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HEPATOXIC EFFECT OF TRICLOSAN: A COMPREHENSIVE REVIEW

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Abstract

This review explores the toxicity of Triclosan (TCS), a common antibacterial agent with widespread use in various products, including personal hygiene and medical items. The author concentrated on both experimental and non-experimental studies in this review on the toxicity of TCS. While generally deemed safe, evidences indicate that TCS exposure is linked to adverse environmental and health effects, including liver dysfunction, oxidative stress and endocrine disruption. Mechanistically, TCS disrupts cellular processes, compromises mitochondrial function, and alters metabolic pathways, potentially leading to conditions such as non-alcoholic fatty liver disease (NAFLD) and other liver-related disorders.

Key words: Triclosan, General Toxicity, Liver Toxicity, Endocrine disruption, Oxidative stress.

Introduction:

Triclosan (TCS) a widely used antibacterial agent in pharmaceutical and cosmetic products, is generally considered safe and well-tolerated (Priyatha and Chitra, 2018). Chemically known as 5-chloro-[2,4-dichlorophenoxy] phenol, extensively utilized in personal hygiene products, household goods, medical equipment, and clinical settings (Fang *et al.*, 2010). Since its introduction over 40 years ago, its use has steadily increased, with TCS being an active ingredient in over 700 antibacterial products between 1992 and 1999 (Jones *et al.*, 2000; Schweizer, 2001; Russell *et al.*, 2004). It is marketed under names like Irgasan DP300, Aquasept, and Sapoderm and incorporated into fibers and materials such as Ultra-Fresh and Microban (Adolfsson- Erici *et al.*, 2002).

Despite its widespread use, studies have raised concerns regarding its environmental and

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physiological impacts. TCS has been linked to reduced muscular contraction, endocrine disruption, and apoptosis in the rat nervous system, with accumulation primarily in the liver and adipose tissues (Cherednichenkoa *et al.*, 2012; Geens *et al.*, 2012; Wang and Tian, 2015; Park *et al.*, 2016). Prolonged exposure to TCS can lead to oxidative stress, stimulating carcinogenesis and hepatic fibrogenesis (Yueh *et al.*, 2014). In mice, long-term dietary exposure to TCS has been associated with hepatocellular adenomas, carcinomas, and an increased risk of liver cancer (Wang *et al.*, 2017).

As a critical organ for immunity, metabolism, detoxification and infection prevention, liver dysfunction caused by TCS can lead to various disorders, including developmental and immune-related diseases (Wilkins and Pack, 2013). Additionally, exposure to heat and UV light can convert TCS into toxic dichlorodibenzo-p-dioxin (Lores *et al.*, 2005).

Triclosan Effects

Triclosan (TCS) can enter the body through the skin in animals (Moss *et al.*, 2000) and via food and beverages in humans, where it is quickly absorbed and distributed (Sandborgh-Englund *et al.*, 2006). It can penetrate the blood-brain barrier (Van der *et al.*, 2017) and is eliminated as conjugates through urine within three hours of ingestion, processed by xenobiotic-metabolizing enzymes (Sandborgh-Englund *et al.*, 2006; Yao *et al.*, 2018; Li *et al.*, 2019). TCS exposure is linked to enoyl-acyl carrier protein-reductase-related disorders (Bhardwaj *et al.*, 2019).

At the cellular level, TCS disrupts calcium homeostasis by causing mitochondrial uncoupling and plasma membrane depolarization (Popova *et al.*, 2018). It activates Pregnane X receptor (Jacobs *et al.*, 2005). This mediated transcription in liver and intestinal tissues, influencing detoxification and steroid metabolism. TCS also induces mitochondrial ROS, cytosolic Ca^{2+} ion generation and membrane depolarization (Zhang *et al.*, 2017). Oxidative stress triggered by TCS affects apoptosis and cell cycle regulation (Fu *et al.*, 2019; Li *et al.*, 2019). Hormonal disruption from environmental contaminants like TCS, phthalates, and bisphenol A (BPA) is well-documented (Zhang *et al.*, 2018; Bai *et al.*, 2019), with TCS linked to osteoporosis in postmenopausal women (Cai *et al.*, 2019). TCS and similar compounds interfere with iodide uptake, disrupting thyroid hormone homeostasis (Wu *et al.*, 2016).

In animal studies, TCS impaired placental growth and nutrient transport in pregnant mice (Cao *et al.*, 2017), reduced estradiol sulfotransferase activity in fetal sheep (Jackson *et al.*, 2018), and hypermethylated the proopiomelanocortin promoter, potentially leading to obesity in offspring (Hua *et al.*, 2019). However, low TCS doses showed no reproductive system effects in female rats (Montagnini *et al.*, 2018). TCS affects pluripotency markers Oct4, Sox2, and Nanog in zebrafish embryos and embryonic stem cells, hindering development (Chen *et al.*, 2015). Computational studies suggest TCS targets apoptosis-related proteins like B-cell lymphoma-2, apoptosis signal-regulating kinase-1, and human receptor-interacting protein-1 kinase (Bhardwaj *et al.*, 2019).

EFFECT OF TRICLOSAN TOXICITY ON LIVER

Weight Response

Several studies have examined the effects of triclosan on liver function and health across various species. Paul *et al.*, (2010) exposed female Long-Evans rats to triclosan (0–1000 mg/kg/day) for 4 days, resulted in dose-dependent decreases in serum T4 and T3 levels (up to 57% and 25%, respectively) without clinical toxicity, though liver weight and liver-body weight ratio increased in the high dose group. Tang *et al.*, (2018) treated wild-type and PPARα-humanized mice dermally with triclosan (0, 58, or 125 mg/kg/day) for 13 weeks, observing increased liver weight and PPARα target gene expression, alongside skin lesions in some mice. Huang *et al.*, (2020) exposed male mice (C57BL/6) to 10 or 100 mg/kg/day for 13 weeks, noted significant hepatic hypertrophy (51% increase in liver weight) and disrupted lipid metabolism, including elevated ceramides and triglycerides, which contributed to liver dysfunction. Gyimah *et al.*, (2020) studied zebrafish exposed to triclosan from 6 hours post-fertilization to 90 days post-fertilization, finding increased liver weight, lipid accumulation, oxidative stress, and hepatocyte apoptosis, with activation of the MAPK/p53 signaling pathway. Aswathy *et al.*, (2021) exposed *Anabas testudineus* fish to 9 µg/L triclosan for up to 60 days, revealing reduced liver weight, impaired antioxidant defense, and severe liver lesions.

Biochemical Analysis

Lipid

Chai *et al.*, (2017) exposed *Bufo gargarizans* tadpoles to triclosan concentrations of 0, 10 ,30, 60, 150 mg/L for 30 days, finding significant lipid accumulation in hepatocytes at concentrations as low as 30 mg/L and mitochondrial injury at 150 mg/L, alongside down-regulation of lipid metabolism-related genes. According to Belosludtsev *et al.*, (2018) triclosan induced permeabilization of lecithin liposomes and mitochondrial swelling, highlighting its effect on lipid membranes. Ena *et al.*, (2018) treated Sprague-Dawley rats with doses of 0.25, 25, 250, 750 mg/kg for 60 days, revealing liver damage and altered liver enzyme activity. Yueh *et al.*, (2020) exposed C57BL/6 mice to 0.35 mM triclosan for 4–4.5 months, observed significant accumulation of lipid in the liver and a 50% increase in abdominal fat. Gyimah *et al.*, (2020) found that zebrafish exposed to triclosan showed lipid droplet accumulation and liver injury. Hanafy *et al.*, (2020) observed increased malondialdehyde (MDA) levels and decreased glutathione (GSH) levels in pregnant rats exposed to 13 mg triclosan, indicating oxidative stress. Chen *et al.*, (2023) exposed zebrafish to triclosan at 0, 5, 10, and 20 µg/L for 7 days, the result revealed that lipid accumulation, elevated triglyceride (TG) and total cholesterol (T-CHO) levels at 10 and 20 µg/L, and dysregulated lipid metabolism due to miR-27b upregulation and suppression of the AMPK pathway.

DNA

Triclosan has been shown to induce DNA-related effects in several studies. Ma *et al.*, (2013) found that treating HepG2 liver cells with triclosan reduced global DNA methylation and increased oxidative stress markers, including 8-OHdG. Wu *et al.*, (2014) found that triclosan, at concentrations ranging from **0.1 to 20 µM**, enhanced DNA synthesis and induced apoptotic cell death in mouse hepatoma Hepa1c1c7 cells and human hepatoma HepG2 cells. Wang *et al.*, (2017) treated male mice with doses of 0, 10, 100, 200 mg/kg/day for 14 or 28 days, observed increase in inflammation and cell proliferation gene expression, suggesting potential DNA damage. Paul *et al.*, (2020) exposed Pangasianodon hypophthalmus to sub-lethal triclosan concentrations 96 hours, finding increased DNA damage and micronuclei frequency, especially at pH 6.5.

RNA

Zhou *et al.*, (2017) observed that triclosan exposure in zebrafish liver cells led to significant inhibition of Cyp1a mRNA expression (up to 37.5-fold at 2.5 µM after 4 hours), with median lethal concentrations (LC50) between 1.26 and 1.46 µM in zebrafish embryos and larvae after 96 hours post-hatching. Sun *et al.*, (2021) found that triclosan (2.5, 5.0, and 7.5 µM for 24 hours) significantly downregulated mRNA and protein levels of fatty acid synthase (FASN) in HepG2 cells, reducing intracellular lipid content to 88.9%, 74.3%, and 58.8% of the control at doses of 2.5, 5.0, and 7.5 µM, respectively. Chen *et al.*, (2023) reported that triclosan (0, 5, 10, and 20 µg/L for 7 days) in zebrafish significantly upregulated miR-27b, leading to dysregulation of downstream lipid metabolism genes, with suppression of the AMPK pathway and a decrease in m6A-RNA levels, contributing to lipid metabolism disorders.

Protein

Yueh *et al.*, (2014) found that male mice (C57BL/6) fed a chow diet containing 0.08% triclosan for 8 months exhibited significant increases in hepatocyte proliferation, as indicated by elevated protein expression of Ki-67, c-Myc, and Cyclin D1, and a higher incidence of liver tumors with increased tumor multiplicity and size. Wu *et al.*, (2014) observed that triclosan (0.1–20 µM) activated mouse peroxisome proliferator-activated receptor alpha (PPARα) but not human PPARα in Hepa1c1c7 and HepG2 cells. Triclosan treatment also decreased cell viability to 64% of the control at 20 µM, changes in apoptosis-related protein levels.

Carbohydrate

Pereira *et al.*, (2022) found that triclosan, administered at doses ranging from 10^{-5} to 10^{-4} M, significantly decreased gluconeogenesis and increased glycolysis and ammonia output in isolated perfused rat livers, indicating altered carbohydrate metabolism.

Liver enzymes

Triclosan exposure has been shown to significantly affect enzyme activities in various studies. Wu *et al.*, (2017) observed that human HepG2 cells overexpressing cytochrome P450 (CYP) enzymes exhibited increased resistance to triclosan-induced cytotoxicity at doses of 15, 30, and 60 µM for 48 hours, with metabolism leading to less toxic metabolites. Ena *et al.*, (2018) found

increased liver enzyme levels, including ALT and AST, in Sprague-Dawley rats given daily oral doses of triclosan (0.25, 25, 250, or 750 mg/kg) for 60 days, indicating hepatotoxicity. Jackson *et al.,* (2018) showed a negative correlation between triclosan exposure (0.1 mg/kg/day for two days) and estradiol sulfotransferase activity in the fetal liver of ewes, suggesting disrupted enzyme function. Liu *et al.,* (2019) demonstrated that triclosan exposure in adult zebrafish (50, 100, and 150 µg/L for 30 days) led to significant decreases in antioxidant enzyme activities (SOD, CAT, GPx), indicative of oxidative stress and liver damage. Paul *et al.,* (2020) reported significant decreases in metabolic (GOT, GPT, LDH) and antioxidant (SOD, CAT, GST) enzyme activities in Pangasianodon when hypophthalmus exposed to sub-lethal concentrations of triclosan. Penuela *et al.,* (2021) observed significant increases in alanine aminotransferase (ALT) activity in striped catfish exposed to triclosan for 30 days, suggesting liver damage and metabolic stress.

Mitochondrial function

Newton *et al.,* (2005) found that triclosan (1.25–60 nmol/mg) decreased oxygen consumption during active respiration and increased it during resting states in rat liver mitochondria over 2 days, indicating an uncoupling effect on oxidative phosphorylation. Teplova *et al.,* (2017) observed that triclosan caused a dose-dependent depolarization of mitochondrial membrane potential, induced oxidative stress, apoptosis, and inhibited complex II activity in liver cells over 24 hours, contributing to liver dysfunction. Belosludtsev *et al.,* (2018) showed that triclosan induced permeabilization of liver mitochondria, leading to mitochondrial swelling and disrupting mitochondrial integrity.

Oxidative stress enzymes

Triclosan induces oxidative stress across various models. Teplova *et al.,* (2017) showed that triclosan depolarized mitochondrial membrane potential and increased superoxide anion production, leading to liver dysfunction and oxidative stress. Wang *et al.,* (2017) found that triclosan increased inflammatory markers and cell proliferation, indicating oxidative stress and potential liver damage. Belosludtsev *et al.,* (2018) observed that triclosan caused membrane permeabilization and mitochondrial dysfunction, indicating oxidative stress. Liu *et al.,* (2019) reported that triclosan (50, 100, 150 µg/L for 30 days) reduced antioxidant enzymes (SOD, CAT, GPx) and increased oxidative damage markers (MDA, 8-OHdG) in zebrafish. An *et al.,* (2020) found that triclosan treatment on HepG2 cells inhibited cell proliferation and increased oxidative stress, with changes in glycolytic enzymes and signaling pathways after 24 hours. Huang *et al.,* (2020) found that triclosan (10 and 100 mg/kg/day for 13 weeks) disrupted lipid metabolism, leading to oxidative stress and inflammation in mice. Gyimah *et al.,* (2020) showed that triclosan reduced SOD activity and increased MDA levels in zebrafish liver. An *et al.,* (2021) observed that methyl triclosan induced ROS production and inhibited cell proliferation at higher doses. The triclosan (0.05, 0.5, 5 µg/L for 24–168 hours) altered Nrf2 and antioxidant-related gene expression, suggesting oxidative stress in mosquitofish Bao *et al.,* (2021). Aswathy *et al.,* (2021) demonstrated that triclosan exposure (9

µg/L) over 4 to 60 days in Anabas testudineus resulted in reduced activities of superoxide dismutase and glutathione peroxidase, indicating impaired antioxidant defense.

Apoptosis

Wu *et al.,* (2014) reported apoptosis in Hepa1c1c7 and HepG2 cells with increased caspase 3/7 activity. Li *et al.,* (2019) found that methyl-triclosan (0, 5, 10, 20, 40 µM, 24 hours) increased apoptosis in HepG2 cells, with elevated ROS. The triclosan (0.08, 0.16, 0.25 mg/L, 90 days) induced apoptosis in zebrafish hepatocytes, activating MAPK/p53. Apoptosis in mice liver with triclosan (10 mg/kg, 12 weeks) linked to ferroptosis and fibrosis. Gyimah *et al.,* (2020) and Liu *et al.,* (2024)

Histological changes

Triclosan exposure led to notable histological changes in various species. Chai *et al.,* (2017) found increased hepatosomatic index, melanoma-macrophages, nucleus pyknosis, and collagen fiber deposition in Bufo gargarizans tadpoles exposed to 0, 10, 30, 60, 150 mg/L for 30 days. Ena *et al.,* (2018) and Liu *et al.,* (2019) observed liver structural damage in rats hepatocyte atrophy and necrosis in zebrafish. Yueh *et al.,* (2020) found lipid accumulation and altered liver structure in mice exposed to 0.35 mM for 4–4.5 months and Gyimah *et al.,* (2020) showed lipid droplet accumulation and hepatocyte apoptosis in zebrafish. Found liver disorganization in rats exposed to triclosan. And reported melanomacrophage aggregation and hepatocyte degeneration in Anabas testudineus exposed to 9 µg/L for 30–60 days Hanafy *et al.,* (2020) and Aswathy *et al.,* (2021).

Hormones

Yueh *et al.,* (2020) reported that triclosan exposure (0.35 mM for 4–4.5 months) significantly suppressed fibroblast growth factor 21 (FGF21) expression in male C57BL/6 mice on a high-fat diet, leading to disrupted lipid metabolism and increased abdominal fat. This hormonal dysregulation, mediated by the transcription factor ATF4, contributed to hepatic steatosis and altered triglyceride biosynthesis.

Table: Showing Effect of Triclosan on Liver

S.N.	Author, Journal Name and Year	Title	Doses and No. of Animal used	Duration and Parameters	Findings	Remark

1.	Newton, A. P. N., Cadena, S. M. S., Rocha, M. E. M., Carnieri, E. G. S., and De Oliveira, M. B. M.,*Toxicology Letters*, 2005.	Effect of triclosan (TRN) on energy-linked functions of rat liver mitochondria .	1.25 to 60 nmol per mg ,10 male albino rats	2 days; Oxygen consumption during active respiration (state 3) and resting states (state 4), mitochondrial respiratory chain components.	Triclosan decreased oxygen consumption during state 3, increased it during state 4, uncoupling oxidative phosphorylation, inhibited components of the mitochondrial respiratory chain.	Potential toxic effects on mitochondrial function.
2.	Paul, K. B., Hedge, J. M., DeVito, M. J., and Crofton, K. M., *Toxicological Sciences*, 2010.	Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in young Long-Evans rats.	0-1000 mg/kg/day in 120 weanling female Long-Evans rats.	4 days; Serum levels of total thyroxine (T4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), hepatic enzyme activity, mRNA expression related to phase I and II metabolism, liver weight, body weight gain.	No clinical toxicity signs, but 12% increase in liver weight and 13% increase in liver-body weight ratio at 1000 mg/kg/day. Dose-responsive decrease in total serum T4 and T3 levels, with significant reductions at higher doses.	Triclosan induces hypothyroxinemia and affects liver weight and function.
3.	Ma, H., Zheng, L., Li, Y., Pan, S., Hu, J., Yu, Z., and Fu, J., Chemosphere, 2013.	Triclosan reduces the levels of global DNA methylation in HepG2 cells.	1.25, 2.5, 5, 10 µM; In vitro study (HepG2 cells).	24 hours; Global DNA methylation, 8-hydroxy-2'-deoxyguanosine (8-OHdG) accumulation, DNMT1 activity, MBD expression.	Reduced global DNA methylation, increased 8-OHdG, inhibited DNMT1 activity, decreased MBD expression.	Potential epigenotoxic effects, liver toxicity, and carcinogenesis.

4.	Yueh, M. F., Taniguchi, K., Chen, S., Evans, R. M., Hammock, B. D., Karin, M., and Tukey, R. H., *Proceedings of the National Academy of Sciences*, 2014.	The commonly used antimicrobial additive triclosan is a liver tumor promoter.	0.08% triclosan in chow diet ; male C57BL/6 mice.	8 months; Liver cell proliferation, tumorigenesis, xenobiotic receptor screening assay, expression of Ki-67, c-Myc, Cyclin D1.	Increased hepatocyte proliferation, elevated expression of Ki-67, c-Myc, and Cyclin D1, higher incidence of liver tumors, increased tumor multiplicity, size, and incidence.	Triclosan acts as a liver tumor promoter and significantly affects liver function.
5.	Wu, Y., Wu, Q., Beland, F. A., Ge, P., Manjanatha, M. G., and Fang, J. L., *Toxicology Letters*, 2014.	Differential effects of triclosan on the activation of mouse and human peroxisome proliferator-activated receptor alpha.	0.1 to 20 µM in Hepa1c1c7 and HepG2 cells	Not specified; PPARα activation, cell viability, DNA synthesis, apoptosis (caspase 3/7 activity, protein levels)	Activated mouse PPARα, not human PPARα; decreased cell viability at 20 µM, enhanced DNA synthesis, induced apoptosis.	Highlighted species differences in triclosan's effects on PPARα and cell viability.
6.	Teplova, V. V., Belosludtsev, K. N., and Kruglov, A. G., *Toxicology Letters*, 2017.	Mechanism of triclosan toxicity: Mitochondrial dysfunction including complex II inhibition, superoxide release and uncoupling of oxidative phosphorylation.	1.25, 2.5, 5, 20, and 50 µM in HaCaT cells; mitochondria from adult male Wistar rats.	24 hours; Mitochondrial membrane potential (ΔΨm) via JC-1, liver function, apoptosis, ATP production, oxidative stress, complex II activity, superoxide anion production.	Dose-dependent depolarization of ΔΨm, chronic liver damage, activated apoptosis in hepatocytes, disrupted ATP production, increased oxidative stress, inhibited complex II activity, increased superoxide anion production.	Significant disruption of mitochondrial function and oxidative stress in liver cells.

7.	Wu, Y., Chitranshi, P., Loukotková, L., Gamboa da Costa, G., Beland, F. A., Zhang, J., and Fang, J. L., *Archives of Toxicology*, 2017.	Cytochrome P450-mediated metabolism of triclosan attenuates its cytotoxicity in hepatic cells.	15, 30, and 60 μM in HepG2 cells .	48 hours; Cytotoxicity via MTT assay, metabolite analysis via UPLC-ESI–MS and HPLC.	Triclosan converted into less toxic metabolites (2,4-dichlorophenol and 4-chlorocatechol), reduced cytotoxicity, CYP-overexpressing cells showed greater resistance to triclosan-induced toxicity.	Highlights the role of cytochrome P450 in reducing triclosan cytotoxicity through metabolic conversion.
8.	Zhou, Z., Yang, J., and Chan, K. M., *Aquatic Toxicology*, 2017.	Toxic effects of triclosan on a zebrafish (Danio rerio) liver cell line, ZFL.	0, 0.5, 1.0, and 2.5 μM in ZFL cells; 1.26 to 1.46 μM in zebrafish embryos/larvae	4, 12, 24, and 96 hours; Delayed hatching, Cyp1a mRNA expression, luciferase assays, EROD assay.	Delayed hatching, significant inhibition of Cyp1a mRNA, TCS as weak Cyp1a agonist, no effect on zfTRβLBD or AhR.	Significant toxic and endocrine-disrupting effects of triclosan in zebrafish liver cells.
9.	Chai, L., Chen, A., Luo, P., Zhao, H., and Wang, H., Chemosphere, 2017.	Histopathological changes and lipid metabolism in the liver of Bufo gargarizans tadpoles exposed to Triclosan.	0, 10, 30, 60, 150 mg L^{-1}; No. of tadpoles not specified	30 days; Morphometric, histological, ultrastructural, and gene expression analyses	Reduced size at metamorphosis, Increased HSI, histopathological changes, lipid accumulation, mitochondrial injury, down-regulation of antioxidant and lipid metabolism genes.	Significant liver health deterioration at higher doses.
10.	Wang, Z., Li, X., and Klaunig, J. E., Regulatory Toxicology and Pharmacology, 2017.	Investigation of the mechanism of triclosan induced mouse liver tumors.	0, 10, 100, 200 mg/kg diet/day; 110 male mice (55 CD-1 and 55 C57BL/6)	14 or 28 days; Hepatic DNA synthesis (BrdU incorporation), serum ALT and AST, gene expression (cell proliferation and inflammation).	increased gene expression of inflammatory markers and cell proliferation at 200 mg/kg/day; No significant elevation in serum enzyme activities.	Potential liver damage through oxidative stress, cytotoxicity, and inflammation.

11.	Belosludtsev, K. N., Belosludtseva, N. V., Tenkov, K. S., Penkov, N. V., Agafonov, A. V., Pavlik, L. L., and Dubinin, M. V., *Biochimica et Biophysica Acta (BBA)-Biomembranes*, 2018.	Study of the mechanism of permeabilization of lecithin liposomes and rat liver mitochondria by the antimicrobial drug triclosan.	10–70 μM triclosan (26 μM, 34 μM) in lecithin liposomes; rat liver mitochondria.	Membrane permeability, release of SRB, mitochondrial swelling, membrane potential.	26 μM led to partial SRB release, 34 μM led to nearly complete release; induced swelling of rat liver mitochondria, significant effects at 34 μM and above.	Significant influence on lipid membranes and mitochondrial integrity, potential for membrane permeabilization and oxidative stress.
12.	Tang, Y., M Vanlandingham, M., Wu, Y., Beland, F. A., Olson, G. R., and Fang, J. L., *Archives of Toxicology*, 2018.	Role of PPARα and PPARα-mediated species differences in triclosan-induced liver toxicity.	0, 58, or 125 mg/kg body weight/day in wild-type and PPARα-humanized mice.	13 weeks; Liver weight, expression of PPARα target genes, skin lesions.	Increased liver weight in wild-type mice, elevated PPARα gene expression, skin lesions in some mice.	Significant impact of triclosan on liver function, differential responses between mouse and human PPARα.
13.	Ena, L., Lim, J. S., Son, J. Y., Park, Y. J., Lee, Y. H., Kim, J. Y., and Kim, H. S., Journal of Toxicology and Environmental Health, Part A, 2018.	Evaluation of subchronic exposure to triclosan on hepatorenal and reproductive toxicities in prepubertal male rats.	0.25, 25, 250, 750 mg/kg; 24 Sprague-Dawley rats	60 days; Biochemical analyses (ALT, AST levels), protein expression of hepatic cytochrome P450 enzyme CYP2B1, histological examination.	Significant increases in ALT (150 U/L at 750 mg/kg) and AST levels, increased CYP2B1 expression, structural liver damage.	Indicated hepatotoxicity at higher doses.

14.	Jackson, E. N., Rowland-Faux, L., James, M. O., and Wood, C. E., Toxicology Letters, 2018.	Administration of low dose triclosan to pregnant ewes results in placental uptake and reduced estradiol sulfotransferase activity in fetal liver and placenta.	0.1 mg/kg/day triclosan; Pregnant ewes.	2 days; Triclosan concentration in placenta and fetal liver, estradiol sulfotransferase activity.	Higher concentrations of triclosan in placenta than fetal liver; Reduced estradiol sulfotransferase activity with higher triclosan levels.	Potential effects on enzyme activity and placental function.
15.	Li, X., An, J., Li, H., Qiu, X., Wei, Y., and Shang, Y., *Ecotoxicology and Environmental Safety*, 2019.	The methyl-triclosan induced caspase-dependent mitochondrial apoptosis in HepG2 cells mediated through oxidative stress.	Various concentrations (0, 5, 10, 20, and 40 μM) in HepG2 cells.	24 hours; Cell viability, apoptosis (flow cytometry), ROS levels, LDH release, glucose uptake, ATP production, gene expression (RT-qPCR).	Reduced cell viability, increased apoptosis, dose-dependent rise in ROS levels.	Methyl-triclosan induces apoptosis through oxidative stress and caspase-dependent pathways.
16.	Liu, M., Ai, W., Sun, L., Fang, F., Wang, X., Chen, S., and Wang, H., *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, 2019.	Triclosan-induced liver injury in zebrafish (Danio rerio) via regulating MAPK/p53 signaling pathway.	50, 100, and 150 μg/L in adult zebrafish.	30 days; Activities of antioxidant enzymes (SOD, CAT, GPx), oxidative damage markers (MDA, 8-OHdG), histological changes in liver and brain.	Decreased activities of SOD, CAT, and GPx; increased MDA and carbonyl proteins; liver and brain structural alterations (atrophy and necrosis of hepatocytes).	Significant oxidative stress and histological damage in liver and brain tissues.
17.	An, J., He, H., Yao, W., Shang, Y., Jiang, Y., and Yu, Z., Environment International, 2020.	PI3K/Akt/FoxO pathway mediates glycolytic metabolism in HepG2 cells exposed to triclosan (TCS)	HepG2 cells (in vitro); No specific dose	24 hours, Cell viability (CCK-8), ROS (DCF-DA), SOD activity, Western blotting	Triclosan inhibited cell proliferation, increased ROS, altered glucose metabolism, affected enzyme expression.	Highlights significant cytotoxic effects of triclosan on liver cells.

18.	Huang, W., Xie, P., and Cai, Z., *Journal of Hazardous Materials*, 2020.	Lipid metabolism disorders contribute to hepatotoxicity of triclosan in mice.	10 mg/kg/d and 100 mg/kg/d in male, C57BL/6 mice.	13 weeks, analysis via HPLC, gene expression via qRT-PCR.	Significant hepatic hypertrophy, increased liver weight, fatty liver, oxidative stress, inflammation.	Insights into lipid metabolism disruption and hepatotoxicity mechanisms.
19.	Yueh, M. F., He, F., Chen, C., Vu, C., Tripathi, A., Knight, R., and Tukey, R. H., *Proceedings of the National Academy of Sciences*, 2020.	Triclosan leads to dysregulation of the metabolic regulator FGF21 exacerbating high fat diet-induced nonalcoholic fatty liver disease.	0.35 mM triclosan in 0.2% DMSO ; male C57BL/6 mice (chow diet or HFD)	4 to 4.5 months; Serum FGF21 levels, gene expression related to lipid metabolism, histological examinations	Blunted FGF21 expression, increased abdominal fat, liver lipid accumulation.	Triclosan significantly impacts liver health, contributing to hepatic steatosis and metabolic disturbances .
20.	Gyimah, E., Dong, X., Qiu, W., Zhang, Z., and Xu, H., *Environmental Science and Pollution Research*, 2020.	Effects of triclosan on liver health in zebrafish.	0, 0.08, 0.16, and 0.25 mg/L .	90 days; Lipid staining, histopathology, oxidative stress markers (MDA, SOD), gene expression (qRT-PCR, Western blotting)	Increased liver weight, lipid droplet accumulation, elevated MDA, reduced SOD, enhanced hepatocyte apoptosis.	Triclosan causes liver injury via oxidative stress and apoptosis involving MAPK/p53 pathway.
21.	Hanafy, S. M., Abo-Ouf, A. M., Mohamed, A. F., Arafa, M. A., and Shawky, L. M., The Anatomical Record, 2020.	Triclosan treatment to pregnant albino rats affects offspring numbers and the liver of both the pregnant rats and their offspring, and these effects are ameliorated by co-treatment with bee honey.	0.3 mg, 13 mg triclosan; 1.68 ml honey; 72 pregnant albino rats.	Throughout pregnancy and 14 days post-delivery; Histological and biochemical analyses of liver health.	High-dose triclosan caused significant liver damage (disorganization of hepatic architecture, increased MDA, decreased GSH); Honey co-treatment mitigated liver damage.	Potential protective role of honey against triclosan-induced liver toxicity.

22.	Paul, T., Kumar, S., Shukla, S. P., Pal, P., Kumar, K., Poojary, N., Biswal, A., & Mishra, A. Environmental Pollution, 260 (2020).	A multi-biomarker approach using integrated biomarker response to assess the effect of pH on triclosan toxicity in Pangasianodon hypophthalmus (Sauvage, 1878).	910 µg/L at pH 6.5, 1110 µg/L at pH 7.5, 1380 µg/L at pH 8.5; Number of animals not specified.	96-hour exposure; Metabolic enzyme activities (GOT, GPT, LDH), Antioxidant enzymes (SOD, CAT, GST), DNA damage, Micronuclei frequency.	Significant alterations in liver function; Decrease in metabolic and antioxidant enzyme activities at lower pH levels; Increased DNA damage and micronuclei frequency.	Highlights the liver's vulnerability to triclosan toxicity and underscores the potential of using these biomarkers for environmental monitoring.
23.	Sun, D., Zhao, T., Long, K., Wu, M., and Zhang, Z., *European* *Journal of Pharmacology*, 2021.	Triclosan down-regulates fatty acid synthase through microRNAs in HepG2 cells.	2.5, 5.0, and 7.5 µM in HepG2 cells.	24 hours; mRNA and protein levels of FASN, intracellular lipid content, microRNA expression.	Triclosan significantly down-regulated mRNA and protein levels of FASN, decreased intracellular lipid content, upregulated specific microRNAs promoting FASN mRNA degradation.	Triclosan may influence lipid metabolism through microRNA modulation and regulate metabolic pathways in HepG2 cells.
24.	Aswathy, P. K., Priyatha, C. V., Nikhil, J., and Chitra, K. C., Aquaculture Research, 2021.	Triclosan at environmental concentration alters the hepatic antioxidant defense system in the fish, *Anabas testudineus* (Bloch, 1792).	9 µg/L; 10 fish per group	4, 7, 30, 60 days; Absolute and relative liver weights, antioxidant enzyme activities (superoxide dismutase, glutathione peroxidase), histopathological examination.	Reduced liver weights, decreased antioxidant enzyme activities, severe liver lesions.	Indicates impaired antioxidant defense and adverse effects on liver function.

25.	An, J., Yao, W., Tang, W., Jiang, J., and Shang, Y., *ACS Omega*, 2021.	Hormesis effect of methyl triclosan on cell proliferation and migration in human hepatocyte L02 cells.	0.1, 0.5, 1, 5, 10, 20, 40, and 60 μM ; human hepatocyte L02 cells.	14 days; Cell proliferation, migration, ROS production, gene expression via RT-qPCR and Western blotting.	Low doses stimulated cell proliferation and migration, high doses inhibited these processes.	Hormesis effect observed, mediated through oxidative stress response.
26.	Bao, S., He, C., Ku, P., Xie, M., Lin, J., Lu, S., and Nie, X., Aquatic Toxicology, 2021.	Effects of triclosan on the RedoximiRs/ Sirtuin/Nrf2/ ARE signaling pathway in mosquitofish (*Gambusia affinis*).	0.05, 0.5, 5 μg/L; 30 female mosquitofish.	24 hours and 168 hours; Expression levels of Nrf2, antioxidant genes, and sirtuins measured by qRT-PCR and Western blotting.	Altered RedoximiRs/Sirtuin/Nrf2/ARE signaling pathway.	Suggests potential liver toxicity due to oxidative stress.
27.	Peñuela, G. A., and Martínez-López, E., Chemosphere, 2021.	Enzymatic activity changes in striped catfish *Pseudoplatystoma magdaleniatum*, induced by exposure to different concentrations of ibuprofen and triclosan.	25, 50 mg/L ibuprofen; 25, 50 mg/L triclosan; 60 fish.	30 days; Plasma biomarkers (enzymes and proteins).	Significant increase in ALT activity with triclosan; suggesting liver damage and metabolic stress.	Indicates potential liver toxicity due to triclosan exposure.
28.	Pereira-Maróstica, H. V., Bracht, L., Comar, J. F., Peralta, R. M., Bracht, A., and Sá-Nakanishi, A. B., Toxicology and Applied Pharmacology, 2022.	The rapid transformation of triclosan in the liver reduces its effectiveness as inhibitor of hepatic energy metabolism.	10^{-5} to 10^{-4} M; Isolated perfused rat livers.	Not specified; Gluconeogenesis, glycolysis, ammonia output.	Decreased gluconeogenesis, increased glycolysis and ammonia output in the liver.	Indicates significant impact of triclosan on liver metabolism.

29.	Chen, S., Wang, X., Yan, J., Wang, Z., Qian, Q., and Wang, H., Science of the Total Environment, 2023.	Mechanistic illustration on lipid-metabolism disorders induced by triclosan exposure from the viewpoint of m6A-RNA epigenetic modification.	0, 5, 10, 20 µg/L; 30 zebrafish per treatment group.	7 days; Lipid accumulation, triglyceride (TG) and total cholesterol (T-CHO) levels, locomotor activity, miR-27b, AMPK signaling pathway, m6A-RNA levels	TCS exposure caused lipid accumulation, reduced locomotor activity, and disrupted AMPK signaling pathway.	Highlights the role of m6A-RNA modification in TCS-induced lipid metabolism disorders.
30.	Liu, J., Zhang, L., Xu, F., Zhang, P., and Song, Y., Journal of Environmental Sciences (China), 2024.	Chronic administration of triclosan leads to liver fibrosis through hepcidin-ferroportin axis-mediated iron overload.	10 mg/kg triclosan; 30 male BALB/c mice.	12 weeks; Hepatic iron levels, hepcidin and biomarkers of iron homeostasis, hepatocyte ferroptosis.	Significant hepatic fibrosis, increased hepatic iron levels, elevated hepcidin, mitigated by Ferriprox.	Highlights the harmful effects of triclosan on liver function.

Conclusion:

The present review brings us to the conclusion that triclosan is a widely used antimicrobial agent found in many consumer products, known for its effectiveness in reducing bacterial contamination. However, its extensive use has raised significant concerns about its environmental persistence and potential health impacts. It does not easily degrade and can accumulate in aquatic ecosystems, leading to bioaccumulation and adverse effects on wildlife, such as endocrine disruption. It has also been linked to the development of antibiotic-resistant bacteria, which poses a serious public health threat. In humans, triclosan can disrupt endocrine functions, affecting growth, metabolism, and reproductive health. Research also indicates that triclosan can cause cytotoxicity and genotoxicity, potentially leading to long-term health issues. Due to these concerns, there is a push for regulatory action to limit or ban triclosan in consumer products.

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