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A REVIEW: TOXIC EFFECTS OF TRICLOSAN IN DEODORANT STICKS

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ABSTRACT

Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether) is a broad spectrum, antimicrobial agent active against most gram-negative and gram-positive bacteria. It has been found in wide range of personal care products, including deodorant soaps, underarm deodorants, shower gels, and handwashes. In this article we reviewed the structure, properties, pharmacokinetics (absorption, distribution, metabolism and excretion), pharmacological properties and toxicities of triclosan.

KEYWORDS: Triclosan, Antimicrobial agent, Toxicity, Gram negative bacteria, Gram positive bacteria.

INTRODUCTION

Triclosan (2,4,4'-trichloro-2'-hydroxydiphenylether) is a non-ionic antibacterial agent effective against a wide range of both gram-positive and gram-negative organisms.[1] It is commonly found in products such as antibacterial soaps, deodorants, skin creams, toothpastes, and plastics.[2] In oral care, triclosan is used in toothpaste and mouth rinses to control plaque and gingivitis.[1] The FDA regulates triclosan as an over-the-counter drug for hand soaps, toothpaste, deodorants, laundry detergents, fabric softeners, facial tissues, wound care antiseptics, and medical devices.[7] Additionally, the EPA regulates it under the Federal Insecticide, Fungicide, and Rodenticide Act as an antimicrobial agent for protecting polymers and plastics.[7] Triclosan has a low solubility in water ($<10^{-6}$ g/mL), which increases in more alkaline conditions.[4]

With a partition coefficient (log P_{ow}) of 5.4, it is considered lipophilic.[4] The widespread use of triclosan raises concerns for ecosystems and human health, as it can accumulate in the human body and pose long-term health risks. Moreover, it can lead to the formation of toxic and persistent compounds like methyl triclosan, chlorinated phenols, and biphenyl ethers after biological methylation or chlorination.[4] Methyl triclosan, being more lipophilic than triclosan, has a higher potential for persistence and bioaccumulation in wildlife and humans.[4]

STRUCTURE OF TRICLOSAN[3]

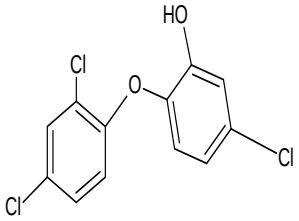

Table 1: General Characteristics of Triclosan.[3]

Molecular formula	$C_{12}H_7C_{l3}O_2$
Molecular weight	289.5 g/mol
IUPAC name	5-chloro-2-(2,4-dichlorophenoxy)phenol

Triclosan is an aromatic ether containing phenol that has 2,4-dichlorophenoxy and chloro groups replaced at positions C-2 and C-5. It is frequently used as an antibacterial and preservative in personal care products like toothpaste, skin creams, soaps, and deodorants as well as home goods including plastic cutting boards, athletic equipment, and shoes.[4]

PROPERTIES OF TRICLOSAN

- **Physical Properties**

The crystalline powder of triclosan is white to off-white in colour and has a subtle aromatic smell. Solid version of the chemical is commercially available. For commercial use, triclosan must be at least 99% pure.

Below are a few published data on triclosan's physical characteristics. Table 2 presents a summary of values derived from data submitted by the applicants and published sources.

Table 2: Physical Properties of Triclosan.[6]

Property	Value	Reference
Melting point	54 °C to 57.3 °C	Merck Index (1983)
Decomposition temperature	280 °C to 290 °C	Fiege et al. (2000)
Density	1.55 g/cm 3 at 22 °C	Ciba-Geigy Limited (1990a)
Specific gravity	1.58 ± 0.03	Ciba Specialty Chemicals (2001a)
Solubility Water n-hexane ammonium hydroxide acetone	0.001g/100g (1x10-5 g /mL) at 20 °C 8.5 g/100g (0.085 g/mL) at 25 °C 0.30 g/100g (0.003 g/mL) at 25 °C > 100 g/100g (> 1.0 g/mL) at 25 °C	Ciba Specialty Chemicals (2001a)
P_{Ka} (acid dissociation constant)	7.9	Merck Index (1983)
Vapour pressure	4 x 10 –6 mm Hg (4 x 10 –4 Pa) at 20 °C 2.6 x 10 –2 mm Hg (2.6 Pa) at 100 °C	Merck Index, (1983) Fiege et al. (2000)
Partition coefficient (Log Pow)	4.8	Ciba-Geigy Limited (1990b)
Henry's Law Constant	0.000000005 (estimated) atm/m 3 mole at 25 °C	PBT Profiler (2004)
Auto ignition temperature	> 350 °C	Ciba Specialty Chemicals (2001a)

- **Chemical Properties**

Utilizing aluminium chloride in benzene under reflux, 2,4,4′-trichloro-2′-methoxydiphenyl ether is converted to triclosan. Changes to chlorinated dibenzo-p-dioxins can happen in harsh environments, like high alkalinity and high heat.

Triclosan is easily soluble in the majority of organic solvents, just slightly soluble in diluted alkaline solutions, and sparingly soluble in water. While triclosan in powder form is extremely stable under extreme heat, solutions under intense UV light may exhibit instability. Furthermore, solutions only moderately stabilize when oxidizing chemicals are present and are not stable when exposed to chlorine. There is some fluctuations in triclosan in steam. 180–200 mg of triclosan are discovered in the first 500 mL of the distillate, which is obtained by distilling a suspension of 1000 mg of triclosan in 800 ml of water.

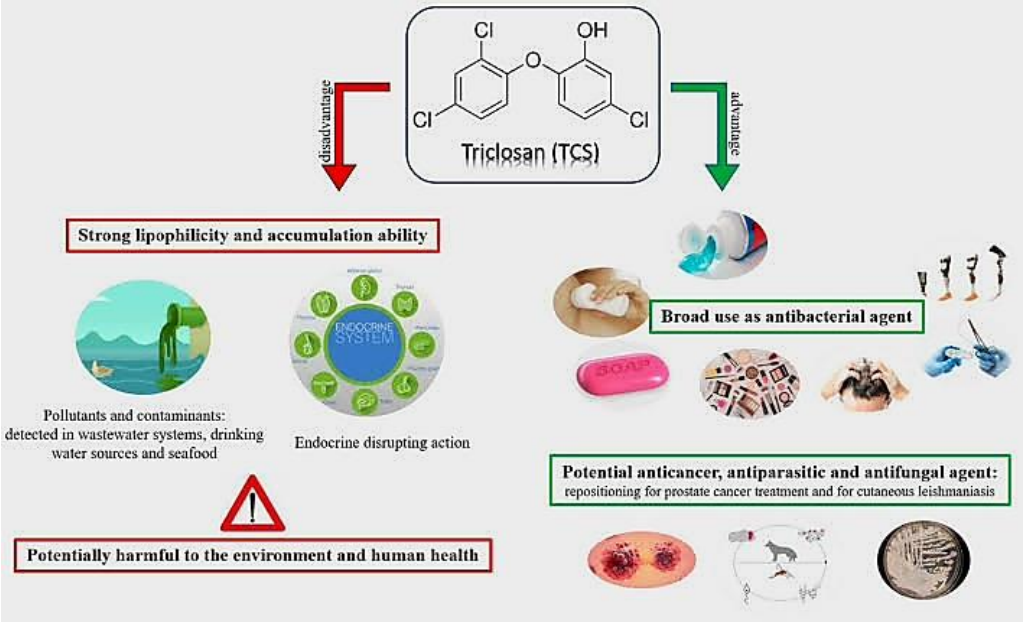

Fig. 1: Advantages and Disadvantages of Triclosan (TCS).

MECHANISM OF ACTION

Triclosan has been shown to intercalate into bacterial cell membranes and disrupt membrane activities, without causing leakage of intracellular components. In addition, triclosan is an inhibitor of the enoyl-reductase of type II fatty acid synthase involved in the bacterial lipid biosynthesis. At low doses, triclosan is bacteriostatic and, at higher doses, it becomes bactericidal. At sub-lethal concentrations, triclosan specifically targets type II fatty acid synthase enoyl-reductase (FabI). However, at bactericidal concentrations, triclosan seems to act against multiple targets, including FabI specific targets such as the cell membrane. Triclosan also has anti-viral, anti-fungal and anti-malarial activity. While triclosan has in vitro activity against a broad spectrum of bacteria, it is generally more effective against gram-positive than gram-negative bacteria. Triclosan is particularly effective against *Staphylococcus aureus.*[8]

Flowchart for Mechanism of Action

TRICLOSAN

↓

Intercalate into bacterial cell membranes

↓

Act on cytoplasmic membrane

PHARMACOKINETICS OF TRICLOSAN

Absorption

Triclosan exhibits Z-pattern absorption, indicating the breakdown of a structure, most likely the membrane, and the formation of a new adsorption site. TCS can be absorbed and enter the systemic circulation via the mucous membrane of the oral cavity, dermal exposure through the skin, and, following oral exposure, through the GI tract (GIT). Triclosan is easily absorbed through the skin due to its lipophilic properties. TCS is absorbed dermally by guinea pig, mouse, rat, and human skin. TCS absorption into human skin may occur at millimolar concentrations. Triclosan may also undergo buccal absorption, resulting in oral and plaque retention, and TCS metabolite detection in plasma. TCS is also absorbed through the gastrointestinal tract after oral exposure has saturated.[7]

Distribution

TCS is broadly dispersed in mammalian blood, urine, and soft tissues (liver, brain, kidneys, heart, lung, muscle, and body fat), with the liver having the largest concentration. Adipose tissue had the second greatest concentration, followed by the brain, which had the lowest TCS content.[7]

Metabolism

Triclosan gets metabolized quickly into glucuronide and sulfate conjugates. Triclosan conjugation was demonstrated via in vitro experiments in the presence of human liver microsomes or cytosol, as well as in the skin. TCS is metabolized through Phase I and II processes.[7]

Excretion

In humans, urine excretion is the primary route of elimination, followed by faecal elimination. Rats and mice primarily excrete bile into the stool, whereas guinea pigs excrete the majority of the dose through the kidney. Urinary excretion in people increases within 24

hours after oral intake. The half-life of TCS following oral exposure was found to be 21 hours.[7]

PHARMACOLOGICAL PROPERTIES OF TRICLOSAN

Antimicrobial Activity

Triclosan is a broad-spectrum antimicrobial agent that has been shown to be effective against many gram-positive and gram-negative bacteria. The antimicrobial properties of TCS include antibacterial, antifungal, and anti-biofilm activity, as shown in several studies. Triclosan acts by blocking biosynthesis of bacterial fatty acids. The accumulation of triclosan in the bacterial phospholipid membrane seems to be a chief mode of action of membrane destabilization.[10]

TCS has proven excellent biocidal and long-lasting action on polyester and cotton surfaces for medical textile applications. To a lesser extent triclosan is used in fabrics and plastics, including sportswear, bedding, shoes, and carpets, to prevent the growth of germs that cause odour. Recently the use of TCS in self-disinfecting paints is a viable method for cleaner indoor settings since it prevents bacteria from colonizing wall surfaces.[10]

- **Antibacterial and Antifungal Activity**

TCS works well as an antimicrobial agent against fungi and Gram-positive and Gram-negative bacteria. Cutting boards containing TCS may only offer a hygienic barrier in specific situations such as low humidity, extended exposure duration, and clean settings and not against all bacterial species. It has been demonstrated that TCS exposure decreases E. Coli isolates from urine samples resistance to therapeutic antimicrobials such ciprofloxacin and levofloxacin. A recent study looked at the treatment of denture stomatitis in complete denture wearers using a solution containing 0.15% TCS and this treatment encouraged the remission of denture stomatitis and a reduction in the microbial load of Gram-negative bacteria, including Staphylococcus species and S. mutans, on the intaglio surface of dentures, as well as Candida spp., particularly *Candida albicans.*[10]

- **Antibiofilm Activity**

TCS has demonstrated remarkable biofilm activity. The biofilm formation on the wires used to permanently connect anterior teeth to orthodontic treatment sites in order to keep the teeth from reversing to their pre-treatment positions was examined in a study. The amount of biofilm on the wires was only slightly decreased by using antibacterial toothpastes, but the

biofilm organisms' vitality was greatly decreased. Using a toothpaste containing TCS in combination with a mouthwash containing essential oils produced significant changes in the composition of the biofilm. Simply using toothpaste containing TCS increased adherent S. oralis/ S. mitis, S. sanguinis, and S. mutans prevalence significantly. A recent study on a mouthwash that contains 0.03% TCS shown that the mouthwash inhibits the growth of S. mutans.[10]

- **Antiparasitic Activity**

TCS exhibited antileishmanial activity against *Leishmania donovani* in both in vitro and ex vivo drug testing conducted on promastigotes and amastigotes with a half minimal inhibitory dose (IC50) of 30 µM. Research conducted in silico revealed that TCS's interaction with L. donovani enoyl-acyl carrier protein reductase was responsible for this effect. The antitubercular pharmacological activity of TCS has been investigated and it has been demonstrated to directly block InhA, hence suppressing mycobacterial growth at low concentrations. TCS has been shown in multiple tests to be effective in treating malaria by targeting two distinct targets. TCS targets P. vivax and wild-type and pyrimethamine-resistant P. falciparum dihydrofolate reductases, which are traditional targets for the parasite's blood stage.[10]

TOXIC EFFECTS OF TRICLOSAN

Triclosan, a common antimicrobial agent, has been used in various personal care products, including deodorants, due to its ability to reduce or prevent bacterial contamination and growth.[9]

The products are

- Soaps
- Deodorants
- Dental Care
- Cosmetics
- Other personal care products.[9]

The toxic effects of triclosan in deodorant sticks are.

1. **Acute Toxicity**

Acute toxicity refers to the harmful effects that occur shortly after exposure to a toxic substance.[9]

For triclosan, acute toxicity are the following.

Oral Toxicity

- Humans: Ingestion of triclosan even in small amounts, can lead to symptoms such as nausea, vomiting, diarrhoea, gastrointestinal discomfort.[9]
- Animals: Studies on rats have shown that the oral LD_{50} (lethal dose for 50% of the population) of triclosan is around 4,300 to 5,000 mg/kg body weight, indicating low to moderate toxicity.[9]

Dermal Toxicity

- Triclosan is not highly toxic when absorbed through the skin. However, it can cause skin irritation and allergic reactions in some individuals, particularly with prolonged or repeated exposure. Symptoms may include redness, itching, and swelling.[9]

Inhalation Toxicity

- Triclosan is not commonly encountered in a form that can be inhaled, but if aerosolized (e.g., in sprays) it can cause respiratory irritation.[11]

Symptoms may include coughing, wheezing and shortness of breath.[11]

Ocular Toxicity

- Direct contact with the eyes can cause irritation, redness and watering.Triclosan is not typically associated with severe ocular damage, but it can be uncomfortable and painful upon contact.[11]

Acute Toxicity in the Environment

- Aquatic life: Triclosan is highly toxic to aquatic organisms. It can cause acute toxicity in fish and invertebrates at relatively low concentrations, leading to symptoms like reduced mobility, abnormal behaviour, and mortality.[11]
- Plants and Microorganisms: Triclosan can inhibit the growth of algae and other aquatic plants, disrupting the balance of ecosystems.[11]

2. Sub-Chronic Toxicity

Sub-chronic toxicity refers to the adverse effects of a substance resulting from repeated exposure over an intermediate duration, typically ranging from one month to less than three months.[9]

The sub-chronic toxicity of triclosan are the following:

- **Liver Enlargement and Pathology**: Triclosan exposure has been associated with increased liver weights and hepatocellular hypertrophy. These effects suggest liver stress and adaptive responses to detoxify triclosan.[9]
- **Thyroid Hormone Disruption**: Triclosan can alter thyroid hormone levels, including reductions in serum thyroxine (T4) and increases in thyroid-stimulating hormone (TSH). These changes indicate potential disruption of the hypothalamic-pituitary-thyroid axis.[9]
- **Kidney and Reproductive Organ Effects**: Triclosan results in histopathological changes in the kidneys and reproductive organs, although these effects are less consistent.[9]
- **Endocrine Disruption**: Triclosan is a suspected endocrine disruptor. Prolonged exposure has shown potential to interfere with hormone regulation in both animal and in vitro studies.[9]

Key findings include

i. **Oestrogen and Androgen Activity**: Triclosan has been shown to have weak estrogenic and anti-androgenic activities. This means it can mimic oestrogen to a minor extent and inhibit the activity of androgens, which could impact reproductive health and development.[9]
ii. **Developmental and Reproductive Activity**: Continuous exposure to triclosan during critical periods of development has been associated with developmental delays and reproductive system abnormalities in animal models.[9]

- **Immunotoxicity**

i. **Immune System Effects**: Sub-chronic exposure to triclosan has been linked to immuno-toxic effects, such as altered immune cell counts and function. For example, some studies have observed changes in spleen and thymus weights, as well as variations in white blood cell counts, suggesting potential immunosuppressive effects.[9]

- **Human Health Implications**

i. **Liver and Thyroid Health**: Prolonged exposure to triclosan through personal care products may cause risks to liver and thyroid function, especially in susceptible populations such as children and pregnant women.[9]
ii. **Potential Carcinogenicity**: Chronic exposure and the resulting endocrine disruption and liver pathology could potentially increase the risk of carcinogenic outcomes.[9]

3. Skin Sensitization

Skin sensitization refers to the process by which exposure to a substance can lead to an allergic reaction upon subsequent exposures. Triclosan, an antimicrobial agent found in many personal care products, has been evaluated for its potential to cause skin sensitization. Triclosan is considered to have a low skin sensitizing potential. Skin sensitization tests have been conducted in guinea pigs.[11]

Animal Studies

- **Guinea Pig Maximization Test**: The Guinea Pig Maximization Test (GPMT) is a well-established method used to assess the skin sensitization potential of chemicals. This test has shown that triclosan can cause skin sensitization in guinea pigs. When formulation containing triclosan is applied onto the skin of guinea pig and kept for observation for 24-48hrs and the site is observed for signs of an allergic reaction such as redness, swelling, and erythema.[11]
- **Local Lymph Node Assay (LLNA):** The Local Lymph Node Assay (LLNA) is an in vivo test used to assess the potential of a chemical substance to cause skin sensitization. It is an alternative to traditional guinea pig tests, such as the Guinea Pig Maximization Test (GPMT). Triclosan has demonstrated potential to induce sensitization in this test, which measures lymphocyte proliferation in the lymph nodes following exposure.[11]

Human Studies

- **Patch Tests**: Clinical patch testing in humans has shown that triclosan can cause contact dermatitis in sensitized individuals. Repeated exposure to triclosan in products like deodorants, soaps, and lotions can lead to allergic reactions in sensitive individuals.[11]

4. Reproductive/Developmental Toxicity

- **Reduced Fertility**: Prolonged exposure to high doses of triclosan has been associated with reduced fertility in both male and female rodents.[11]
- **Altered Hormone Levels**: Triclosan exposure can alter levels of reproductive hormones such as testosterone and oestrogen, affecting reproductive organ development and function.[11]
- **Histopathological Changes**: Changes in the histology of reproductive organs, including reduced testicular and ovarian weights and abnormalities in sperm morphology and motility, have been observed.[11]

- **Foetal Development**: Following are the foetal development changes after exposure to triclosan.

a. **Growth and Morphology**: Offspring of rodents exposed to triclosan during pregnancy have shown reduced foetal weight, delayed bone development, and other morphological changes.[11]

b. **Neurodevelopmental Effects**: Triclosan shows some neurodevelopmental impacts, such as altered behaviour and change in brain structure in offspring, but these impacts are less consistent.[11]

c. **Oxidative Stress**: Triclosan induce oxidative stress, which can damage cells and tissues, contributing to reproductive and developmental toxicity.[11]

d. **Gene Expression**: Triclosan can affect the expression of genes involved in reproductive and developmental processes.[11]

5. Genotoxicity and Mutagenicity

- **Genotoxicity**: It is the ability of a substance to cause damage to the genetic information within a cell, leading to mutations, which may result in cancer or other health issues.[11]
- **Mutagenicity**: It refers to the ability of a substance to induce genetic mutations, which cause changes in the DNA sequence of a cell.[11]

These studies included in vitro test systems (bacterial reverse mutation assays, genetic mutation in yeast, gene mutation in mouse lymphoma cells, chromosomal aberration test in Chinese hamster bone marrow cells and sex-linked recessive lethal test in *Drosophila melanogaster*) and in vivo assays (mouse-dominant lethal and spot tests, chromosomal aberration test in Chinese hamster, micronucleus test in Chinese hamster bone marrow cells, and chromosomal aberration test in mouse germinal epithelium).[11]

6. Carcinogenicity

It refers to the ability of a substance to cause cancer by inducing genetic mutations or promoting cellular environments conductive to cancer development. The carcinogenicity action of triclosan involves a combination of endocrine disruption, oxidative stress, activation of nuclear receptors, and interference with normal cellular processes.[11]

- **Endocrine Disruption**

Triclosan is known to act as an endocrine disruptor. It can interfere with the normal functioning of hormones, particularly thyroid hormones, and sex hormones like oestrogen

and testosterone.[11] Disruption in these hormonal pathways can lead to various adverse effects, including.

a. **Altered Hormone Levels**: Changes in hormone levels can influence cell growth and differentiation, potentially leading to uncontrolled cell proliferation, a hallmark of cancer.[11]
b. **Receptor Modulation**: Triclosan can bind to hormone receptors, altering their normal activity and leading to abnormal cellular responses that could contribute to carcinogenesis.[11]

- **Oxidative Stress**

Triclosan has been shown to induce oxidative stress, which involves an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these harmful by-products.[11] Oxidative stress can lead to.

a) **DNA Damage**: ROS can cause mutations in DNA, which, if not properly repaired, can result in the initiation of cancer.[11]
b) **Inflammation**: Chronic oxidative stress can lead to inflammation, which is a known risk factor for cancer development.[11]

- **Activation Of Nuclear Receptors**

Triclosan can activate certain nuclear receptors, such as the constitutive androstane receptor (CAR) and pregnane X receptor (PXR). These receptors play a role in regulating the expression of genes involved in detoxification processes in the liver.[11] Activation of these receptors can lead to.

a) **Liver Hypertrophy**: Increased liver size due to the proliferation of liver cells, which can be a precursor to tumour formation.[11]
b) **Increased Metabolic Activity**: Enhanced metabolism of xenobiotics (foreign chemicals) can result in the generation of reactive intermediates that may be carcinogenic.[11]

- **Cellular Proliferation and Apoptosis**

Triclosan exposure has been associated with alterations in cell cycle regulation and apoptosis (programmed cell death).[11]

Key effects include.

a) **Inhibition of Apoptosis**: By inhibiting apoptosis, triclosan can allow damaged cells to survive and proliferate, increasing the risk of cancer.[11]

b) **Promotion of Cell Proliferation**: Increased cellular proliferation can lead to the expansion of mutated cells, contributing to tumour growth.[11]

- **Interaction with Environmental Contaminants**

Triclosan can interact with other environmental contaminants to form potentially carcinogenic compounds.

a) **Formation Of Dioxins**: When exposed to sunlight and chlorine, triclosan can degrade into dioxins, some of which are known carcinogens. These dioxins can accumulate in the environment and enter the food chain, posing long-term health risks.[11]

CONCLUSION

Triclosan (TCS) is a unique, synthetic, phenolic antimicrobial agent with a long history of human use. TCS is highly recognised in commerce and healthcare owing to its antibacterial, antiviral and antifungal properties. Triclosan exerts its activity by intercalating into the bacterial cell membrane and disrupt the membrane activities. It is used against several tooth related disease due to its antibiofilm activity. Even though it is a widely used antimicrobial agent, due to its extensive use numerous researches conducted reported that triclosan shows several toxic effects including acute toxicity, sub chronic toxicity including liver enlargement, thyroid hormone disruption, endocrine disruption, genotoxicity and mutagenicity.

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