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Review

Reproductive endocrine-disrupting effects of triclosan: Population exposure, present evidence and potential mechanisms

Cai-Feng Wang [a, b], Ying Tian [a, c, *]

[a] Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University, Shanghai, China
[b] School of Nursing, Shanghai Jiao Tong University, Shanghai, China
[c] MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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ABSTRACT

Triclosan has been used as a broad-spectrum antibacterial agent for over 40 years worldwide. Increasing reports indicate frequent detection and broad exposure to triclosan in the natural environment and the human body. Current laboratory studies in various species provide strong evidence for its disrupting effects on the endocrine system, especially reproductive hormones. Multiple modes of action have been suggested, including disrupting hormone metabolism, displacing hormones from hormone receptors and disrupting steroidogenic enzyme activity. Although epidemiological studies on its effects in humans are mostly negative but conflicting, which is typical of much of the early evidence on the toxicity of EDCs, overall, the evidence suggests that triclosan is an EDC. This article reviews human exposure to triclosan, describes the current evidence regarding its reproductive endocrine-disrupting effects, and discusses potential mechanisms to provide insights for further study on its endocrine-disrupting effects in humans.

Triclosan (5-chloro-[2,4-dichlorophenoxy] phenol, TCS) is a synthetic, lipid-soluble, broad spectrum antibacterial agent that is commonly added to a variety of personal care and industrial products, including hand soap, shampoo, toothpaste, and textile goods (Daughton and Ternes, 1991). Due to its widespread use over the past 40 years, TCS has become a new source of prevalent anthropogenic contaminants in the aquatic environment worldwide (Kolpin et al., 2002; Lishman et al., 2006; Sabaliunas et al., 2003; Ying and Kookana, 2007; Nakada et al., 2006).

TCS has long been regarded as a well-tolerated and safe antimicrobial. The human body is exposed to TCS daily through direct contact with personal care and household products as well as exposure to the whole ecosystem including the water, soil and other organisms. Continuous exposure to TCS has led to frequent detection of the antimicrobial in human milk (Adolfsson–Erici et al., 2002; Dayan et al., 2007), plasma (Hovander et al., 2002; Allmyr et al., 2006) and urine (Calafat et al., 2008; Li et al., 2013).

Limited laboratory evidence from aquatic species and rodent models has demonstrated the potential for TCS to act as an endocrine-disrupting chemical (EDC), and reproductive disruption has been regarded as one of the most important potential effects. Similar to much of the early evidence on the toxicity of EDCs (WHO-UNEP, 2012), limited epidemiological studies on the effects of TCS in humans are mostly negative but conflicting. Therefore, it is unknown whether daily exposure to TCS disrupts the human endocrine system. This article reviews human exposure to TCS, summarizes the current evidence regarding its reproductive endocrine-disrupting effects and discusses its potential mechanisms to provide insight for future studies on TCS's endocrine-disrupting effects in humans.

1. Human exposure to TCS

Ingestion and dermal absorption are the key routes of human

Abbreviations: TCS, triclosan; EDCs, endocrine-disrupting chemicals; PCPs, personal care products; NOAEL, no observed adverse effect level; NHANES, national health and nutrition examination survey; PCBs, polychlorinated biphenyls; PBDEs, polybrominated diphenyl ethers; BPA, bisphenol A; Vtg, vitellogenin; AR, androgen receptor; LH, luteinizing hormone; FSH, follicle stimulating hormone; PPS, preputial separation; EE, ethinyl estradiol; ER, estrogen receptor; ERE, estrogen response element; DHT, dihydrotestosterone; P450scc, cytochrome P450 side-chain cleavage; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase; StAR, steroidogenic acute regulatory protein; rhCG, recombinant human chorionic gonadotropin.

* Corresponding author. Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University, No. 280 South Chong Qing Road, Shanghai, 200025, China.
E-mail addresses: fliwing2005@126.com (C.-F. Wang), tianmiejp@sjtu.edu.cn (Y. Tian).

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absorption of TCS (Moss et al., 2000; Sandborgh-Englund et al., 2006). TCS is relatively hydrophobic (i.e., Log K_{ow} = 4.76) and has been shown to have an insignificant accumulation potential. It is rapidly excreted primarily as conjugated metabolites in urine (Queckenberg et al., 2010). TCS has been detected in various biological samples, including human milk, blood and urine, among which urinary detection has been frequently used in human exposure assessment.

1.1. Exposure levels in human milk and plasma

The first report on TCS exposure came from the detection in human milk. Adolfsson–Erici tested five randomly selected human milk samples in Sweden. Three samples were found of high levels of TCS (LOD = 20 μg/kg lipid weight), with the highest at 300 μg/kg lipid weight (Adolfsson–Erici et al., 2002). The presence of TCS in human milk raised concerns regarding the safety of newborns and infants as well as the potential for reproductive toxicity.

Based on this finding, Allmyr compared the TCS levels in plasma and in human milk among 36 Swedish nursing mothers (Allmyr et al., 2006). The concentration in plasma (0.010–38 ng/g) was significantly higher than but well correlated with that in milk (<0.018–0.95 ng/g). Moreover, women using TCS-containing personal care products (PCPs) were found to have higher concentrations of TCS in both plasma and milk, indicating that PCPs were one of the main sources of TCS in women. Dayan detected TCS from 62 random samples of human milk from California and Texas (Dayan, 2007) and conducted a risk assessment by comparing the estimated exposure of neonates via human milk with the estimated NOAEL (no observed adverse effect level) based on toxicity tests. As a result, the NOAEL (50 mg/kg/d) was far higher (i.e. 6760-fold) than the calculated exposure level in human milk (7.4 μg/kg/d). Therefore, the minute amount of TCS in human milk was not likely to affect the health of babies.

Evidence from human milk stimulated the research interest in plasma and serum. However, due to limitations regarding the accessibility of blood samples, most studies used relatively small sample sizes. Sandborgh-Englund detected TCS in plasma from 10 healthy volunteers in Sweden and found a wide range of concentrations (0.1–8.1 μg/L) (Sandborgh-Englund et al., 2006). Allmyr detected TCS in serum from a pooled sample in Australia and compared the concentrations among people who lived in different regions and were of different ages and both genders. The concentration of TCS was higher in males (4.1–19 ng/g) than in females (6.2–14 ng/g). Among all the age groups (from 0 to over 60 years old), the group of 31- to 45-year-olds had the highest concentration (19 ng/g in males and 7.5–11 ng/g in females) (Allmyr et al., 2008).

1.2. Exposure levels in urine

Compared with blood and human milk, urine is much more accessible and available, which makes it possible to collect larger samples from both general population and special groups (such as children and pregnant women). Epidemiological studies have been increasingly focusing on exposure to TCS. For example, the U.S. National Health and Nutrition Examination Survey (NHANES) has provided the largest database on TCS exposure in the general population from all age groups (U.S. CDC, 2013). The survey included a collection of 10,418 urine samples from 2003 to 2010, which reported the geometric mean of urinary TCS concentrations ranged from 13.0 μg/L to 18.5 μg/L. The survey also compared TCS concentrations among different age groups, genders and race/ethnicity groups. Overall, people over 20 years old (13.6–19.3 μg/L), males (14.8–21.3 μg/L) and Mexican Americans (14.6–26.7 μg/L) had higher TCS concentrations than those of younger age (8.16–18.8 μg/L), females (10.6–16.2 μg/L) and Non-Hispanic blacks and Non-Hispanic whites (12.9–17.5 μg/L) (U.S. CDC, 2013).

Studies from other countries, despite having smaller samples, have also contributed greatly to the global assessment of TCS exposure. Table 1 summarizes the evidence of TCS exposure in general population from various countries. Apparently, urinary TCS levels in the U.S. population were much higher than those in other countries, which may be mainly due to differences in exposure sources (e.g., PCPs) and the usage habits associated with such products. Liao conducted a survey of TCS in PCPs from China and the U.S. and estimated daily dermal absorption of TCS for adult women from the two countries (Liao and Kannan, 2014). Among U.S. women, four times as much exposure to TCS was associated with PCPs, compared to Chinese women. Body lotions, face creams and liquid foundations accounted for the majority of the total dermal exposure.

Various studies have specifically focused on TCS exposure among particular populations, such as children and pregnant women, because they are much more vulnerable to EDCs. Table 2 and Table 3 summarize the currently available evidence on the topic. Table 2 indicates that urinary TCS levels tend not to be distinct among children of various age groups, but there was an apparent gap between children from various countries. Children from the U.S. had much higher urinary TCS levels than children from other countries.

Table 3 lists evidence regarding pregnant women. Mortensen compared TCS and other phenol levels from pregnant women (National Children's Study, n = 506) and nonfertile women in the same age range (30–44 years old) (NHANES, n = 524) (Mortensen et al., 2014). Urine specimens from the two studies, collected during the same time period (i.e., 2009–2010), were quite similar to each other, indicating that exposure to phenols, including TCS, occurred regardless of pregnancy status. Additionally, as listed in Table 3, urinary TCS in pregnant women exhibited dramatic variation among countries and slight variation within a country, which again suggests a significant impact of living habits and life style on TCS exposure.

1.3. Summary

Overall, TCS has been widely detected in various human samples, mainly in urine, blood and human milk, from all age groups and races. In particular, researchers have made efforts to assess TCS exposure among potentially vulnerable populations, such as infants, children, and pregnant women, which also indicated wide and persistent exposure. As TCS is ubiquitous and has been suspected of being an EDC (WHO-UNEP, 2012), it is very likely to be harmful to humans, which urges further studies on its adverse effects on human, especially on vulnerable populations.

2. Evidence of reproductive endocrine-disrupting effects and its potential mechanisms

Potential endocrine-disrupting effects of TCS were suspected based on its molecular structure. TCS contains two phenol functional groups, indicating its potential to act as an endocrine-disrupting agent. Additionally, the structure of TCS closely resembles anthropogenic estrogens as well as estrogenic and androgenic EDCs (e.g., polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), bisphenol A(BPA), and dioxins) (Jacobs et al., 2005; Veldhoen et al., 2006; Allmyr et al., 2008). This suggests that TCS may also disrupt the reproductive endocrine system. Studies in aquatic species and mammals also found that TCS influences reproductive endocrine function. The report, State of the science of endocrine-disrupting chemicals-2012