Article title: Role Of Triclosan (TCS)-Containing Hand Washes In Hormonal Imbalance And Impotency

Authors: Abah Moses Owoicho[1], Mustapha Bakare[2], Deborah Oganya Ogenyi[3], Ogu Stephen[4], Ujah Moses Okwori[5]

Affiliations: Biotechnology/Medical Biochemistry Department, Royal Society of Clinical and Academic Researchers of Nigeria, Abuja, Nigeria[1], Department of Clinical Chemistry, University of Abuja Teaching Hospital Gwagwalada, Abuja, Nigeria[2], Integrated Science Education Department, Federal College of Education (Technical) Bichi[3]

Orcid ids: 0000-0001-9439-1302[1]

Contact e-mail: abakh.m@phystech.edu

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ROLE OF TRICLOSAN (TCS)-CONTAINING HAND WASHES IN
HORMONAL IMBALANCE AND IMPOTENCY

A SEMINAR PRESENTED

BY

ABAH, MOSES OWOICHO

AT THE LABORATORY DEPARTMENT OF THE UNIVERSITY OF
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ABSTRACT

A research shows that, triclosan disrupts the biosynthesis of testosterone. when tested on isolated testicular leydig cells with various dosages, it was found out that triclosan dose-dependently decreases testosterone, and the mechanism is as follows: triclosan decreases the activity of adenylyl cyclase enzyme, resulting in the drop of cAMP (cyclic adenosine monophosphate). Another research shows that, triclosan completely hammered thyroid hormones, lowered luteinizing hormone levels, follicle stimulating hormone levels, and cholesterol synthesis. 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. Another study associated exposure to low levels (0.03 microg/L) of triclosan with disrupted thyroid hormone. Due to the close resemblance of triclosan to certain estrogens, a more recent paper in Environment International shows that triclosan inhibits estrogen sulfotransferase in sheep placenta, an enzyme which helps metabolize the hormone and transport it to the developing fetus. The suspicion is that triclosan would be dangerous in pregnancy if enough of it gets through to the placenta to affect the enzyme. Conclusively, it is recommended that hands should be washed with detergent and warm water, or with bleach and complement with alcohol-containing hand sanitizers rather than using triclosan containing hand washes; also when selecting products such as hand washes, antiseptic soaps, facial cleansers, toothpaste, deodorants, always watch out for Triclosan trade names/chemical names on the ingredient list such as trichlorocarbanalide, irgasan®, Irgacare® and Microban®, triclosan is used as a built-in antimicrobial for product protection.

INTRODUCTION

Triclosan is a phenylether, or chlorinated bisphenol, with a broad-spectrum antimicrobial action; classified as a Class III drug by the Americans FDA. It's also a potent endocrine disruptor and a known carcinogen (Ali 2015).

People are exposed to these chemicals by applying antimicrobial products to their skin or using them in their mouth. Most of these products get washed down the drain after bath, where they enter our waterways and are then transported widely throughout the environment.

Triclosan is diagnosed using HPLC chromatographic technique. The 2003-2004 U.S survey showed that 75% of Americans have been diagnosed to have triclosan in their urine samples. When the Environmental Working Group (EWG) tested 49 participants for triclosan, 42 tested positive for the chemical. It was also found in pregnant women and in breast milk, suggesting that majority of babies are already in contact with the chemical from the very first moments of their lives.

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LITERATURE REVIEW

Current Scenario of Triclosan (TCS) Use and Safety

Generally, TCS comes in the form of white powder. TCS has a weak aromatic, phenolic scent as it is a chlorinated aromatic compound. Ever since its invention, TCS has been widely used in numerous consumer products. It is used as an active ingredient in dental products since 1980s in Europe and the mid-1990s in the United States after approval by the Food and Drug Administration. More specifically, TCS is used in numerous personal care products, such as toothpastes, antibacterial soaps (bars and liquids), dishwashing liquids, deodorant soaps (bars and liquids), cosmetic and antiseptic products, and antiperspirants/deodorants. Triclosan is also used in other consumer products, such as kitchen utensils, toys, bedding, clothes, fabrics, and trash bags (Fuchsman, et al 2010).

According to the FDA monograph for health care antiseptic drug products, which covered antibacterial soap products containing TCS, the recommended limits are up to 1% TCS for use in antiseptic washes and surgical hand scrubs in health care settings. According to Governmental regulations in the European Union (EU) and the United States, only specified amount of triclosan can be used in cosmetic. TCS possesses a broad range of antimicrobial activity that encompasses several, types of nonsporulating bacteria and a few fungi, such as *Plasmodium falciparum* and *Toxoplasma gondii* (Schweizer, 2001). At low concentrations, TCS inhibits the growth of microorganisms; at higher concentrations, it kills microorganisms. Different microorganisms show varied response to TCS. Triclosan blocks the active site of enoyl-acyl carrier protein reductase enzyme (ENR) thus impairing the production of bacterial lipids (Levy et al 1999). In consequence, cell membranes are not properly produced and bacterial proliferation stops. Therefore, only a small TCS dose is required to inhibit bacterial growth. As humans lack ENR enzyme, TCS has been considered harmless to them. Studies carried out by FDA found that TCS-fluoride paste

prevented tooth deformities, such as gingivitis, tartar and plaque in a way that was superior to fluoride-only toothpastes. Over the last 30 years, TCS has also been successfully used as an antimicrobial agent in hospitals and for other biomedical purposes. The successful control of methicillin-resistant *Staphylococcus aureus* (MRSA) outbreaks in several clinical settings using TCS based products (Brady et al 1990). This led to the recommendation of showering/bathing with 2% TCS for the decolonization of patients whose skin is carrying MRSA (Coia et al, 2006). However, susceptibility of MRSA strains to TCS has changed little over the last decade (Tuffnell et al 1987). Later on there has been no relation found between TCS response in MRSA and other strains of *S. aureus* and antibiotic susceptibility or resistance (Suller et al 1999)

Endocrine Disruption Activity and Toxicity of Triclosan

Mechanism of endocrine disruption by exogenous agents can take many forms (Colborn et al. 1993), the commonly encountered is the inhibition of the hormone (agonist) from binding its receptors by competing for the receptor binding sites with the antagonist. This is one mechanism through which TCS exhibits its endocrine disruption activity (Ahn et al. 2008). The occupation of the receptor site by a ligand is known to induce conformational change in the receptor leading to the generation of the transcription factors required for the expression of the hormone-sensitive genes. The expression of oestrogen sensitive genes through the antagonist leads to various uncontrolled physiological effects, such as hypospadias, cryptorchidism and cancer (Meng, 2005). TCS oestrogenic, anti-oestrogenic, androgenic and anti-thyroid activities *in vitro* and *in vivo* in laboratory and aquatic animals have been demonstrated (Arancibia et al. 2009) at environmentally relevant concentrations. Its anti-estrogenic effect in sheep (James et al. 2010) and anti-androgenicity in albino rats (Kumara et al. 2009) have also been demonstrated. The observed physiological effects such as precocious puberty (Stoker et al. 2010) and carcinogenicity (Lee et al. 2012b) could be explained as a consequence of overstimulation

of the receptors presumably by the high TCS concentration (Henry and Fair 2013) or as a consequence of its occupation of the ligand binding domain of the receptor (Ahn et al. 2008). More data are required relating environmentally relevant TCS concentration with the reported physiological effects such as adverse reproductive effects in animals (Kumara et al. 2009). Data appear to be accumulating supporting aetiologic role for TCS in carcinogenesis (Lee et al. 2012b). Hepatic tumourigenesis in mice exposed to TCS has been reported to be mediated by peroxisome proliferator-activated receptor α (PPAR α) signalling pathway (Rodricks et al. 2010). But the work of Yueh et al. 2014 in which tumour was promoted in mice exposed to 0.1 mol/kg TCS in drinking water for 8 months following diethylnitrosamine, (a pro-carcinogen) pre-treatment did not activate PPAR α in cancer promotion. Additional data would be needed to deny or confirm these contrasting reports. PPAR α is a ligand-activated transcription factor belonging to the nuclear receptor superfamily (Corton et al. 2014). It plays a key role in the regulation of lipid metabolism. Its activation by peroxisome proliferators is a well-characterized mode of action of hepatocarcinogenesis in rodents (Corton et al. 2014). TCS hepatocarcinogenesis via PPAR α signalling pathway is not expected in humans because the pathway is known to be several times less active in humans than in mice (Health Canada 2012; US EPA 2008). The report of Lu and Archer (2005) in which mammary tumour was inhibited in methylnitrosourea-treated rats fed with diets containing TCS may appear contrasting to the previous reports of tumour promoting activity of TCS but actually lends credence to the anti-oestrogenic effect of TCS since the presence of oestradiol is a requirement for developing breast cancer (Fernandez and Russo 2010; Gee et al. 2008; Henry and Fair 2013). But report from more recent studies (Lee et al. 2014) showed that TCS induced-cancer progression in MCF-7 human breast cancer cell occurred via oestrogen receptor-mediated signalling pathway implying that TCS participates through multiple mechanisms in breast cancer progression. TCS perturbs thyroid homeostasis (Kodavanti and Curras-Collazo 2010). It reduces circulating levels of the hormones (hypothyroxinaemia) in the exposed animals (Crofton et al. 2007). The compound

interferes with thyroid-mediated developmental processes of tadpoles into frogs (Fort et al. 2010, 2011). The effects are expected to be shared by all animals including humans whose cellular metabolism involves thyroid signalling pathway. Multiple mechanisms including induction of phases I and II enzymes through activation of pregnane X receptor are thought to be responsible for the anti-thyroid activity (Hanioka et al. 1996). Sodium/iodide symporter is the protein normally responsible for iodide uptake but its role in this scenario has not been defined (Friesema et al. 2005). TCS toxicity has been demonstrated in a number of cells including human cancer cells (Arancibia et al. 2009) exhibiting different toxicities in different cells. It is pro-apoptotic at ≥ 1 nM and cytotoxic at ≥ 50 μ M in human choriocarcinoma-derived placental JEG-3 cell line when exposed

Fate of triclosan in environmental water

Waste water treatment plants (WWTPs) are not designed to remove pharmaceuticals; rather removals are based on the physical and chemical properties of the compounds. The efficiency of WWTPs is measured using parameters, such as biochemical oxygen demand (BOD) and chemical oxygen demand (COD). TCS is not completely removed from influents of WWTPs, (Bock et al. 2010) or not at all during primary treatment (Lozano et al. 2013) and whatever remains in the aqueous phase is released into the receiving water body which may impact on the aquatic ecosystems. TCS is stable to hydrolysis; laboratory studies showed it was stable at pH 4, 7 and 9 (US EPA 2008b). TCS is not expected to volatilize significantly given its low vapour pressure of 4×10^{-6} mm Hg at 20 °C (Ciba Speciality Chemicals 2003), however it undergoes biodegradation, photolysis and photochemical reactions, which are processes thought to be responsible for its reduction in natural waters. In conventional treatment plants, substantial amount of TCS is removed from wastewater but advanced treatment processes such as ozonation, photolysis and microfiltration/nanofiltration with reverse osmosis (membrane process) have achieved somewhat total removal of pharmaceuticals (Watkinson et al. 2007). In

wastewater treatment plants employing membrane bioreactor, an estimated amount of over 90 % mass of triclosan is expected to have been removed from the water (Wijekoon et al. 2013). The high proportion of TCS reported to have been removed in wastewater treatment plants especially those plants which employ the conventional activated sludge process may be attributed to biodegradation under aerobic conditions (Bester 2003). Sludge treatment plants with biological treatment process showed the highest removal of TCS (Tohidi and Cai 2016). The abundance of bacterial TCS degraders namely, ammonia oxidizing bacteria (AOB) and *Sphingopyxis* strain KCY1 in activated sludge systems has been reported (Lee and Chu 2015). It is thought that ammonia monooxygenase expressed by AOB is responsible for TCS degradation (Roh et al. 2009) while dioxygenase in the strain KCY1 co-metabolize TCS (Lee et al. 2012b). *Sphingopyxis* strain KCY1, a wastewater bacterium dechlorinates TCS presumably via 2,3-dioxygenase pathway (Lee et al. 2012b) producing androgenic metabolites (Lee et al. 2012a). *Trametes versicolor* and *Pycnoporus cinnabarinus*, species of white rot fungi which grow naturally on dead wood can degrade TCS. *Trametes versicolor* converts TCS into 2-O-(2,4,4'-trichlorodiphenyl ether)- β -D-xylopyranoside, 2-O-(2,4,4'-trichlorodiphenyl ether)- β -D-glycopyranosid

. CONCLUSION

Contamination by TCS has been detected in different environmental matrices including terrestrial, aquatic and biosolids resulting from WWTPs. TCS has also been found in drinking waters. There are concerns that the widespread use of TCS in various applications might lead to a preferential selection for microbial resistance to antibiotics. Microbial resistance has become an increasingly serious problem worldwide, and the continued use of biocides including TCS may exacerbate this problem. Increasing accumulation of TCS in the environment was also found to have adverse impacts on the growth of aquatic organisms.

RECOMMENDATIONS

Wash hands with detergent and warm water, or with bleach and complement with alcohol-containing hand sanitizers rather than using triclosan containing hand washes. When selecting products such as hand washes, antiseptic soaps, facial cleansers, toothpaste, deodorants. always watch out for Triclosan trade names/chemical names on the ingredient list such as trichlorocarbanalide, irgasan®, Irgacare® and Microban®, triclosan is used as a built-in antimicrobial for product protection

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