazards of TCS use (Halden Rolfet al. 2017). Toxicological studies have shown that TCS causes adverse effects on reproduction, the endocrine system, the immune system, and muscle function, as well as genetic toxicity in aquatic organisms and higher vertebrates (Dhillon et al. 2015; Maharana et al. 2015; Solá-Gutiérrez et al. 2018). TCS can also accelerate the spread of antibiotic-resistance genes in the environmental microbiome, potentially causing severe public health concerns (Lu et al. 2022). Therefore, many countries have established regulations on TCS. In 2017, the European Commission banned TCS in human hygiene products (Zhang et al. 2019) and over-the-counter hand and body washes were prohibited by the United States Food and Drug Administration (FDA) in 2016 and 2017 (Skarha et al. 2019).

Antibacterial agents and antiseptic wash products are essential to control and prevent the spread of highly contagious viruses (Laue et al. 2024; Mukherjee et al. 2021). However, the overuse and disposal of TCS-containing disinfectants have raised concerns about adverse environmental and human health effects (Dhamaet al. 2021). A number of reviews on the occurrence, exposure, and toxicity of TCS in the environment and in humans have been published, providing crucial information on human exposure and toxicity (Daret al. 2022; Lee et al. 2024; Rehman et al. 2021). However, the potentially increase in toxicity during the transformation and metabolism of TCS can induce more adverse health effects (Ashrap et al. 2017; Zheng et al. 2008) and TCS toxicity evolution during environmental transformation and human metabolism has not been summarized. Hence, this review mainly focused on the environmental and health effects of TCS exposure, particularly health concerns during its environmental transformation and human metabolism. Moreover, potential diseases involving TCS exposure were also summarized based on toxicological and epidemiologic studies. This review will further understanding of the potential adverse effects of TCS on human health during environmental occurrence, transformation, and human metabolism.

2. Methodology and bibliometric analysis

A systematic search was performed using the Web of Science core collection database from 2004 to 2023 (last search date 19 April 2024). The following search terms were used: "triclosan" AND "exposure* or human health or health effect*" AND "metaboli* or transformation or conversation or *degradation or photolysis or product*" AND "toxic* or adverse effect.*" Document types, such as books, patents, conference papers, meeting abstracts, case reports, dissertation theses, and correction additions, were excluded from this review. A total of 659 papers written in English were identified.

The number of papers on this topic has increased dramatically in 20 years (Fig. 1**A**). The major keywords and similarities of all papers were identified through network analysis using VOS viewer software (version 1.6.18.0). A total of 3,546 keywords and 52 keywords met the criteria (occurring more than 20 times). These keywords were grouped into five clusters (Fig. 1**B**), and the top five keywords in each cluster are listed in Fig. 1**C**. The listed keywords are mainly related to similar contaminants (Group 1), sample types (Group 2), transformation (Group 3), and adverse effects (Group 4). Accordingly, all publications were further split into four categories: exposure, transformation and metabolism, toxicology, and toxicity evolution. Most studies (42 %) focused on the

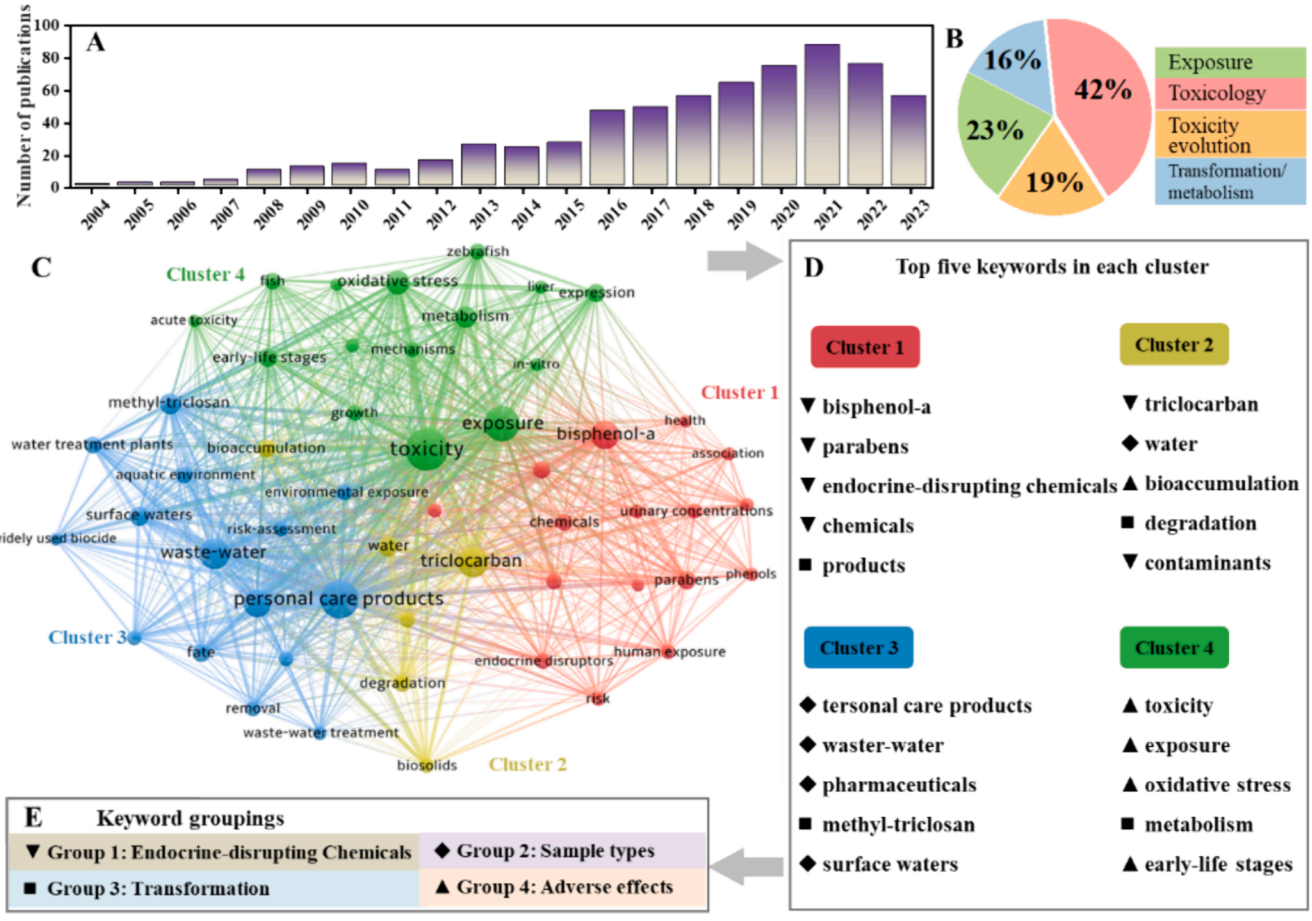

Fig. 1. (A) The number of published papers per year from 2004 to 2023. (B) The percentage of papers by category. (C) Network analysis of keywords from retrieved papers. (D) Top five keywords in the four clusters. (E) Keyword groupings (represented by symbols: ▼◆■▲).

toxicological study of TCS. In contrast, studies regarding the "toxicity evolution" of TCS accounted for only 19 % (Fig. 1**D**), indicating that more attention should be paid to this field in the future.

3. Environmental and human exposure

Humans are mainly exposed to TCS through dermal absorption from TCS-containing personal care products (Ao et al. 2017). Drinking water, food, dust, and the atmosphere can also be sources of human exposure to TCS (Weatherly and Gosse 2017), which are summarized in **Table S1**. The global concentration of TCS in surface water ranges from 1 to 40,000 ng/L (Daret al. 2022). Wastewater treatment plants (WWTPs) are important control measures to prevent TCS from polluting the environment. However, TCS cannot be removed entirely from WWTPs, which are one of the major sources of surface water pollution (Kumar et al. 2010; Montaseri and Forbes 2016). Furthermore, the resulting solid waste from WWTPs could become recurring biosolids; the agricultural availability of these biosolids containing TCS presents a potential risk for human dietary exposure via ingestion of agricultural products (Dhillonet al. 2015). TCS can be further incorporated into crop plants (such as carrots and soybeans) via sewage sludge application (Macherius et al. 2012; Wu et al. 2010). The presence of TCS in indoor air has received limited attention, because TCS with low volatility in the atmosphere is nearly undetectable (Aoet al. 2017; Canosa et al. 2007; Fan et al. 2010; Geens et al. 2009). However, TCS as a relatively lipophilic compound can be absorbed in airborne particulate matter, which has been detected in numerous sites including offices, apartments, day nurseries, and houses (Laborie et al. 2016), and is also present in settled dust from kitchens, bedrooms, and living rooms (Tran et al. 2020). Despite the relatively low human health risk from TCS from these sources, a more comprehensive risk assessment based on the multiple exposure pathways of TCS is needed (Zhang and Lu 2023).

TCS has been found in human urine, breast milk, blood, and nails (Chen et al. 2023; Sandborgh-Englund et al. 2006), including adipose tissue, cord blood, and amniotic fluid from clinical specimens (Goodman et al. 2018). **Table S2** summarizes the concentrations of TCS in various human biological samples. Differences in TCS concentrations may be due to consumer product consumptions, behavioral, and dietary patterns (Kim et al. 2020): lifestyles vary in different regions, especially the usage habits of TCS-containing cosmetics. A global analysis of urine samples found that TCS exposure is significantly higher in high-income regions than in developing regions (Zhang and Lu 2023). However, taking age into account, among Korean adults aged 18–69 years, the urinary TCS concentration was highest in participants aged 60–69 years (2.2×10^3 ng/L) (Kim et al. 2011). In Belgium, the urinary TCS concentration of participants aged 20–39 years (range from $1.86\text{-}598.95 \times 10^3$ ng/L) (Pirard et al. 2012). Regarding gender, females are the major consumers of personal care products, and they are potentially the high-exposure population. In fingernail samples from China, TCS levels were higher in females than in males (Yin et al. 2016). However, in a survey on blood serum TCS concentrations from an Australian population, males had significantly higher concentrations than the females (Allmyr et al. 2008). These conflicting results suggest that population-based reports exploring potential factors influencing TCS exposure should be studied in greater depth, including sex, age, living habits, and socioeconomic status.

Furthermore, pregnant and lactating women with physiological and metabolic changes are special populations closely related to fetal and infant exposure, vital to their development. TCS was first detected in breast milk in Sweden in 2002, and in three out of five samples ranged from $<$ 20 ng/g to 300 ng/g (Adolfsson-Erici et al. 2002). Breast milk from 36 mothers was tested in Stockholm, with TCS concentrations of 0.95 ng/g in the exposed groups compared with 0.35 ng/g in the control group (Allmyr et al. 2006). In California and Texas, TCS concentrations in breast milk from 62 samples ranged from 0 to 2,100 ng/g (Dayan 2007). Notably, exclusively breast-fed infants excreted higher amounts of TCS with infants in whom a mixed diet was introduced, which might be attributed to the transmission of TCS to infants through breastfeeding from exposed mothers (Frederiksen et al. 2022). However, there is a 6,500-fold safety margin between the exposure levels obtained in correlative studies and the maximum TCS concentration, inducing any adverse effects on humans (Dann and Hontela 2011). Therefore, there is no definite evidence that the small amounts of TCS in breast milk pose risks for infants. Notably, the limited studies have reported that the concentration level of TCS in pregnancy urine is associated with decreased birth weight of born babies (Patti et al. 2021). Therefore, given that these susceptible populations might be influenced by adverse effects of TCS exposure, additional studies are needed to elucidate the link between exposure and potential human health outcomes. Moreover, TCS metabolism can influence TCS exposure, triggering a potentially synergistic exposure of TCS and its metabolites in humans. Concerning these potential risks, the toxicity of TCS in the process of metabolic transformation needs to be critically determined.

4. Toxicity in metabolism and environmental transformation

TCS in the environment can be gradually removed by photodegradation and biodegradation (Amigun Taiwoet al. 2022). Several toxic products are formed during the transformation of TCS, such as the formation of dioxin analogs under ultraviolet irradiation and methyl-TCS generated from aerobic digestion. These products can migrate into the environment, where humans could be exposed to them. Additionally, TCS and its products enter the human body through various exposure pathways, including oral mucosa, respiratory tract, digestive tract, and skin (Ashrapet al. 2017). These synergistic processes result in potentially adverse effects on organisms and human health (Cochran et al. 2024; Gao et al. 2021). Therefore, this section summarizes the toxicity evolution of TCS in metabolism and environmental transformations to uncover the potential harm to humans.

4.1. Toxicity in human metabolism

TCS is considered non-persistent in the body and can be quickly absorbed, metabolized, and eliminated (Goodmanet al. 2018). A human pharmacokinetic study found that the plasma concentration of TCS rapidly increased after ingestion of an oral solution containing 4 mg TCS, peaked within 1–3 h, and was excreted within hours (Sandborgh-Englundet al. 2006). Further, an statistical study has shown that the half-life of TCS in plasma is 10–15 h for rats, 8–12 h for mice, and 25–32 h for hamsters, while in humans, the metabolic half-life is 13–16 h for children and 15–29 h for adults (Bagley and Lin 2000; Bedoux et al. 2012; DeSalva et al. 1989; Siddiqui and Buttar 1979). These results suggest the metabolism of TCS in organisms and the metabolic cycle of TCS is species dependent. Although TCS can be gradually eliminated by the human body, it also slightly accumulates in organs through blood circulation (Milanovićet al. 2023).

Evidence from 11 patients showed that TCS could be detected in the liver and adipose during the autopsy, with the highest concentration in the liver (3.14 ng/g) (Geens et al. 2012). The liver is the primary source of TCS metabolism, and these complex processes require the combined action of multiple enzymes, especially the cytochrome P450 enzyme system (CYP450) (Weatherly and Gosse 2017). CYP450 is a large family of heme-oxidized proteins of the monooxygenases, which play a crucial role in various physiological pathways such as synthesis and metabolism (Guengerich 2017). TCS can perform the hydroxylation and cleavage of the ether bond under CYP450 metabolism (Wu et al. 2017), part of phase I metabolism. The main metabolites of TCS, including multiple hydroxylated TCS, 2,4-dichlorophenol, and 4-chlorocatechol (Fang et al. 2010; Fang et al. 2014; Zhu et al. 2018), have been detected in mouse liver, bile, and feces, as well as plasma and urine, hydroxylated TCS was also identified in human feces samples (Zhang et al. 2021b). Notably, chlorophenols are catalogued as one of the priority pollutants according

to the US EPA because of their toxicity and potential carcinogenicity (Ferreiro et al. 2021). Moreover, hydroxylated TCS is recognized as a reactive metabolite (Liu et al. 2020), and its toxicity should be taken seriously (Zhanget al. 2021b). These metabolites can be covalently modified on multiple proteins, including hormone response (ten proteins), immune system process (eight proteins), and inflammatory response (seven proteins), suggesting endocrine and immune systems may be disrupted (Liuet al. 2020).

Furthermore, TCS also can produce TCS-O-TCS through the phase I metabolic CYP450 in perch, quail, mice, and human microsomes. The lipophilic metabolite TCS-O-TCS has been detected in urine samples from the general population (Ashrapet al. 2017). Meanwhile, some new lipophilic ether metabolic analogs, including TCS-O-bisphenol A, TCS-O-benzo(a)pyrene, and TCS-O-estradiol, have been found in mice and humans, formed by the reaction of TCS and other substances (such as phenolic xenobiotics and endogenous metabolites) via CYP450 catalysis (Ashrapet al. 2017; Liu et al. 2022). This mentioned metabolic reaction is a widespread pathway for TCS, inducing possible adverse cross-talk reactions in organisms. The hepatocarcinogenic potential of TCS is related to the activation of the constitutive androstane receptor (CAR) (Yueh et al. 2014). Alarmingly, these above-mentioned lipophilic ether metabolites may exhibit higher biological activity than the parent compounds. The CAR activity of TCS-O-TCS is about 7.2 times higher than that of TCS (Ashrapet al. 2017), potentially interfering with the metabolism of other carcinogens (such as diethylnitrosamine) and increasing the susceptibility to tumorigenesis (Yuehet al. 2014). These lipophilic ether metabolites can also affect metabolic toxicity, significantly reducing the levels of endogenous vitamin E and disturbing endocrine homeostasis (Liuet al. 2022). Furthermore, the increase of reactive oxygen species (ROS) levels during TCS metabolism can exacerbate the downregulation of endogenous antioxidants and lipid peroxidation, posing considerable risks to human health (Peng et al. 2019).

TCS and hydroxylated TCS can undergo phase II metabolism via glucuronidation and sulfonation (Zhanget al. 2021b). These metabolites have been widely detected in human HepG2 cells (Wuet al. 2017), liver microsomes or cytosol (Wang et al. 2004), urine (Provencher et al. 2014), serum (Zhanget al. 2021b), and skin (Fanget al. 2014). In human liver, TCS-glucuronide was the main metabolite at 20 μM exposure dose, while exposure to dose below 1 μM led to sulfonation, generating TCS-sulfate (Penget al. 2019). Therefore, human exposure to TCS might interfere with major metabolic pathways. Compared with the human liver, human skin has a low ability to metabolize TCS: in 24 h, the skin metabolized approximately 3 % of TCS exposure dose, and TCS-sulfate was the only metabolite in the skin up to 8 h after application (Fanget al. 2014). However, TCS-glucuronide is excreted faster from HepG2 cells than TCS-sulfate (Zhanget al. 2019), and the metabolites of TCS-glucuronide and TCS-sulfate have more polarity, thus enhancing their water solubility, and therefore excretion (Weatherly and Gosse 2017). However, one concern about these metabolites is the potential regeneration from circulating the conjugates to TCS and hydroxylated TCS, due to deconjugation enzymes (Ginsberg and Rice Deborah 2009). Another concern is that intestinal flora affects the conversion of these metabolites into free TCS (Zhang et al. 2022). Potential reabsorption of TCS and hydroxylated TCS would occur by the liver, in a process known as "enterohepatic circulation," delaying the elimination of toxicants from the body (Claus et al. 2016).

Overall, TCS undergoes metabolize during phase I and II metabolism and forms more polar metabolites. The metabolic mechanism of TCS is summarized in Fig. 2. The toxicological effects of metabolites generated from phase I metabolism are greater than those from phase II metabolism. Notably, the disruption of endogenous metabolite homeostasis by CYP450 catalysis should be studied in the future as it implies a disorder of the metabolic system, posing a potential risk to human health.

4.2. Toxicity in environmental transformation

In the environment, TCS can be converted into various degradation products via biotransformation, photolysis, oxidation, and chlorination, as summarized in Fig. 3. During photodegradation of TCS in aquatic environments, one of the main products from TCS cyclization is 2,8-dichlorodibenzo-P-dioxin (2,8-DCDD) (Gao et al. 2014; Mezcua et al. 2004; Sanchez-Prado et al. 2006). Significantly, in excessive active chlorine (such as disinfection and seawater environments), TCS can be transformed into more dioxin congeners via cyclization after TCS chlorination, including 1,2,8-TCDD, 2,3,7-TCDD, 1,2,3,8-TCDD, and 2,3,7,8-TCDD (Buth et al. 2009; Wu et al. 2019). Ultraviolet light can also promote the formation of these dioxin congeners (Wuet al. 2019). Once dioxin congeners in the environment enter the body, they are stored due to their chemical stability and last a long time (Buth et al. 2010). Dioxin is a potent multisite carcinogen (Zhenget al. 2008), with chronic exposure causing several types of cancer in animals (Berg 2006). Exposure to dioxin congeners causes severe damage to human beings and animals,

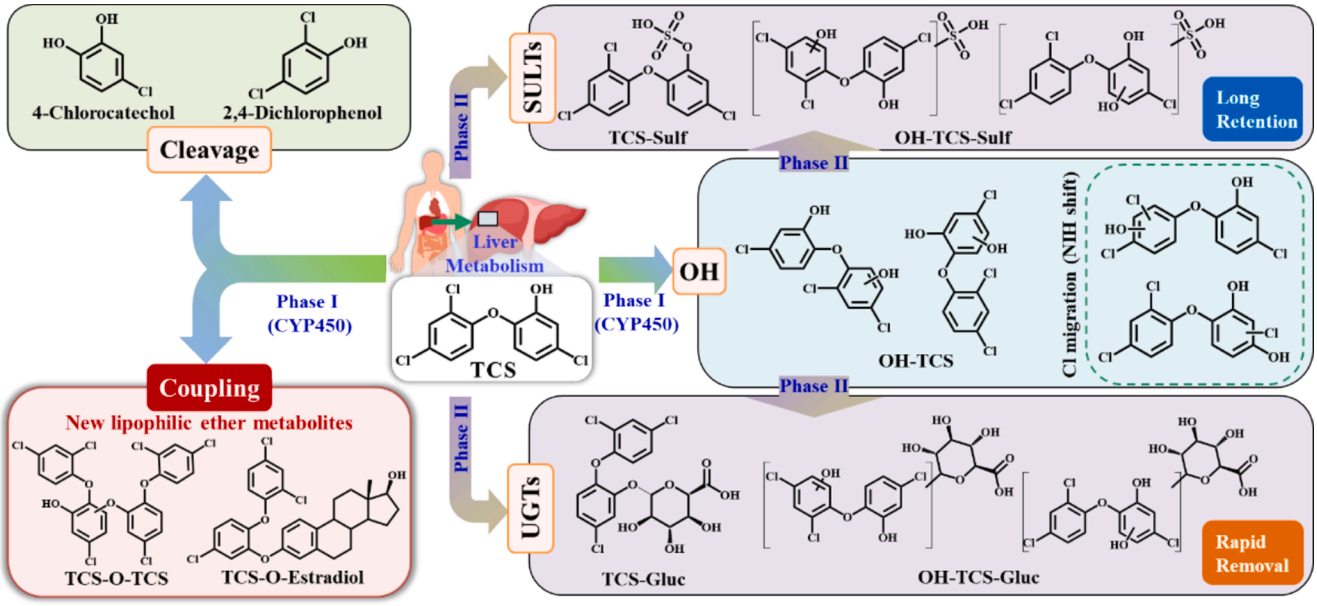

Fig. 2. Metabolic mechanism of triclosan.

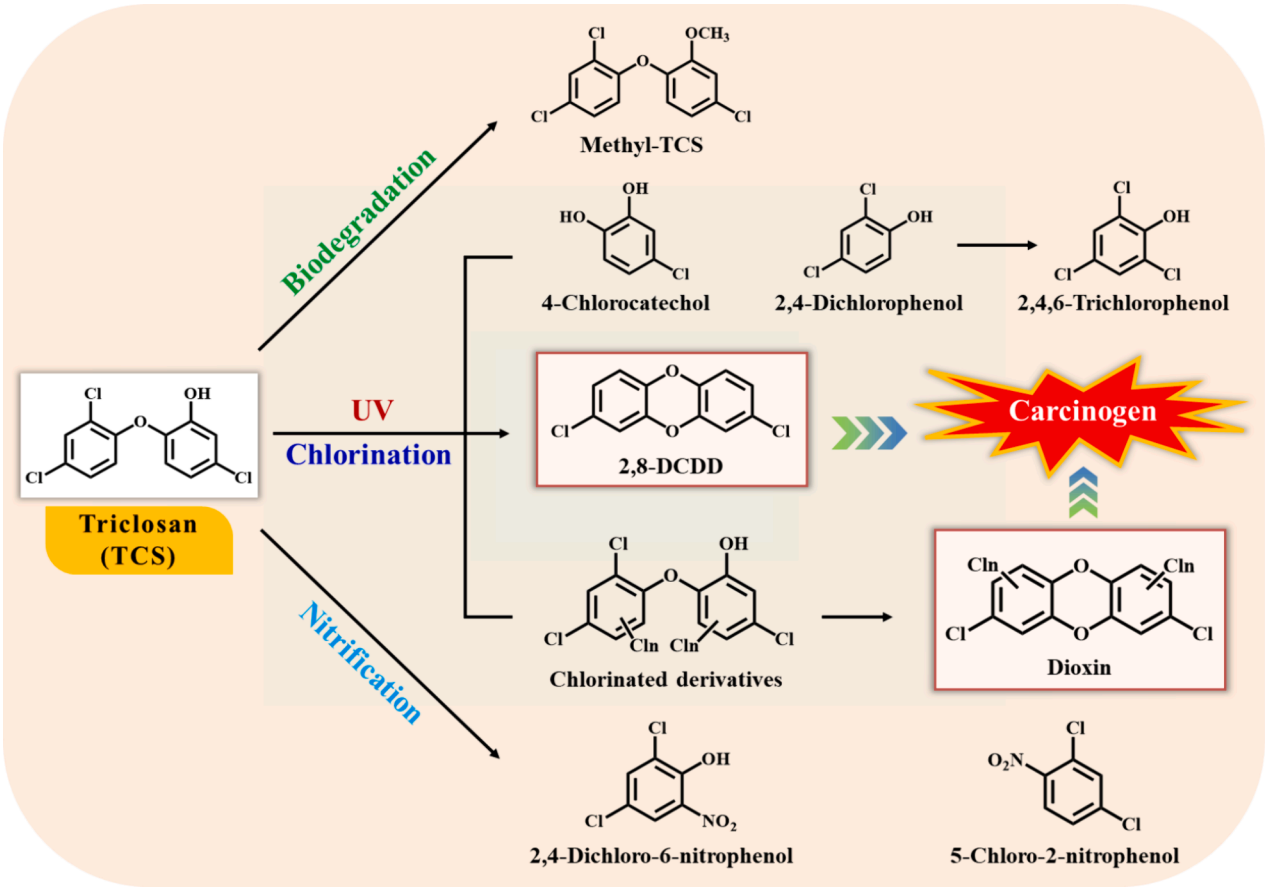

Fig. 3. Environmental transformation products of triclosan.

inducing disruption of the nervous, immune, reproductive, and endocrine systems (Marinković et al. 2010; Neel and Sargis 2011).

Furthermore, under conditions of sunlight or chlorination, TCS can also transform to produce toxic substances, such as 2,4-dichlorophenol and 2,4,6-trichlorophenol (Solá-Gutiérrez et al. 2020). 2,4-dichlorophenol is formed from the cleavage of the ether link in TCS and then undergoes chlorination of the phenolic ring to form 2,4,6-trichlorophenol (Iovino et al. 2019). Both are known endocrine disruptors that potentially cause cancer, congenital disabilities, and developmental diseases, and have been flagged as priority pollutants in the USA (Dann and Hontela 2011). TCS also reacts with free chlorine to produce chloroform, which might happen in the processes in household dish soap usage (Tsai et al. 2008). Chloroform has been linked to liver and kidney toxicity and mild teratogenicity (Fiss et al. 2007). It is worth noting that the chlorinated derivatives of TCS are significantly more toxic than TCS itself, and these chlorinated derivatives are often precursors of dioxins (Fig. 3) (Buthet al. 2009; Wuet al. 2019).

In wastewater treatment, up to 60 % of TCS is bio-transformed, and approximately 7.4 % of TCS is converted to methyl-TCS by aerobic digestion (Chen et al. 2011; Tohidi and Cai 2017). Methyl-TCS can reduce growth inhibition of microorganisms and avoid the formation of UV-driven dioxins (Farré et al. 2008). However, methyl-TCS is more persistent than TCS in the environment (Lozano et al. 2013). For example, the half-life of methyl-TCS (104 d) in soil is four times that of TCS (443 d) (Lozano et al. 2012). Methyl-TCS is more hydrophobic; therefore, it can accumulate more easily in organisms (Balmer et al. 2004; Coogan et al. 2007). Several studies have reported that methyl-TCS has potential ecological toxicity, including inducing cytotoxicity in hemocytes (the immune cells of mollusks) (Gaume et al. 2012) and impacting the embryonic development of zebrafish (*Danio rerio*) and sea urchin (Paracentrotus lividus) (Macedo et al. 2017). Considering the limited ecotoxicological data on methyl-TCS, more detailed assessments are warranted.

In the atmosphere, previous field monitoring has indicated that the photochemical conversion of TCS could result in the formation of gaseous polychlorinated dibenzodioxin and polychlorinated dibenzofuran, such as 2,7/2,8-DCDD (Friedman et al. 2012). Moreover, photonitrification will produce nitro compounds and other photo-toxic substances. In brief, TCS in the atmosphere can react with HONO, leading to the formation of 2,4-dichlorophenol, which can be further oxidized by nitrous acid to generate 2,4-dichloro-6-nitrophenol and 5-chloro-2-nitrophenol (Ma et al. 2017). These products are photo-toxic and harmful to organisms and humans in the rain and atmosphere (Maet al. 2017). Evidence has proven that 2,4-dichloro-6-nitrophenol is an endocrine-disrupting chemical, resulting in developmental toxicity of aquatic organisms, such as Chinese rare minnow embryos (Chen et al. 2017). Furthermore, 2,4-dichloro-6-nitrophenol can also induce hypertrophy of hepatocytes, inhibit of spermatogenesis, and the degeneration of oocytes (Chen et al. 2016).

These environmental transformation products of TCS may have higher degradation resistance and toxicity than their parent compound. The transformation products may pose a greater health risk to humans, which deserves more attention in future research.

5. Adverse health effects involved from TCS exposure

Numerous studies have proven the toxicity of TCS in many organisms, both in vivo and in vitro, using animal and cell models (Kumar et al. 2021; Rehmanet al. 2021). These toxicological mechanism studies provide data support for epidemiology. Notably, although these toxicological conclusions are described around TCS, the results presented here suggest that there may be combined adverse effects of TCS and its

metabolites. Therefore, based on epidemiological and toxicological studies, the following section briefly summarizes the adverse health effects and potential diseases involved of TCS. Fig. 4 illustrates the adverse health effects currently documented by TCS.

TCS is an endocrine-disrupting chemical with multiple interference mechanisms, including disrupting hormone metabolism, displacing hormones from hormone receptors, and disrupting steroidogenic enzyme activity (Wang and Tian 2015). Moreover, reproductive disruption is considered one of the most critical potential effects of TCS (Milanovićet al. 2023). TCS exhibits antagonistic effects on sex hormones, thyroid hormones, and glucocorticoids (Kenda et al. 2020; Kolšek et al. 2015; Paul et al. 2010), while an agonist effect of TCS is also observed on sex hormones (Huang et al. 2014). In luciferase reporter gene assays in cells, TCS promotes the estrogen response and suppress the androgen response, suggesting that the estrogenic/ androgenic effects of TCS may be mediated via the signaling pathways involving estrogen/androgen receptors (Chen et al. 2007; Kolšeket al. 2015; Rodríguez and Sanchez 2010). Furthermore, TCS also can compete with the thyroid hormone thyroxine for binding to transthyretin (Hamers et al. 2020). However, epidemiological studies have not shown proof-positive evidence that TCS can affect the thyroid hormone system in humans (Berger et al. 2018; Derakhshan et al. 2019; Guo et al. 2020a). Although some studies have found a negative correlation between TCS and thyroxine, the evidence for a positive correlation with stimulating thyroid hormone is still limited (Braun et al. 2018). The reduction mechanism of thyroxine may be due to the up-regulation of metabolism-related enzymes induced by TCS metabolism, including CYP450, glucosyltransferase, and sulfotransferase (Paul et al. 2012; Paulet al. 2010; Zorrilla et al. 2009).

Studies have shown that interference with thyroid hormones, estrogen signaling, androgen activity, and the hypothalamic-pituitary axis may further induce adverse human health outcomes, related to birth, reproduction, and puberty in girls (Goodmanet al. 2018; Krause et al. 2012). Epidemiological studies have shown that TCS exhibits a small inverse association with pubic hair stage, indicating a potential relationship between TCS exposure and pubertal development in girls (Wolff Mary et al. 2010). Significantly, increased levels of TCS were found in children with a low development quotient and the mothers of fetuses with malformations (Guo et al. 2020b; Wei et al. 2017). Gestational TCS exposure is also negatively associated with infant birth weight (Aker et al. 2019; Etzel et al. 2017; Huo et al. 2018; Pattiet al. 2021); however, prenatal TCS exposure may not affect early-childhood growth (Wu et al. 2018). Adverse associations between gestational TCS exposure and placental steroidogenic enzyme concentration levels have also been found, inducing more vulnerable reproductive development of the male fetus (Wang et al. 2018). These results may explain the shortened anogenital distance in a Danish 3-month-old boy with prenatal exposure to TCS (Lassen et al. 2016).

In addition to their impact on hormones, TCS adversely affects immune and inflammation functions in humans (Rees Clayton Erin et al. 2011). For example, TCS can mediate the downregulation of pro-inflammatory factors at the cellular level, such as prostaglandin E2, cyclooxygenase, interleukin, and leukotrienes (Rehmanet al. 2021). TCS can also increase the intracellular Ca^{2+} concentration and induce lymphocyte membrane hyperpolarization. Since changing the membrane potential of lymphocytes affects cellular immune function, TCS may adversely affect the human immune system (Kawanai 2011). Several epidemiological studies have suggested that TCS exposure may increase the risk of specific asthma and allergen sensitization (Rees Clayton Erinet al. 2011; Spanier et al. 2014), which might be due to a cellular imbalance caused by a disturbance in the body's microbes (Okada et al. 2010). However, some reports did not find a relationship between TCS and total immunoglobulin E (IgE) levels (Savage et al. 2012). Therefore, there is still a lack of consistent evidence on the effect of TCS on the incidence of immune diseases, such as allergies and asthma.

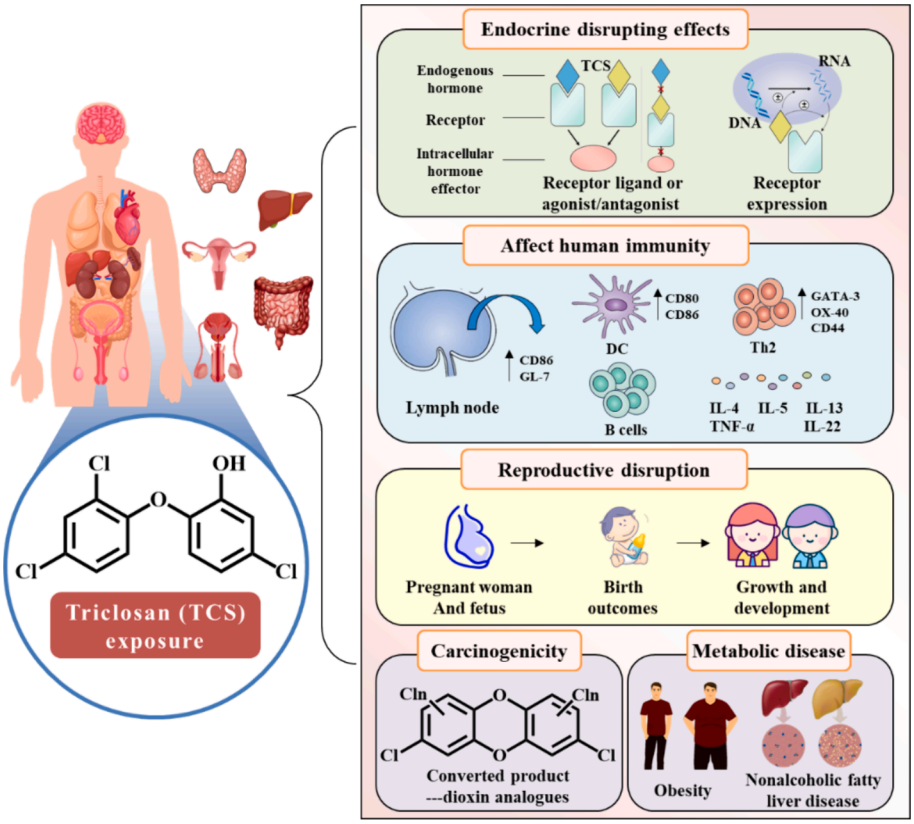

Fig. 4. Adverse health effects of triclosan, including endocrine disrupting effects, human immunity, reproductive disruption, carcinogenicity, and metabolic disease.

TCS has also been associated with cancer development. In earlier studies, TCS has been shown to induce hypertrophy and vacuolation of rodents hepatocytes mediated through the peroxisome proliferation activating receptor α (PPARα) (Rodricksetal. 2010). Further long-term exposure experiment studies reported that TCS could stimulate hepatocyte proliferation and the fibrotic response, accompanied by oxidative stress. Importantly, TCS, as a liver tumor promoter, significantly accelerates the development of hepatocellular carcinoma (Yuehet al. 2014). TCS also induces liver-free fatty acid synthesis by up-regulating fatty acid intake and fat. These changes in lipid homeostasis may lead to membrane instability, lipid accumulation, oxidative stress, and inflammation. TCS exposure may induce liver lipid metabolism disorders, further aggravating the liver damaging effect of TCS (Huang et al. 2020). Another study reported that TCS could increase basal calcium levels in human prostate cancer stromal cells through direct activation of membrane ion channels, which would induce the release of vascular endothelial growth factor and significantly impact prostate carcinogenesis (Derouiche et al. 2017).

TCS exposure can also cause other problems, such as oxidative stress, obesity, and osteoporosis (Binelli et al. 2009; Cai et al. 2019; Li et al. 2015). The effects of TCS on oxidative stress have been reviewed previously (Rehmanet al. 2021). Epidemiological studies on the relationship between TCS and obesity/ osteoporosis may represent isolated findings, lacking the consistency of similar studies. In summary, increasing evidence indicates that TCS exposure may have adverse effects on human health. This review focuses on endocrine disruption, adverse effects on human immune and inflammation functions, and carcinogenicity. These results also remind us to pay more attention to the safety and human impacts of TCS.

6. TCS exposure: Misgivings in the post-pandemic era

Since the COVID-19 pandemic outbreak, TCS-containing disinfecting cleaning products have been increasingly consumed. In UK alone, the sales of hand soaps surged by 102 % (Chirani et al. 2021) while the proportion of consumers using hand sanitizers rose to 89.9 % in South Korea (Choi et al. 2021). In people using TCS-containing gel sanitizers, the TCS intake through hand-to-mouth exposure is twice as high as before the COVID-19 pandemic (Wanget al. 2022). However, this does not apply to countries or regions that have prohibited TCS added to certain types of soaps. Environmental and human exposure levels of TCS have already shown a significant downtrend in the USA (Adhikari et al. 2022; Han et al. 2016; Kim et al. 2021). Surprisingly, despite 21.3 % of hand sanitizers in China containing TCS, a significantly higher percentage compared to countries such as India, Brazil, Nigeria, the UK, and the USA, and the Arab Emirates (Wanget al. 2022), the internal exposure level to TCS in southern China has increased following the pandemic. For instance, in 2021, the mean concentration of TCS in adult urine was reported to be 14.2 ng/mL (Tian et al. 2023), which is significantly higher compared to the pre-pandemic concentration of 1.87 ng/mL in the same region (Zhang et al. 2021a). Unfortunately, there are no more experimental data and evidence to prove and explain the above trend, that is, that human exposure to TCS has decreased overall. We speculate that these phenomena may be due to increased consumer self-awareness of the adverse effects of TCS. However, continuous human exposure to TCS in the post-pandemic era, health hazards remain unknown due to the metabolism and environmental transformation of TCS.

TCS in healthcare products has not been prohibited in countries other than the USA and the European Union (Daret al. 2022). In Canada, continuous annual detection from 2012 to 2018 of surface water has found a general increase in TCS concentration (Lalonde et al. 2019). Consequently, the sustained consumption of TCS in non-controlled regions could lead to the increased TCS in the environment. Alarmingly, TCS can promote the development of antibiotic resistance, threatening public health (Lu et al. 2018), even at trace TCS concentrations (Martin et al. 2020). TCS-induced bacteria extend their resistance to antibiotics by acquiring antibiotic-resistance genes via horizontal gene transfer (Lu et al. 2020). These conjunction transfers mediated by TCS are primarily related to excessive oxidative stress and increased membrane permeability (Luet al. 2022). The relative abundance of antibiotic-resistance genes [*erm*(X), a 23S rRNA methyltransferase implicated in resistance to several antibiotics] in house dust is linked to the TCS concentration (Hartmann et al. 2016). TCS can even mediate the conjunction transfer of the RP4 plasmid to opportunistic human pathogens (*Legionella spp*, a common cause of severe pneumonia in community settings) (Fields et al. 2002), potentially resulting in serious public health risks (Luet al. 2022). However, after TCS exposure ceased, the antibiotic tolerance of the adapted cells declined over time, revealing that reduced TCS release may mitigate the propagation of antibiotic resistance (Li et al. 2019). Nonetheless, the threshold concentration of TCS, the sensitive microbial populations, an evaluation of the degree of horizontal gene transfer, and the breakthrough time point for triggering pathogenic evolution remain unclear. Especially, TCS transformation can occur in environmental microbial consortia (Yin et al. 2022), even in intestinal microbiota (Zhang et al. 2023). highlighting the importance of risk assessment for the spread of antimicrobial resistance in microbiota during TCS transformation.

7. Conclusions and future perspectives

The vast global presence of TCS in the environment and in humans suggests a large-scale and potentially global contamination trend. Especially in the context of pandemic viruses and pathogenic bacteria, human exposure to TCS could increase rapidly. There are currently limited toxicological assessments of TCS during environmental transformation and human metabolism. Existing studies have observed that the human body can rapidly metabolize TCS, and the metabolic process might cause adverse health effects. Environmental transformations aimed at detoxification also lead to the formation of carcinogenic dioxins. Accordingly, despite accruing epidemiological studies on TCS, the adverse effects on human health during environmental transformation and human metabolism of TCS remain unclear. The following suggestions are necessary for future research:

1) **Extensive toxicological studies and assessment of toxicity evolution.** Existing studies have reported that TCS has multiple toxic effects. However, the evolution of these toxic effects in various transformation pathways remains largely unknown. Particularly the human metabolism of TCS may trigger a chain reaction of signaling pathways. Therefore, it is urgent to conduct extensive and effective research on the human health impacts of TCS metabolism.
2) **Identification and quantification of toxic transformation products.** It is very important to identify the toxic transformation products of TCS and individually assess the toxicity of these products. Furthermore, considering the toxic effects associated with exposure dose, these toxic products of TCS transformation should be monitored quantitatively monitored.
3) **Relationship between toxic mechanisms and potential adverse health outcomes.** Existing adverse effects of TCS in humans mainly focus on two aspects: the toxicological mechanisms and epidemiology. Although several studies on the mechanisms of TCS toxicity have guided the adverse health outcomes in humans, the available information is still limited, which is crucial for the adequate protection of human health. Namely, further investigations into the relationship between toxic mechanisms and potential adverse health outcomes are urgently needed.
4) **Synergistic effect between microbial metabolism and development of antibiotic resistance to TCS.** Reversible antibiotic resistance to TCS and its resistance mechanisms have been revealed. Considering TCS transformation in microbes, the synergistic effect between microbial metabolism and the development of antibiotic

resistance for TCS should be determined for public health assessments of TCS.

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CRediT authorship contribution statement

Na Luo: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Jia Chen:** Writing – original draft, Investigation, Formal analysis, Data curation. **Xiaoyi Chen:** Investigation, Formal analysis. **Mei Wang:** Investigation, Formal analysis. **Xiaolin Niu:** Investigation, Formal analysis. **Guanhui Chen:** Investigation, Formal analysis. **Chuyue Deng:** Investigation, Formal analysis. **Yanpeng Gao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Guiying Li:** Supervision, Conceptualization. **Taicheng An:** Supervision, Conceptualization.

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

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108927.

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