

ADDENDUM



Triclosan, a common antimicrobial ingredient, on gut microbiota and gut health

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ABSTRACT

Triclosan (TCS) is an antimicrobial compound incorporated into more than 2,000 consumer products. This compound is frequently detected in the human body and causes ubiquitous contamination in the environment, raising concerns about its impact on human health and environmental pollution. Our recent research showed that exposure to TCS exaggerates colonic inflammation and exacerbates development of colitis-associated colon tumorigenesis, via gut microbiome-dependent mechanisms. In this review, we discussed recent research about TCS, as well as other consumer antimicrobials, on the gut microbiome and gut health.

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Triclosan (TCS) is an antimicrobial compound incorporated into more than 2,000 consumer products, such as toothpaste, mouthwash, clothes, kitchenware, and toys.^{1,2} This compound is frequently detected in the human body: the National Health and Nutrition Examination Survey showed that TCS was detected in ~ 75% of the urine samples of individuals tested in the United States.³ Also, TCS causes ubiquitous contamination in the environment and is listed among the top-ten pollutants found in the rivers of the United States.¹ Previous studies have shown that exposure to TCS could cause some adverse effects, such as endocrine disruption, antibiotic resistance, liver fibrosis, and liver tumorigenesis.⁴ Our recent study showed that exposure to low-dose TCS exaggerates colonic inflammation and exacerbates the development of colitis-associated colon tumorigenesis in mouse models, suggesting that TCS could have adverse effects on gut health.⁵ Exposure to TCS alters the gut microbiome and fails to induce colonic inflammation in mice lacking a gut microbiome (germ-free mice) or mice lacking Toll-like receptor 4 (*Tlr4*^{-/-} mice), a critical regulator of host-microbiome interactions, supporting that the gut microbiome contributes to the pro-inflammatory effect of TCS.⁵ Because TCS is so

widely used in our daily lives, the research from us and other investigators supports that it is of critical importance to further evaluate its impact on gut health, in order to provide science-based regulatory policies. In this essay, we will discuss the importance of studying the effects of TCS, as well as other consumer antimicrobials, on the gut microbiome and gut health.

Effects of TCS exposure on the gut microbiome

Our study showed that a 3-week treatment of TCS via diet reduced the diversity and altered the composition of the gut microbiome in C57BL/6 mice, demonstrating that TCS can disrupt the gut microbiome.⁵ This finding is largely in agreement with previous studies which showed that TCS exposure disturbs gut microbiota in various animal model systems, including fathead minnows,⁶ zebrafish,⁷ rats,⁸ and mice.⁹ Notably, previous studies demonstrated that TCS had an extremely potent effect to disturb the gut microbiome. Treatment with TCS, at environmentally relevant concentrations (0.1–1 ppb, equivalent to ~ 0.35–3.45 nM), reduced the diversity of the gut microbiome in fathead minnows (*Pimephales promelas*).⁶ Considering that TCS is found to be among the top-ten most abundant pollutants in the rivers of

the United States,¹ this study suggest that TCS could have potential adverse effects on aquatic ecosystems. In addition, to put the concentrations in perspective, previous studies showed that after routine usage of TCS-containing consumer products such as toothpastes, the plasma concentration of TCS can reach ~ 90–1000 nM,^{10,11} which is several magnitudes higher than the concentration used in the fish study.⁶ These results suggest that routine exposure to TCS could also alter the gut microbiome in humans. Indeed, recent human studies support that routine exposure to TCS alters the gut microbiome in humans. Bever et al. reported that the gut microbiomes of infants who received breast milk containing TCS had significantly lower alpha diversity compared with the infants who received breast milk with non-detectable levels of TCS.¹² In addition, the relative abundances of certain bacteria were also modulated in the infants who were fed TCS-containing breast milk.¹² In another human study, Ribado et al. reported that routine usage of TCS-containing toothpaste increased the relative abundance of broadly antibiotic-resistant *Proteobacteria* species in adults, as well as in the infants with high urinal concentrations of TCS.¹³ We need to acknowledge that there are also inconsistent results, which failed to demonstrate that TCS exposure has significant impact on the gut microbiome in humans.¹⁴

Effects of TCS exposure on colonic inflammation and colon tumorigenesis

Our study showed that exposure to 10–80 ppm TCS via diet induced colonic inflammation, exaggerated dextran sodium sulfate (DSS)- or interleukin 10 (IL-10) knockout-induced colitis, and exacerbates the development of azoxymethane (AOM)/DSS-induced colon tumorigenesis in mouse models, suggesting that TCS has potential adverse effects on gut health.⁵ We performed a short-time (several weeks) treatment, therefore it would be worthwhile to look into the possibility of adverse effects on gut health due to long-term exposure to TCS at lower doses. Regarding the mechanisms by which TCS exposure exaggerates colonic inflammation and colon cancer, our study supports that the gut microbiome plays an essential role. Indeed, TCS exposure induces colonic inflammation in conventionally raised

mice, but not in germ-free mice; this result supports that the gut microbiome is required for the pro-inflammatory effects of TCS.⁵ Again, since substantial studies, including our current study, have shown that TCS has potent effects to alter the gut microbiome in model systems.^{6–9} and human subjects,^{12,13} we think that it is of critical importance to reassess the potential adverse effects of TCS on the gut microbiome and gut health, in order to generate science-based regulatory policies.

One critical question is whether the effects observed in our animal experiments could reflect the responses of human exposure. Our dose regime was based on several considerations including the average human exposure levels of TCS from using consumer products. These levels were calculated to be 0.047–0.073 mg/kg/day¹⁵ which is equivalent to ~ 0.56–0.88 mg/kg in mice.¹⁶ This dose range is comparable to the lower dose of 10 ppm TCS in diet, with administration of TCS at a dose of ~ 1 mg/kg/day based on a diet of 3 g daily chow, used in our animal experiment. Also, the No-Observed-Adverse-Effect Level (NOAEL) of TCS was reported to be 25–40 mg/kg/day,¹⁷ which leads to a calculated Acceptable Daily Intake (ADI) of 0.25–0.4 mg/kg/day of TCS.¹⁸ Again, the ADI dose is comparable to the lower dose of 10 ppm in diet used in our study. Finally, a previous human study has shown that after weeks of daily use of TCS-containing toothpaste, the plasma concentrations of TCS were increased from 0.03–2.7 nM to 90–1,000 nM.^{10,11} We found that after mice were exposed to 10–80 ppm TCS via diet for three weeks, the plasma concentration of TCS in the mice was 246 ± 30 nM for 10 ppm and $2,422 \pm 345$ nM for 80 ppm. These concentrations were comparable to those reported in human studies. We acknowledge that there could be differences in metabolism of TCS in humans and mice,¹⁵ but our approach is a direct comparison of the same analytes in the circulation of humans and mice.

Though it is always difficult to translate mouse studies to investigate human health, based on our findings and above considerations, we think the effects observed in our animal experiments support that there is an urgent need to better understand the actions of TCS on gut health, which could lead to significant impact on public health and regulatory policies.

Effects of other antimicrobials on colonic inflammation and colon tumorigenesis

Beyond TCS, other high-volume chemicals are also used as antimicrobial ingredients in many consumer products and less is known about their impacts on human health. Benzalkonium chloride (BAC), benzethonium chloride (BET), and chloroxylenol (PCMX) are antimicrobial ingredients used in many consumer products and are potential candidate compounds to replace TCS. We found that exposure to BAC and BET, but not PCMX, exacerbated DSS-induced colonic inflammation; in addition, exposure to BAC also exaggerated AOM/DSS-induced colitis-associated colon tumorigenesis.¹⁹ These results support that other antimicrobial compounds besides TCS could also have adverse effects on colonic inflammation and colon cancer.

Further work

Our study, using germ-free mouse models, supports that the gut microbiome is required for the pro-inflammatory effects of TCS. However, the functional roles of the microbiome, as well as the specific gut bacteria, involved in the biological actions of TCS are unknown. Elucidation of the specific bacteria involved will help to design human studies to validate the impact of TCS exposure on human health and clarify potential inter-individual variations in metabolism and responses to TCS exposure.

Conclusion

The regulatory policy of TCS, as well as other antimicrobials, is an intensively debated topic now. Our study, as well as the research from other laboratories, support that TCS and other widely-used antimicrobials could have adverse effects on the gut microbiome and gut health. More studies are needed to better characterize the impact of these compounds on gut health in humans.

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