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Triclosan- Elucidating Its Pharmacological Properties And Impact Of Long Term Exposure On Environment

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Abstract: ***Triclosan is a multipurpose compound that has been used as major ingredient in most of the household products. It is found to be effective against both gram-positive and gram-negative bacteria. Besides being a broad-spectrum anti-microbial agent, other pharmacological properties such as anti-inflammatory effects have also been reported. However, continuous exposure to increasing levels of triclosan has become a major concern for both public health and environment. Several studies revealed triclosan has become an emerging contaminant which may adversely affect the aquatic animals, human, wildlife and microbial communities. The occurrence of high triclosan levels in various environmental compartments has shown to produce cytotoxic, genotoxic, and endocrine disruptor effects in living organisms of both aquatic and terrestrial environments. In this review, we document physio-chemical properties of triclosan and summarize the current findings on pharmacological benefits from its usage. Considering triclosan induced environmental and health concerns, we have highlighted detrimental effects on different biological systems and emphasize on restrained use of triclosan containing products.***

Keywords: ***Triclosan, bioaccumulation, emerging contaminants, toxicity, antimicrobial agent***

I. INTRODUCTION

Triclosan was first introduced in the early 1970s and has been used increasingly over the past 25 years. Due to its potential to act as broad spectrum antimicrobial agent, it has been used as major ingredient in disinfectants, soap, detergent, toothpaste, mouthwash, fabric, deodorant, shampoo and innumerable other personal care, veterinary, industrial and household products. The main target of triclosan's antimicrobial action is on bacterial cytoplasmic membrane. Triclosan causes cytoplasmic disorganization in the bacterial cytoplasmic membrane at bactericidal concentrations. In addition to its antimicrobial and anti-plaque effect, anti-inflammatory properties of triclosan have also been reported. Because of unique mechanism of action, it has been also considered a potential chemotherapeutic candidate and also as an inhibitor against infectious diseases such as tuberculosis or malaria. Over last few decades, triclosan incorporated in daily use products have been used throughout North America, Europe and Asia. Excessive use of triclosan containing personal care products are subjected to release into environment through various pathways. Triclosan was one of the most frequently detected organic pollutants in both waste water and surface water. The safety, effectiveness and regulation of its usage have become a major concern as the detection limit in the environment is increasing at a continuous rate. Though triclosan is known to be biodegradable, however it has been detected at some levels in sewage water treated samples. Past research has shown triclosan can produce toxic effects such as cytotoxic, genotoxic, and endocrine disruptor effects in aquatic organisms including algae, fishes and crustaceans. Moreover, chemical properties of triclosan suggest its possible bioaccumulation and further environmental persistence. The hydrophobic nature of triclosan has also been responsible for its accumulation in fatty tissues of human samples. For past few years, triclosan is increasingly scrutinized after it emerged as a toxic environmental contaminant. Despite its pharmacological properties, occurrence and toxicity of triclosan have become major issues. In recent years, several studies have been

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targeted towards the evaluation of its fate and distribution in the environment. The objective of this review primarily focuses on the benefits of triclosan usage and also highlights the importance of its judicious use. The potential human health issues and adverse effects on the environment from long term exposure of triclosan have been also addressed in this review.

II. PROPERTIES OF TRICLOSAN

Triclosan (TCS or 2,4,4'-trichloro-2'-hydroxydiphenyl ether) has been widely used in clinical, industrial and household products due to its broad spectrum anti-microbial activity (Bhargava & Leonard, 1996). The molecular weight of TCS is 289.55 $g.mol^{-1}$ and the chemical formula is $C_{12}H_7Cl_3O_2$. It is a chlorinated aromatic hydrocarbon having ether and phenol as functional groups. Phenol groups present in the compound is often responsible for its anti-bacterial properties. The structure of Triclosan is similar to polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and bispenol A which are known to be toxic organic compunds (Allmyr, *et al.* 2008). It is non-ionic, non-volatile and chemically stable compound having high melting point of 55-57 ºC. TCS, a halogenated biphenyl ether derivative, has pKa value of 8.1. It is readily soluble in organic solvents and presents low water solubility (10 mg/L at 20 ºC) (Yalkowsky, *et al.* 2010). The organic carbon–water partitioning coefficient is high with log K_{oc} value of 3.8−4.0 and octanol–water partition coefficient (log K_{ow}) of TCS is 4.76. The photodegradation of triclosan converts it into its photostable phenolate form and it predominates when pH of water is more than 8. High log K_{ow} value suggests it high capacity to adsorb onto the settled sewage sludge resulting in its bioaccumulation in agriculture soils. Although bioaccumulation of triclosan depends on its ionization state in different environmental conditions, still it is likely that triclosan can be a threat to environment (Brausch, *et al.* 2011).

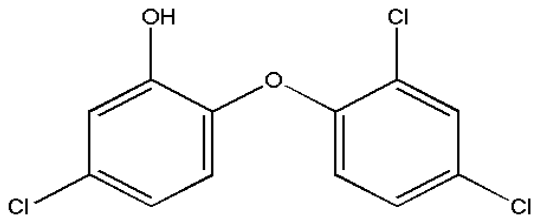

Figure 1: Structure of Triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether)

Irgasan CH 3565	Invasan DP 300TEX	VIV-20	Microbanish R
Irgasan DP300	IrgaguardRB 1000	Gamophen	Vikol THP
Ster-Zac	Irgacare MP	Vinyzene DP 7000	Ultra-Fresh
Tinosan AM110	Lexol 300	Vinyzene SB-30	Microban Additive "B"
Invasan DP 300R	Aquasept	Sanitized Brand	AerisGuard

Table 1: General properties

Chemical name	2,4,4'-trichloro-2-hydroxydiphenyl ether
Synonyms	5-chloro-2-(2, 4-dichlorophenoxy)phenol
Molecular weight	289.5
Melting point	55–57 ºC
pKa value	8.1
General applications	Antimicrobial, antiplaque, disinfectant

Table 2: Trade Names

III. PHARMACOLOGICAL PROPERTIES OF TRICLOSAN

Triclosan act as antibiotic preventing propagation of many different types of bacteria and also certain types of fungi. It is bacteriostatic at low concentrations and is known to target cytoplasmic and membrane sites at high concentration (Russell, 2004). Previous studies demonstrated that the major target of triclosan was fatty acid synthase (FASN), a key metabolic enzyme required for *de novo* synthesis of fatty acids (FA). It mimics the natural substrate and was found to overlap with acyl-substrate binding pocket. Triclosan has been shown to specifically block synthesis of fatty acids through inhibition of fatty acid synthase resulting in incomplete bacterial membrane formation and destabilization leading to cell death (Lupu, *et al.* 2006; Health, *et al.* 1999; McMurry, *et al.* 1998). However, triclosan is ineffective against the bacterial spores (Levy, *et al.* 1999).

Triclosan has shown significant activity against *Mycobacterium tuberculosis* causing tuberculosis and *Plasmodium falciparum* causing malaria. TypeII fatty-acid synthase system (FAS-II) present in various species including *Mycobacterium tuberculosis*, *Plasmodium falciparum*, *Escherichia coli*, *Pseudomonas aeruginosa* etc. has been shown to be an important target of triclosan action (Kuo, *et al.* 2003; Surolia & Surolia 2001; Health, *et al.* 1998; Hoang, *et al.* 1999). Enoyl- acyl carrier reductase (ACP) protein (InhA) is essential enzyme in the FAS-II system that is responsible for the conversion of trans-2-acyl ACP to acyl- ACP in fatty acid chain elongation cycle. FAS-II system in *Mycobacterium* is required for synthesis of cell wall-associated mycolic acids, whose inhibition leads to lysis of the bacterium. In *Plasmodium*, FAS-II system is required for the fatty acid synthesis and the enzymatic components of FAS-II system are present in apicoplast, a plastid organelle essential for the development of the parasite. Since FASN system is expressed in low levels in normal eukaryotic cells, triclosan has long been thought to be fairly harmless. Thus, it was considered a potential candidate as an inhibitor against tuberculosis and malaria.

Previous studies have suggested that triclosan-induced inhibition of fatty acid biosynthesis system emphasizes its potential as a chemotherapeutic candidate (Liu, *et al.* 2002). In initial stages of cancer development, elevated expression levels of Fatty Acid Synthase (FASN) has been found in tumor cells. Recent report suggested that triclosan can induce cytotoxic effect in prostate cancer cells (Martin, *et al.* 2014). The anti-inflammatory effect of triclosan has also been

highlighted previously in vitro studies. Studies have shown ability of triclosan to suppress expression of pro-inflammatory mediators and cytokines including prostaglandin E2 (PGE2), leukotriene and interferon-γ (IFN-γ) pathways on monocytic and fibroblastic cell types in response to bacterial endotoxin (lipopolysaccharide, LPS) (Mustafa, *et al.* 2000; Modeer, *et al.* 1996). In addition to this, usage of triclosan may also have implications in inhibition of molecular signals known to be associated with the transition of gingivitis to periodontitis (Barros, *et al.* 2010; Wang, *et al.* 2004).

Earlier, isoniazid (INH) was used as an effective prodrug which inhibits InhA upon activation in *M. tuberculosis* by KatG, a catalase/peroxidase enzyme (Rowarski, *et al.* 1998). However, mutations in KatG were found to have strong association with INH resistance and evolution of multi-drug resistant strains of *Mycobacterium tuberculosis* (Morlock, *et al.* 2003; Hazbon, *et al.* 2006). To overcome the INH resistance associated with mutations in KatG, compounds that directly inhibit the InhA enzyme without requiring activation of KatG enzyme have been developed. Because of its remarkable properties, a series of triclosan with modifications at 5-chloro of triclosan, 5-substituted triclosan derivatives were synthesized. The substituted triclosan derivatives were found to be more effective than the parent compound - triclosan. Freundlich *et al.* (2009) demonstrated efficacy of triclosan derivatives to inhibit InhA in drug resistant laboratory and clinical strains of *M. tuberculosis*. These triclosan analogues do not require KatG enzyme activation and displays high efficacy against both INH sensitive and INH resistant strains, more than those of isoniazid. Thus, derivatives of triclosan exhibit high potency as novel inhibitors against drug-resistant *M. tuberculosis*. Studies on these analogues will help to acquire information about the interaction among substituents of triclosan with the amino acids located in the active site of target protein that might increase the binding capacity of those inhibitors, and therefore, their potential as next generation drug candidates.

IV. OCCURRENCE AND TOXICITY IN ENVIRONMENT

The prevalence of triclosan in the aquatic and terrestrial environments and its alarming exposure levels has been a major concern for human health and environment. The antimicrobial properties of triclosan have lead to its incorporation in various consumer products such as toothpastes, antibacterial soaps, antiperspirants/deodorant, dishwashing liquids, cosmetic and antiseptic products. Because of its widespread applications and "down the drain disposal", triclosan may represent a potential public health risk and an environmental pollutant.

In human body, triclosan is rapidly and completely absorbed from the gastrointestinal tract while a lower rate of absorption occurs dermally. The compound has low acute oral and dermal toxicity in animals, although there are few evidences supporting higher acute toxicity via inhalation. Studies on toxicity profiles at acute, sub-acute and chronic levels established that triclosan is neither an acute oral toxicant nor that it acts as a carcinogen, mutagen, or teratogen. However, there have been reports of contact dermatitis, or skin irritation, from exposure to triclosan. Despite multiple benefits from its use, triclosan causes photoallergic contact dermatitis (PACD), when the part of the skin exposed to triclosan is also exposed to sunlight (Schena, *et al.* 2008). It has also been observed in human breast milk samples indicating that the compound gets absorbed into the body, often in high quantities (Margaretha, *et al.* 2002). During 2003–2004, National Health and Nutrition Examination Survey (NHANES) was conducted to evaluate nutrition quality and general health of the US population. The urinary data obtained from this survey indicated that triclosan was found in 75% of the analysed urine samples (Calafat, *et al.* 2008). The lipophilic nature of triclosan makes its more susceptible to bioaccumulation in fatty tissues. Major concerns over triclosan interfering with the body's thyroid hormone metabolism led to a study that found that triclosan had a marked hypothermic effect, lowering the body temperature, and overall causing a nonspecific depressant effect on the central nervous system of mice (Crofton, 2004). In two different studies carried out in rats, short term exposure of triclosan resulted in hypothyroxinemia whereas following a month-long triclosan exposure significant decrease in T4 with no change in thyroid-stimulating hormone (TSH) was reported (Crofton, *et al.* 2007; Zorilla, *et al.* 2009).

Excessive exposure of microorganisms to triclosan can also cause mutations leading to overproduction of fatty acid synthase enzyme and eventually microbial resistance to anti-microbial properties of triclosan. Resistance can also arise from impermeability or efflux of triclosan from bacterial membrane. The major concern lies on the possible contribution of triclosan resistance to reduced susceptibility to clinically important antimicrobials. Detail studies elucidating the association between triclosan resistance and resistance to other antimicrobials in clinical isolates have been limited. However, recent laboratory studies have confirmed the potential for such a link in *Escherichia coli* and *Salmonella enterica* (Yazdankhah, *et al.* 2006).

Triclosan are most commonly encountered contaminant which is detected in all different types of environments. However, there are limited monitoring data available for detecting levels of triclosan in the environment. Various effective treatment methods are deployed in wastewater treatment plants (WWTP) in order to remove triclosan from water bodies. Due to differences in treatment processes and high variability rate in triclosan removal, only partial elimination occurs from waste water treatment plant effluent. Besides the incomplete removal from effluent, triclosan exhibits a tendency to accumulate and persist in biosolids. Assessment on triclosan removal during conventional sewage treatment has shown that 50% of triclosan in WWTP influent will remain in biosolids in WWTPs which utilize activated sludge treatments in combination with anaerobic biosolid digestion (Heidler & Halden, 2007). Various studies carried out in different countries have shown wide variability of triclosan concentrations and its concentration is dependent on sample nature and location (Bedoux, *et al.* 2012). The concentrations of triclosan varied with surface water type ranging from 1.4–40,000 $ng.L^{-1}$; sea water <0.001–100 $ng.L^{-1}$; sediment (lake/river/other surface water) <100–53,000 $\mu g.kg^{-1}$ dry weight; sediment (marine) 0.02–35 $\mu g.kg^{-1}$ dry

weight; wastewater influent 20–86,161 ng.L^{-1}; wastewater effluent 23–5370 ng.L^{-1}; biosolids from WWTP 20–133,000 µg.kg^{-1} dry weight; activated/digested sludge 580–15,600 µg.kg^{-1} dry weight; pore water 0.201–328.8 µg.L^{-1} (SCCS, 2010). Because of their high hydrophobicity, triclosan from wastewater adsorb to sludge and biosolids material. Biosolids Treated sewage sludge or biosolids enter the terrestrial environment during the application of sewage sludge to agricultural land and thus leading to high loading of triclosan to environment (Chu & Metcalfe, 2007).

Occurrence of triclosan is not only detected in rivers but also there are reports supporting its presence in drinking water or tap water. According to Li et al. (2010), the concentration of triclosan was found to be very high in tap water in Guangzhou, China where the concentration reached maximum of 9.7 ng/L. Under certain conditions, presence of triclosan in chlorinated drinking water may cause production of chlorophenols, which are more persistent and highly carcinogenic compounds (Rule, *et al.* 2005). Despite continuous effort to reduce its addition in daily use products, high concentration of triclosan and its derivatives is still being released into the environment. Its bioaccumulation in freshwater aquatic organisms mainly in lower trophic-level organisms (such as algae, crustaceans, and fish) has been described in some studies. The concentration of triclosan in blood plasma of fish in the Detroit River of North America was reported to be very high when exposed to downstream WWTP (Valters, *et al.* 2005). There has been increasing concern regarding the toxic effects and persistent nature of triclosan and its derivatives. Besides, continuous triclosan exposure to environment and bioaccumulation capacity has listed it in contaminants with high potential of causing health hazard. Taking the matter into account, more strict regulations to ban the compound from its incorporation in consumer products would help prevent harmful environmental consequences in near future.

V. CONCLUSION

Though triclosan have wide array of pharmacological properties, however its excessive application have major health problem around the world. Due to bioaccumulation potential, triclosan is increasingly getting accumulated in the environment and even low levels of its presence were found to cause adverse toxic effects on aquatic organisms. There is an urgent need to consider issues surrounding the use of triclosan in order to safeguard human health, aquatic ecosystems and the environment.

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