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ORGANOTIN COMPOUNDS: APPLICATIONS AND THEIR TOXICITY

Namita Gandhi[1*], Syed Kashif Ali[2], Afraim Koty[3], Mukul Sharma[4] and Sajid Ali[5]

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Abstract

More organotin compounds exhibit widespread industrial and agricultural applications. These applications include polyvinyl chloride stabilizers, agrochemicals, biocides, and wood. These compounds are also found to have biological activities such as antimicrobial and antitumor. The overuses of these chemicals lead to their bioaccumulation in the ecosystem and thus pose harmful effects on animals, human and environmental health.

Keywords: Organotins, Stannate, Toxicity.

[1]Department of Chemistry, Deshbandhu College, University of Delhi, Kalkaji Main Rd, New Delhi-110019, India

[2]Department of Chemistry, Faculty of Science, Jazan University, Jazan P.O. Box 82817, Saudi Arabia

[3]Department of Chemistry, College of Science, Mahliya Jazan University, Saudi Arabia

[4]Center of Environmental Research and Studies, Jazan University, 42145, Saudi Arabia

[5]Department of Chemistry, Krishna Engineering College, Mohan Nagar, Ghaziabad-201007, India

Authors for correspondence: namitag.111@gmail.com

1. INTRODUCTION

Organotin compound or stannate is defined as the inorganic compound that contains a carbon-tin bond (minimum one in number), which can be represented by R_nSnX_{4-n} (n is 1 to 4, R is an organic group, and X is halogen, hydrogen or a group bonded to tin via O, N, H, etc. Since Frankland isolated a sample of diethyltin di-iodide in 1849, there has been a prolonged history of organotin chemistry [1]. In 1852, Lowich wrote about how alkyl halides react with a tin- sodium alloy to form alkyl tin compounds [2]. Most people consider the final article to be the first in organotin chemistry. By 1935, there were hundreds of articles on organotin chemistry in the literature. At the time, the development of organotin chemistry was significantly influenced by German scientist Krause, United States scientist Kraus, and Russian scientist Kozeshkov.

Tin exists in oxidation states (+2 and +4), where the Sn(II) is less stable in comparison to Sn(IV) compounds. It was considered that Sn is 4-coordinated until 1963 XRD and NMR studies showed the existence penta- and hexa-coordinated geometries for Sn its complexes [3,4]. The bent, tetrahedral (four-coordinated), pentagonal bipyramidal (five-coordinated), and hexagonal (six-coordinated) geometries of tin complexes are shown in figure 1.

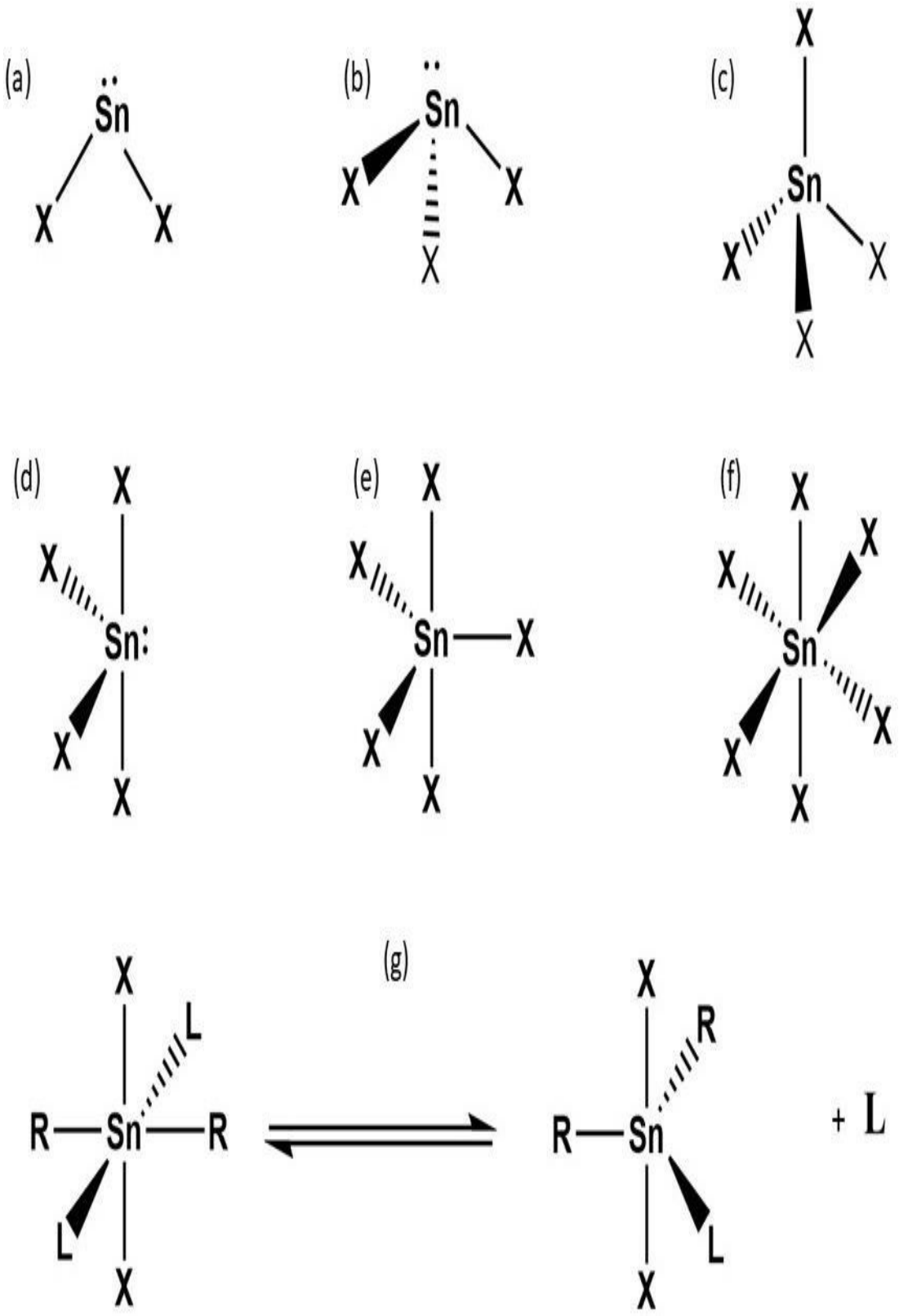

Figure 1: The (a) bent, (b) tetrahedral, sp^3 (four-coordinated), (c) pentagonal bipyramidal, sp^3d (five-coordinated), and (d) hexagonal, sp^3d^2 (six-coordinated) geometries of tin complexes. (g) interconversion of pentagonal bipyramidal and hexagonal geometries

The resurgence of organotin chemistry was brought about by the discovery of organotin compounds for industrial uses such as agrochemicals, wood preservatives, stabilizers, flame retardants and biocides, these developments were influenced by Van der Kerk and his Dutch colleagues [5,6]. Organotin chemicals have a variety of functions and applications [7,8]. In both industry and agriculture, organotin chemicals are used as antifungal biocides [9,10]. Significant antifungal action is shown in salicylaldehyde and phthalic acid derivatives of triphenyltin (IV) [11,12]. Recently, interest in organotin (IV) compounds has increased because of their potential use in medicine as anticancer agents [13]. Additionally, when coupled with di- and triorganotins, carboxylate ligands formed a number of antitumor-active compounds [14]. According to Hubert et al. [15], antitumor-activity of tin compounds is due to the hydrolytic breakdown of liable coordination sites around the tin atom. On the other hand, thioamide-organotin complexes have shown notable anticancer activity, which is due to ligand type rather than compounds geometry [16-19]. Tri-substituted organotin species can also be used as wood preservatives, agricultural pesticides, and antifouling coatings for ships due to their q properties [20]. Organotin compounds exhibit a wide range of applications such as catalysis, paint additives, biocides, glass, etc. This led to the entrance of organotin compounds into the food chain and their bioaccumulation which can be quite toxic to humans and animals causing dermal toxicity, neurotoxicity, renal toxicity etc [21]. This review summarizes the various applications of organotin compounds and their toxicity in the current and future.

2. Applications of Organotin Compounds:

Organotin compounds show a significant expansion in commercial applications as a result of research and rising interest in the 1950s, especially by Van der Kerk and colleagues. The various applications of organotin compounds are summarized in table 1. Organotin compounds can be used as biocides in industry and agriculture, as polymer stabilizers, and as catalytic agents in a number of chemical processes [22]. Figure 2 is a pictorial representation of the wide range of applications of organotin compounds.

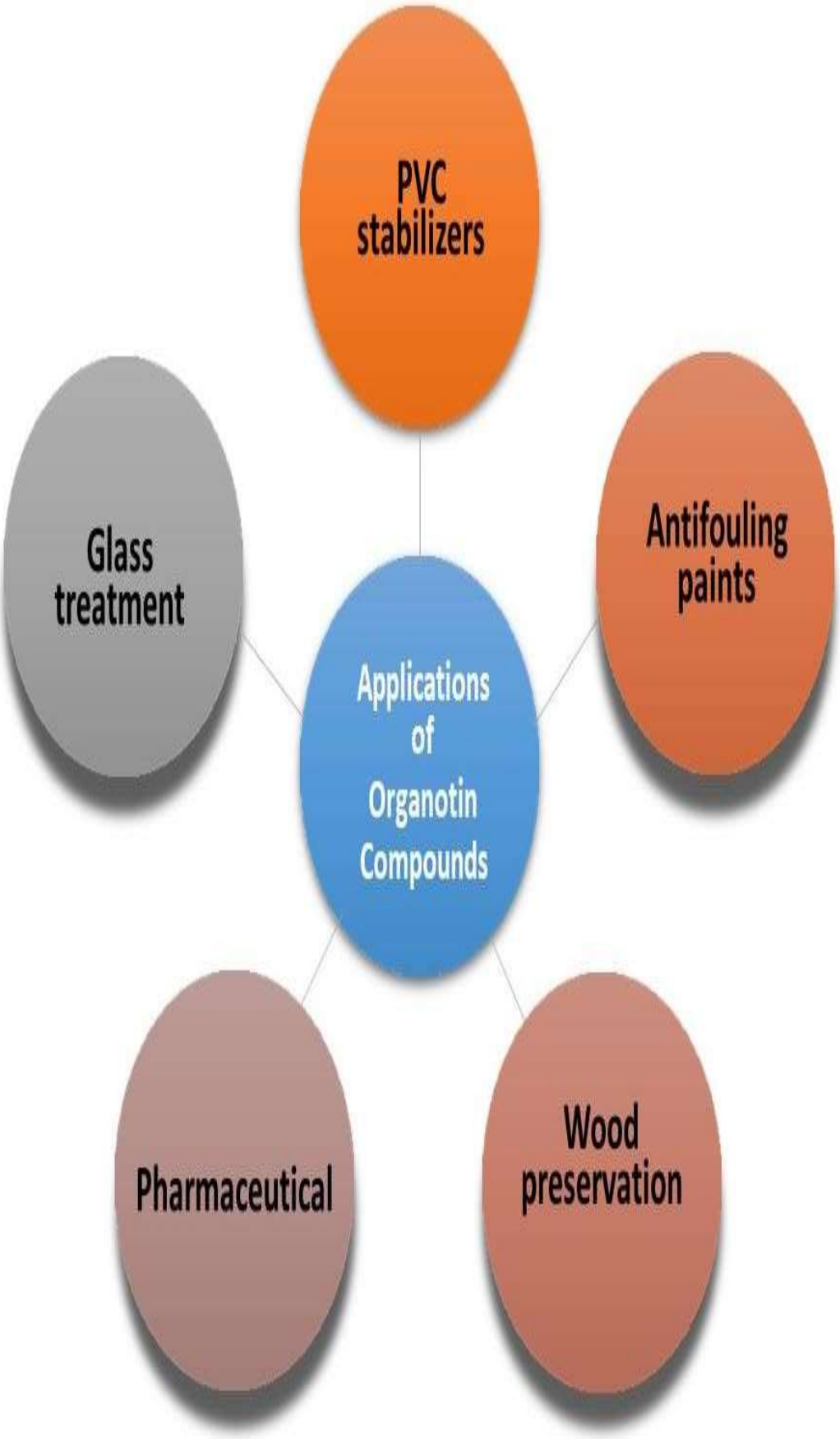

Figure 2: Pictorial representation of applications of organotin compounds

Table 1: The various applications of organotin compounds

S. No.	Compounds	Applications	References
1.	Monobutyltin (MBT)	• PVC Stabilizer • Precursor for glass treatment	[30, 34]
2.	Dibutyltin (DBT)	• PVC Stabilizer • Catalyst	[22, 30]
3.	Tributyltin (TBT)	• Antifouling Paints • Water Paints • Wood treatment	[26, 32]
4.	Triphenyltin (TPT)	• Antifouling Paints • Agrochemical Pesticides	[26]

2.1. Pharmaceutical applications

Metal ions are widely recognized for their pharmacological uses, such as organotin(IV) compounds, which are utilized as efficient biological agents [23]. Metal ions also play a significant part in a number of *in vivo* physical & chemical processes. The efficacy and mode of action of organotin(IV) have been studied where it interacts with different body components like ATPase and haemoglobin [24]. Novel medications are being developed for diverse applications, and thus different types of ligands coordinated have been tailored and coordinated with tin, showing variable geometries have been created. Organotin (IV) complexes have been used as amoebicidal, antibacterial, antifungal, anticancer, and antimalarial medicines due to their potential biological action [25].

2.2.Marine antifouling:

Antifouling paints help in controlling the growth of marine organisms such as seaweed, tubeworms, and barnacles on ships and boats surfaces. Antifouling coatings come in two distinct varieties: those with and those without TBT. There are several TBT- free paint alternatives [26]. In place of copper oxide, which had previously been used to reduce fouling development, triphenyltin and tripbutyltin compounds (oxide, chloride, acetate, etc.) were introduced in the 1960s. As the organotin ingredient eventually diffused out of the hull paint (also known as "free association paints"), it provided protection for 18–24 months. Because the antifoulant had to diffuse to thesurface from deeper inside the paint at

that period, the rate of release dropped [27].

2.3.Stabilization of PVC:

After polyethene and polypropylene, PVC (polyvinyl chloride) is one of the most often used commercial polymers in terms of manufacturing. Its uses in-home items like raincoats, conduits, wallpaper, water sewage & drainage pipes, window frames, and toys, [28], packaging (food and blood-containing bags), decorating, and wire coating, to name a few, are also widespread [29]. Although organotin is inexpensive and non-flammable, but it is not stable at high temperatures and in light which is related to serious environmental and health risks. Contrarily, it is widely known that PVC degrades under these circumstances, releasing successive hydrogen chloride gases (autocatalytic dehydrochlorination) that move up the chain in a zipper-like pattern to produce an extended conjugated polyene. Organotin compounds have extensively been used as stabilizing agent for PVC [30]. Examples of a few earlier times commercial stabilizers are dibutyltin dilaurate, maleate, and methyl maleate. Typically, 0.5-2% of the total weight of the polymer is loaded with the stabilizer. The most effective organotin stabilizer gives two-fold stability to PVC over the long term as well as in the short-term during processing, and the resultant polymer is transparentand colorless [31].

2.4. Protective Coating:

Various woods have been successfully preserved against bacteria, fungi, insects, and wood-boring marine critters in testing. Tributyltin (IV) complexes are utilized for wood preservation because they have good biological actions against microorganisms. One of the most essential qualities of the organotin compounds is that they do not give the treated wood any color or odor. In order to prevent microbial damage, the wood is treated with organotin (IV) compounds in a vacuum. This results in the attachment of organotin (IV) that gets bonded with cellulosic hydroxyl groups [32].

The atmospheric Pressure Chemical Vapor Deposition (APCVD) technique has been employed to prepare transparent and electrically conductive thin coatings on the surface of glass [33]. The coating not only offers oxidation resistance, thermal stability, and strength but also reduces heat loss through the glass. Tin oxide for coating glass has been done for various glass surfaces such as windshields, display screens, security glasses, etc. to provide low electrical and high chemical resistance [34].

2.5. Tributyltin compounds as Biocides:

Due to early work by Luijten and Kaars Sijpesteijn at Utrecht, the use of tributyltin compounds as biocides, notably bis(tributyltin)oxide, is now widespread and quickly increasing field of use [35]. The first study started in 1950, and concentrated on the antifungal and antibacterial activities of triorganotin compounds like tributyl- and triphenyltins [36]. Until recently, around 12,000 tonnes of mercury in the form of organomercurials were utilized yearly for a variety of biocidal purposes throughout the world [37].

3. Organotin Compounds Toxicity:

The major usage of organotin compounds (OTs), which are synthetically persistent organometallic xenobiotics, is in the production of PVC in the plastics industry [38,39]. The management of extracellular fluid osmolality, volume, electrolytes, and acid-base balance are only a few of the critical functions that the kidneys play in maintaining bodily homeostasis [40]. Furthermore, the kidneys contain the majority of the enzymes that are frequently utilized to degrade xenobiotics, including environmental toxins [41]. As a result, such medications frequently increase the kidneys' susceptibility [42]. In fact, renal xenobiotic exposure causes aberrant renal function [43].

The organotin is also used as antifoulants and has resulted in non-targeted toxicity in marine animals. TBT was found to cause abnormalities in marine species such as oysters, mussels, etc. and thus their use was banned after January 2008 [44]. The wide applications of organotin compounds also affected humans and it was found that triorganotin compounds affect the biochemical and physiological systems of humans. The mode of action of these toxic compounds depends on the species and the route of administration [45]. Organotin chemicals exhibit liver and reproductive system toxicity as well as their neurotoxic effects, which include a variety of neurological symptoms [46-48].

3.1.Renal Toxicity

In 1985 while doing research on the biological effects of organotins, the toxic effects of these chemicals on liver came into notice. It was observed that organotins can affect the activities of renal enzymes in rats [49]. The same investigation also revealed enzymatic changes in the liver and brain [49]. Prior to that, rats exposed to TMT were shown to have hydronephrosis and renal tubule vacuolar degeneration [50]. It has been demonstrated that not only blood urea nitrogen levels elevate on TMT exposure but it also leads epithelial vacuolization as well as tubular dilatation [51]. These

observations, however, were at odds with research that claimed there was no appreciable renal damage attributable to organotins exposure [52,53]. Trimethyltin was found to be nephrotoxic in nature during two trials where it was orally fed to rats [54]. Another organotin that has been explored is tributyltin (TBT). Rats received weekly dosages of low sub-chronic oral TBT exposure (2.0 or 6.0 mg/kg) for more than 30 or 60 days, and the kidney morphology was unaffected [55]. On the other hand, in a 30-month chronic toxicity study in rats, a greater doseof TBT (50 mg/kg food) led to lower renal function weight [56]. Only a few studies examined TBT's impact on renal morphology, despite studies demonstrating its danger [57,58]. Rats were given a low and unusual dose of TBT (5 mg/kg), Mitra etal. demonstrated morphological changes: the glomeruli appeared enlarged with increased capsular space. Reactive oxygen species (ROS) and oxidative stress wereelevated in renal tissue even though kidney function was unaffected in this particular investigation. TBT's toxicological renal effect is so convoluted and conflicting. Additionally, TBT was found to cause higher proteinuria levels and a decreased glomerular filtration rate (GFR) in female rats exposed to it (100 ng/kg/day) for 15 days [59]. Additionally, tubulointerstitial collagen deposition and increased glomerular tuft area were noted as aberrant renal structural features. TBT also caused a buildup of tin renal tissue linked to increased renal oxidative stress and apoptosis,which resulted in impaired renal function [59].

Organotin exhibits the inhibitory action on the activities of enzymes H+/K+-ATPase and Na+/K+-ATPase, resulting in hypokalemia (increased K+ leakage) and acidosis (decreased H+ secretion). These imbalances lead to an increase in urinary pH and thus raise the risk of kidney stone formation [60]. The mode of action of organotin compounds on renal intercalated mammalian cells is presented in Figure 3.

In actuality, Syrian hamsters given oral TBT for 65 days showed not only abnormalities in the testis and liver but also in the kidneys. It was found that the TBT doses lead to elevation of bilirubin, creatinine, and uric acid levels in the animal [61]. The fact that TBT therapy reduced the activities of catalase, superoxide dismutase, glutathione peroxidase, vitamins C and E, and enhanced lipid peroxidation in the same organs was evidence of the critical oxidative stress-relateddamage induced by TBT activity [61].

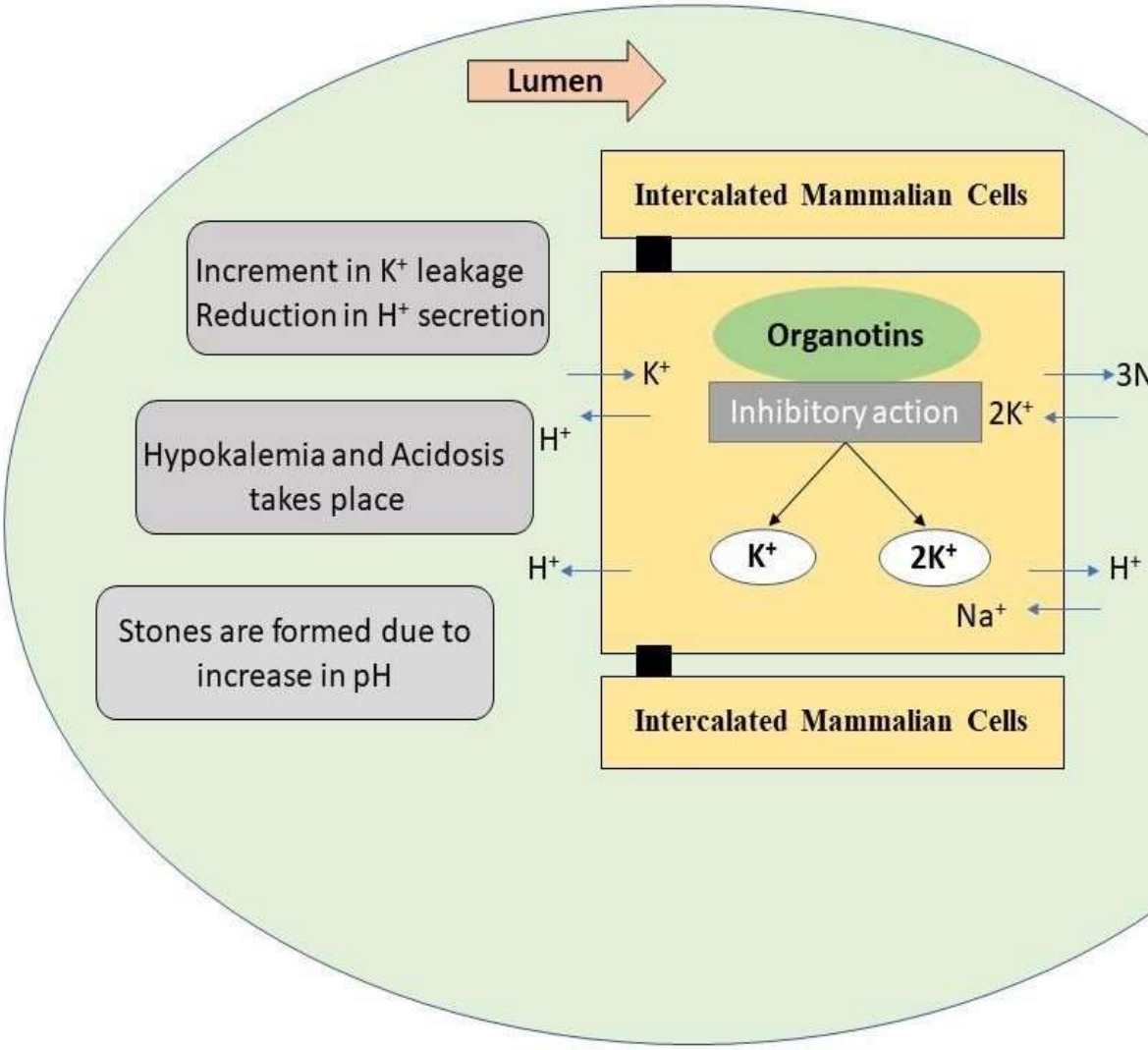

Figure 3: The mode of action of organotin compounds on renal intercalated mam

TBT induces the generation of ROS, which impairs cellular performance and causes tissue damage [61]. It was observed that TBT causes severe renal function impairment and renal inflammation in female rats. It also causes fibrosis, and results in increased glomerular tuft area, it is also responsible for the reduction in GFR and increment of proteinuria. According to a study, TBT's results in renal failure are caused by levels of oxidative stress and apoptosis. The TBT was fed to male Wistar rats in modest doses for a month and it was found TBT not only affected the liver and lungs but also kidneys by the generation of ROS. After receiving 1 mg/kg of TBT for 30 days, the kidney in this examplehad a 1.4-fold rise in the levels of ROS, demonstrating a substantial correlation between TBT exposure and the development of renal ROS [62]. ROS generation contributes to the organotins-induced damage to the kidney, brain, and cardiovascular systems [63,64]. As a result of oxidative damage, depolarization of the mitochondrial membrane, and DNA damage cortical cell death occurs. In the hippocampi and hypothalamus of the rats exposed to TBT, increased oxidative stress results in inflammation and a fibrotic process [65]. Female rats were fed on TBT for 15 days (100 ng/kg/day), and a rise in ROS level was observed in the animals. The formation of Fibrosis in the aortic rings was also observed which resulted in functional and morphological dysfunctions [66,67]. From the literature, it has been inferred that organotins-induced oxidative stress is the primary reason behind renal failure and other toxic effects on the kidney [68,69].

3.2. Other Toxic Effects

After being exposed to interior paints containing tin, workers handling organotins such as dibutyl- and tributyltin have complained of eye discomfort, skin rashes, and mucus irritation [70-72]. The most common signs of organotin toxicity in humans include memory loss and sleeplessness, along with other symptoms like death [71]. Trimethyltin exposure in humans has also been linked to neurotoxicity [70]. Spray triphenyltin acetate based biocides have been known to show liver damage in many users [70]. Exposure to a solution containing 3:1 ratio of dimethyltin trimethyltin for 90 minutes over three days leads to the death of one worker and leaving the rest in hospital [73]. Toxicity organotin compounds depend on the type of complex like triethyltin is toxic to myelin whereas trimethyltin is toxic to neurons in limbic system [74]. Less organic groups on the tin often results in a decrease in toxicity.

Toxicity for mono- and di-methyl tins including butyltins show tissue targeted toxicity. Among di-organotin compounds, di-butyltin is the least harmful, whereas di-methyltin is the most poisonous for brain cells [75]. The organotins like mono-butyltin and di-butyltin demonstrated genotoxicity in the SOS chromotest, whereas mono- and di-methyltin did not [76]. It is reported that only di-butyltin is positive in *Salmonella typhimurium* TA98. The mono-butyltin and dibutyltin both were found to be mutagenic in nature for *Salmonella typhimurium* TA100. At the same time, mono-methyltin and di-methyltin exhibited no significant mutagenicity [77].

Research on the sub-chronic and chronic effects of organotin chemicals in rodents is often lacking, however, research on the developmental toxicity of butyltins has been conducted [78]. Organotin has been linked to immunological [79] and neurological [80] system vulnerabilities, but hepatic (liver) and renal (kidney) toxicity is often less reported.

The organotin complexes are responsible for serious ill effects on human and animal health. Organotin compounds, which serve as EDCs, are linked to endocrine and physiologic disruptor effects and have a variety of biological impacts [81]. Organotin and nuclear receptors (glucocorticoid receptors and retinoid X receptor subtypes) binding is also demonstrated where the resulting complex activated the transcription of target genes [82,83]. This mechanism changes protein expression and encourages mitochondrial and cellular failure. Oxidative stress is the primary mechanism by which OTs harm tissue in several organs, including the kidneys, testicles, liver, lungs, adrenal gland, pituitary, and brain [84-86]. TBT toxicity results in the generation of reactive oxygen species further, initiating lipid peroxidation, and finally, cell death [87]. Additionally, it impairs antioxidative cell defence systems (both enzymatic as well as a non-enzymatic system, for example, catalase, and vitamins C and E). dibutyltin diacetate is reported for its carcinogenic effects [88]. Tributyltin compounds are known for their endocrine disruptor effect [89]. Mode action of organotin-induced neurotoxicity in humans. TBT lead to the reduction in ATP levels and Mfn1 resulting in mitochondrial dysfunction and fragmentation, thus leading to ERK phosphorylation, and OTX2 suppression, which is a marker of neurogenesis [90]. The pictorial representation of the mechanism of cation of TBT-induced neurotoxicity in humans is shown in figure 4.

3.3 Cardiovascular toxicity

Organotins not only have neurotoxic effects but are also known for interfering with heme metabolism and the functioning of the cardiovascular system. [91] Stoner et al. reported that mono-, di-, tri- and tetraalkyltin compounds lead to vasodilatation in rabbits during acute and chronic experiments. The triethyltin was observed to be most toxic and produced muscular convulsions, tremors, and animal death. [92]. The in vitro effect of n-butyltin on hemolysis of red blood cells of rabbits was found to be more than that of dibutyltin, while Bu_4Sn did not show any effect. Dibutyltin-treated mice provided therapeutic and preventive protection against BAL, while in Bu_4Sn-treated animals, BAL lead to a slight delay in death time. [93]. The organotins compounds are also known for affecting the cardiovascular and respiratory systems [94].

4. Future aspects and conclusions

More organotin compounds exhibit widespread industrial and agricultural applications. These applications include polyvinyl chloride stabilizers, agrochemicals, biocides, and wood. These compounds also have biological activities such as antimicrobial and antitumor. The organotin compounds are also reported to have toxicity associated with them. Their toxic effect on the kidney, heart, muscles, nervous system and respiratory system is well known. The overuse of these chemicals lead to their bioaccumulation in the ecosystem and thus pose harmful effects on animals, human and environmental health. Further focused research has to performed in order to understand the effects of organotins on animal and human life. Additionally, toxicity and the mode of action of organotins need to be analyzed well before compound is used for any kind of application.

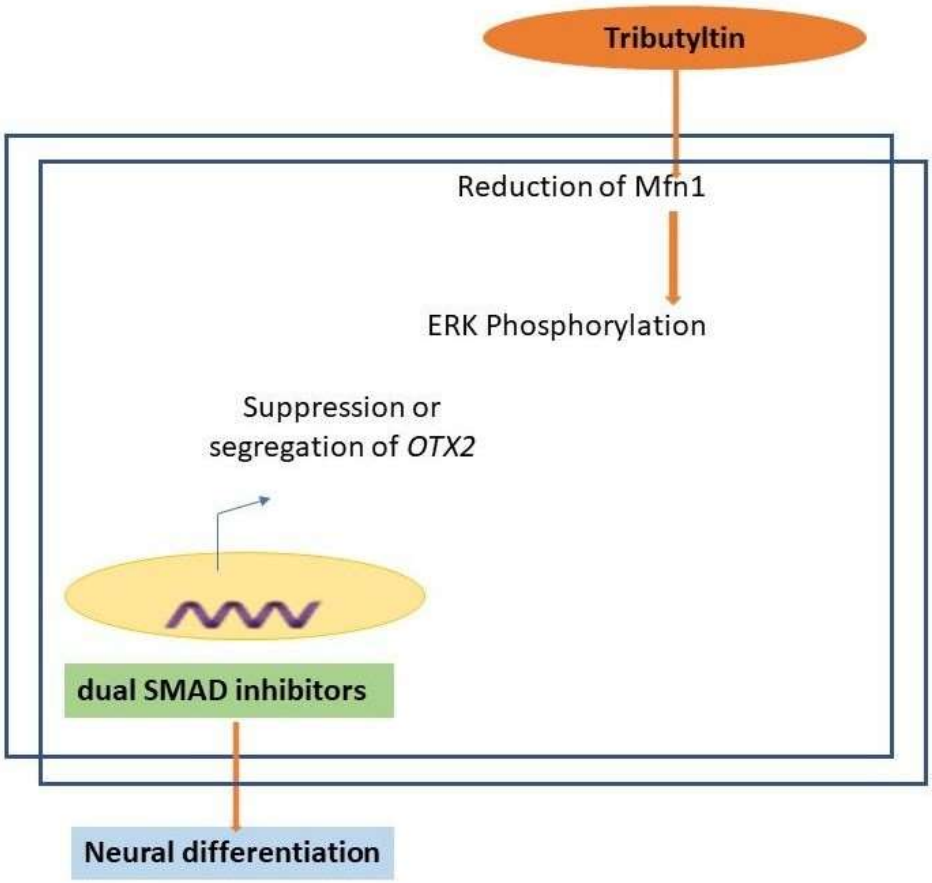

Figure 4: The pictorial representation of the mechanism of cation of TBT-induced neurotoxicity in humans

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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