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Research Article

TRICLOSAN RESISTANCE IN BACTERIA AND ANTIBIOTICS CROSS-RESISTANCE

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ABSTRACT

Triclosan is a polychlorophenoxy phenol that is being used as antibacterial, antiviral and antifungal agent. Triclosan belongs to the class of chemicals suspected of causing cancer. It was initially developed about four decades ago as a surgical scrub for medical professionals and also used in pesticides. Its recent uses transcend beyond the initial use. It is being used in many consumer products to fight bacteria, fungi, viruses and also to eliminate unpleasant odour. This article is necessary since it is evidenced that antimicrobials are important in selection of bacterial resistance and triclosan's use is also confronted with resistance. Also, because its overuse due to its presence in many household products has evolved, selection of resistant organisms can occur either during or after treatment. Since triclosan is categorized as a member of the persistent organic pesticides (POPs), its residues persist in the environment for a long time after use. Apart from triclosan, there are other agents used in destroying bacteria and fungi. All these agents also enter the environment and therefore alter the microbial ecology. This will not only cause resistant and susceptible bacteria but will set a stage for the creation of mutants that will replace normal flora. In order to solve the problems of resistance, normal flora who are the susceptible organisms should be brought back. Also, we must to a great extent limit the use of compounds containing triclosan and other antimicrobial agents except when prescribed or when there is infection or disease.

Keywords: Antimicrobials, Microbial ecology, Normal flora, Mutants, Persistent organic pollutants (POPs)

INTRODUCTION

Triclosan is a synthetic, broad-spectrum antimicrobial agent. It has been available in the market for about four decades. Medical uses of it include: eradication of methicillin-resistant *Staphylococcusaureus* (MRSA) in patients by reducing skin colonization (Glaser, 2004), skin and wounds disinfection, oral hygiene products to control dental plaque accumulation and gingivitis. It is also usedin a wide variety of cosmetic products, fabrics, plastics and other products to prevent deterioration due to microbes. Triclosan is present in many consumer products and brands which includes: soap and dishwashing liquid, towels, mattresses, sponges, personal care products, shower curtains, deodorants, toothbrushes, phones, kitchenware and plastic food containers, shoes, flooring and carpets, cutting boards, clothing and fabrics, children's toys and many other consumer products (Glaser,2004).

Triclosan possesses antibacterial properties along with antifungal and antiviral activities. It is marketed under diverse registered names, including Microban (when used in plastics and clothing), Biofresh (on acrylic fibres), Irgasan *DP-300* (cosmetics), Lexol 300, Ster-Zac, Cloxifenolumand others (Schmid and Kaplan, 2004).

Using a very strong antimicrobial agent such as triclosan domestically or in everyday use causes more harm than benefits. Many antimicrobial treatments are toxic detrimental method to eradicate all microorganisms to which they are applied. This approach includes the risk of toxicity to host organisms, that is, the plants or animals (including humans) exposed to treatment for microbial infections. Also, it could be toxic to humans when food items, kitchen wares, objects and surfaces are treated with antimicrobials. Use of triclosan or other antimicrobials can also destroy the beneficial bacteria which occur naturally in the environment and in our bodies (FSNET,2000). These friendly bacteria cause no harm but produce beneficial effects such as aiding metabolism and inhibiting the invasion of harmful pathogens (Nester *et al.*, 2001). Constant exposure to triclosan can also cause genetic mutations resulting in drug-resistant bacteria, which are harmful microbes that are more resistant (Stenson, 2002). Also, According to United States Food and drug Administration (2010), there is no evidence that triclosan provides extra benefits to health in consumer products except in tooth paste where it prevents gingivitis.

Mechanism of Action of Triclosan

Triclosan acts by blocking the active site of the enoyl-acyl carrier protein reductase enzyme (ENR), which is an essential enzyme in fatty acid synthesis in bacteria(Mcmurry*et al*., 1998; Levy *et al.*,1999). By blocking the active site, triclosan inhibits the enzyme, and therefore prevents the bacteria from synthesizing fatty acid, which is necessary for building cell membranes, for keeping the selective permeability and for reproducing (Mcmurry*et al*., 1998; Levy *et al.*,1999). Triclosan is a very potent inhibitor of ENR. Triclosan binds to bacterial enoyl-acyl carrier protein reductaseenzyme (ENR), which is encoded by the gene FabI. This binding increases the enzyme's affinity for nicotinamide adenine dinucleotide (NAD^+). These results to formation of a stable ENR-NAD^+-triclosan complex, and only low concentrations are needed for powerful bactericidal action (Russel, 2004). Humans do not have this ENR enzyme, and are therefore not affected.

Resistance of Bacteria to Triclosan

Triclosan has activity against many, but not all, types of Gram-positive and Gram-negative bacteria. It is bacteriostatic at low concentrations, but higher concentrations are bactericidal.

*Pseudomonas aeruginosa*is highly resistant due to its outer membrane exclusion properties (Champlin,*et al.*, 2005). *P.aeruginosa*, possesses multi-drug efflux pumps that 'pump' triclosan out of the cell (Chuanchuen*et al*. 2003).Also, Methicillin-resistant *Staphylococcus aureus*strains (MRSA) are inhibited over a rangeof about 0.1–4 mg/l. Triclosan shows significant activity against some mycobacteria, but is notsporicidal. Another way for these bacteria to gain low-level resistance to triclosan is to overexpress *FabI*(Slater-Radosti*et al.,* 2001).Other bacteria, such as some of the *Bacillus* genus, have alternative *Fabl*genes (*FabK*) to which triclosan does not bind and hence are less susceptible.

Under the appropriate settings and conditions, such as in hospitals to prevent hospital-acquired infections, Triclosan has been proven to be effective. But no current data demonstrate any extra health benefits from having antibacterial-containing cleansers in ordinary households. Those households that use antibacterial products do not have any reduced risk of infectious diseases. The Center for Disease Control and Prevention has stated that antibacterial soaps are not

necessary in everyday use, and washing hands with ordinary soap and warm water is an effective way to prevent home infections (Glaser, 2004). In fact, unnecessary everyday domestic use of antibacterial – containing cleansers can aid antimicrobial resistance

Triclosan Resistance and Antibiotics Cross–Resistance

Although, some level of triclosan resistance can occur in some microorganisms, but the larger concern is with the potential for cross-resistance or co-resistance to other antimicrobials. Studies investigating this possibility have been limited (Yazdankhah*et al*., 2006).Triclosan resistance in laboratory experiments may be associated with antibiotic resistance, but clinical and environmental surveys have not demonstrated a conclusive link between triclosan usage and antibiotic resistance development (Kampf and Kramer, 2004).

Antibiotic or biocide resistance occurs when sufficient mutations of a gene cause changes in the spectrum of antibiotic or biocide substrates that the gene product can act upon. It is generally assumed that bacteria rarely acquire resistance to biocides because of their broad spectrum of activity and action at several target sites. This is in contrast with antibiotics that have a very specific site of action which facilitates the emergence of resistance. Since the introduction of penicillin in the 1940s, microbes have evolved resistance to practically all antibiotics.

Bacteria resistant to Triclosan have been reported in diverse species and environments but are not a universal phenomenon (Braoudaki and Hilton, 2004). Although biocide resistance mechanisms are much less understood than antibiotic resistance mechanisms, the central mechanisms for Triclosan resistance concerns efflux pumping (Bradaouki and Hilton, 2005).

However, in a research that was conducted to know whether triclosan had a molecular target or acted non-specifically like alcohols and peroxides**,** *E. coli* mutantsthat are resistant to triclosan were isolated and genetic target for triclosan, enoylreductase, which **is** the product of FabI gene was then identified. The amazing thing is that this protein is also one of the targets for isoniazid, used in the treatment of tuberculosis (Mcmurry*et al*.,1998). Therefore, triclosan joins a group of some other antibiotics including an antibiotic called diazoborine that has FabI as its target; a mutation in this enzyme leads to resistance to all the three drugs mentioned above. This explains why triclosan resistance might cause cross- resistance to antibiotics (Mcmurry*et al*.,1998).

In fact, there has been a lot of research studies that investigated the possible links between triclosan resistance and antibiotics cross-resistance (Mcmurry*et al*., 1998; Rusell *et al*.,1998; Akimitsu *et al*., 1999; Levy, 2000;Chuanchuen*et al.,*2001). Chuanchuen*et al.(*2001) have shown that triclosan is a substrate for three distinct efflux pumps in *Pseudomonas aeruginosa.* The research showed that exposure to triclosan can select for multi- resistant drugs through up-regulation of these same efflux pumps. *P. aeruginosa* deletion mutants defective in these efflux pumps became susceptible to triclosan. Also, from this research, it is clear that exposure to antibiotics and triclosan can select for multi- drug efflux system and hence give rise to triclosan and antibiotics cross- resistance. Recently, in a study of triclosan and antibiotics cross- resistance, it was said that ''it is therefore quite possible that widespread use of triclosan may indeed compound antibiotic resistance'' (American Medical Association, 2000).

Adverse Effects of Triclosan

Environmental Effects

Majority of products containing triclosan are in products that are discharged into residential drains (Reiss *et al.,* 2002).When wastewaters are treated in the plants, triclosan refuses to be removed and persists for long time (Adolfsson-Erici*et al*.,2002). Therefore, larger amount of triclosan is pumped into the environment via waterways. In a research conducted on organic wastewater samples from the streams, it was found that triclosan appears more often and also with the highest concentrations(Kolpin*et al.*,2002).

Triclosan also has adverse effects on the aquatics.It is highly toxic to many algae (Tatarazako*et al*., 2004); possesses both structural and functional effects on algal communities in streams(Wilson *et al*.,2003). Similarly, triclosan has also been reported to be toxic to aquatic bacteria at levels found in the environment and inhibits photosynthesis in diatom algae (Ricart*et al.*, 2010). Since algae are primary producers in the aquatic ecosystems, if triclosan is pumped into the water, it can result to aquatic imbalances. There has also been report presenting the presence of triclosan in the biles of fish enclosed in the downstream of wastewater treatment (Adolfsson-Erici *et al*., 2002).

Toxic Effects

According to Bhargava and Leonard (1996), triclosan is non toxic to humans and animals in very low concentrations. But, reports have shown that exposure to triclosan can cause contact dermatitis and skin irritation at higher concentrations. (Durbize*et al*., 2003; Haz-Map, 2004). When triclosan touches the skin and that part is exposed to the sun,it could result to photoallergic contact dermatitis(PACD) (Durbize*et al*.,2003;Haz-Map, 2004). This could result to an eczematous rash on the part of the body exposed to sunlight(Haz-Map, 2004).Triclosan has been implicated in allergic reactions in children that are exposed to it (Clayton *et al*., 2010).Also, since producers of triclosan- containing soap products maintain that its effects remain active hours after use, it therefore means that users are exposed to any side effects of triclosan hours after washing(Glaser, 2004).

Adverse Health Effects

Bhargava and Leonard(1996) reported that triclosan does not possess carcinogenic, mutagenic or teratogenic effects. However,there was a research study that showed the presence of high levels of triclosan in some human milk samples. This showed that triclosan is effectively absorbed by the body in high rates (Adolfsson-Erici*et al*., 2002). Similarly, Centers for Disease Control and Prevention (2011) reported that presence of some levels of triclosan in urine does not however mean that there are adverse health effects. Biomonitoring need to be conducted to determine whether it has reached toxic level. Also, a research study found out that triclosan is hypothermic in mice; hence causing low body temperature and depressing mice's central nervous system(Miller *et al*.,1983).And since triclosan structurally resemble some estrogens, a study was carried out and found that it has no estrogenic effects on fish, rather, it is somehow androgenic which resulted in alterations in both the fin length and sex ratios (Foran *et al*.,2000).

CONCLUSIONS

Controlled use of triclosan in hospitals and other health institutions, or for people with suppressed immune systems is ideal. Any other use outside these is not proper and hence should be discouraged. Also too much use and exposure to triclosan has negative impacts on both environmental and public health. The most active way of preventing infection in normal persons is through the use of warm water and ordinary soaps for washing and cleaning other than using those with antimicrobials.

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