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**REVIEW**

# Organotin compounds: Toxicology and biomedicinal applications

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**The toxicology and biomedical aspects and applications of organotin compounds are discussed. Factors affecting toxicity are considered first and then the mechanisms of toxicity are described and assessed. A review of the main biomedical applications then follows, covering biochemical, agricultural and other biocidal uses, and recent developments in the field of anticarcinogenesis.**

**Keywords: Organotins, toxicity, mechanisms, applications**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ADP | Adenosine diphosphate |
| ATP | Adenosine triphosphate |
| Bu | Butyl |
| cAMP | Cyclic adenosine monophosphate |
| CNS | Central nervous system |
| Cy | Cyclohexyl |
| Cys | Cysteinyl |
| Et | Ethyl |
| GABA | γ-Aminobutyric acid |
| His | Histidinyl |
| I.p. | Intraperitonial |
| Leu | Leucinyl |
| Me | Methyl |
| Met | Methionyl |
| $mg\,l\,h^{-1}$ | Milligram per inhalation hour |
| $mg\,kg^{-1}$ | Milligram per kilogram |
| $NAD^+$ | Nicotinamide adenine dinucleotide |
| $NADP^+$ | Nicotinamide adenine dinucleotide phosphate |
| Oct | Octyl |
| Ph | Phenyl |
| Phe | Phenylalanyl |
| Pr | Propyl |
| PyO | Pyridine oxide |
| TBTF | Tributyl tin fluoride |
| TBTO | Tributyl tin oxide $(Bu_3Sn)_2O$ |
| Trp | Tryptophanyl |

## INTRODUCTION

Since the studies of Buckton on the toxicity of alkyltin compounds on mucous membranes in 1858,[1] bioorganotin chemistry has seen an upsurge of research activity as evidenced by the number of research papers, review articles and books dealing with almost every aspect of it.[2–5]

Though the first organotin compound found application in 1929 by an American company,[6] the toxic effects of organotin compounds were not studied systematically. In 1954, the first disastrous attempt was made to use organotin compounds in medicine for treatment of *Staphylococcal* infections and the subsequent death of 102 people[7] severely hampered the growth of the applications of organotin compounds. In the early 1950's Van der Kerk and Luijten[8] laid the foundation of bioorganotin chemistry by systematically exploring the biological properties of organotin compounds. The rapid growth of this new field was assisted by the discovery of anticancer activity in platinum compounds in 1969. Before this, inorganic chemists were largely excluded from medical research and medical scientists usually considered metal compounds as poisons. Now after 30 years, organotin compounds have found applications in a very broad spectrum and the day is not far away when their applications may only be limited by the imagination of chemists.

This article is written with the view of giving newcomers to this field an insight into the present state of knowledge and current trends in the area.

The great majority of organotin compounds are toxic to biological systems. However, toxicity of a compound is the basis for its chemotherapeutic and other biocidal applications and as such will be dealt with first, followed by applications.

## TOXICITY

Many articles have appeared recently dealing with various aspects of organotin toxicity and toxicity data for a number of compounds has been compiled.[9-16] Various factors determine the toxicity of organotin compounds. Though their relative importance remains to be completely elucidated, they can be summarised as:

## Factors effecting toxicity

### Introduction of an organic group

Organotin derivatives are substantially more toxic compared to their inorganic tin analogues. Smith et al.[17] have suggested that the metal is probably non-ionized at physiological pH, while oxides are unreactive.

### Nature of organic group

Alkyl groups are generally more toxic than aryl groups,[18,19] and the toxicity passes through a maximum as the chain length of the *n*-alkyl group is steadily increased, and decreases thereafter.[20]

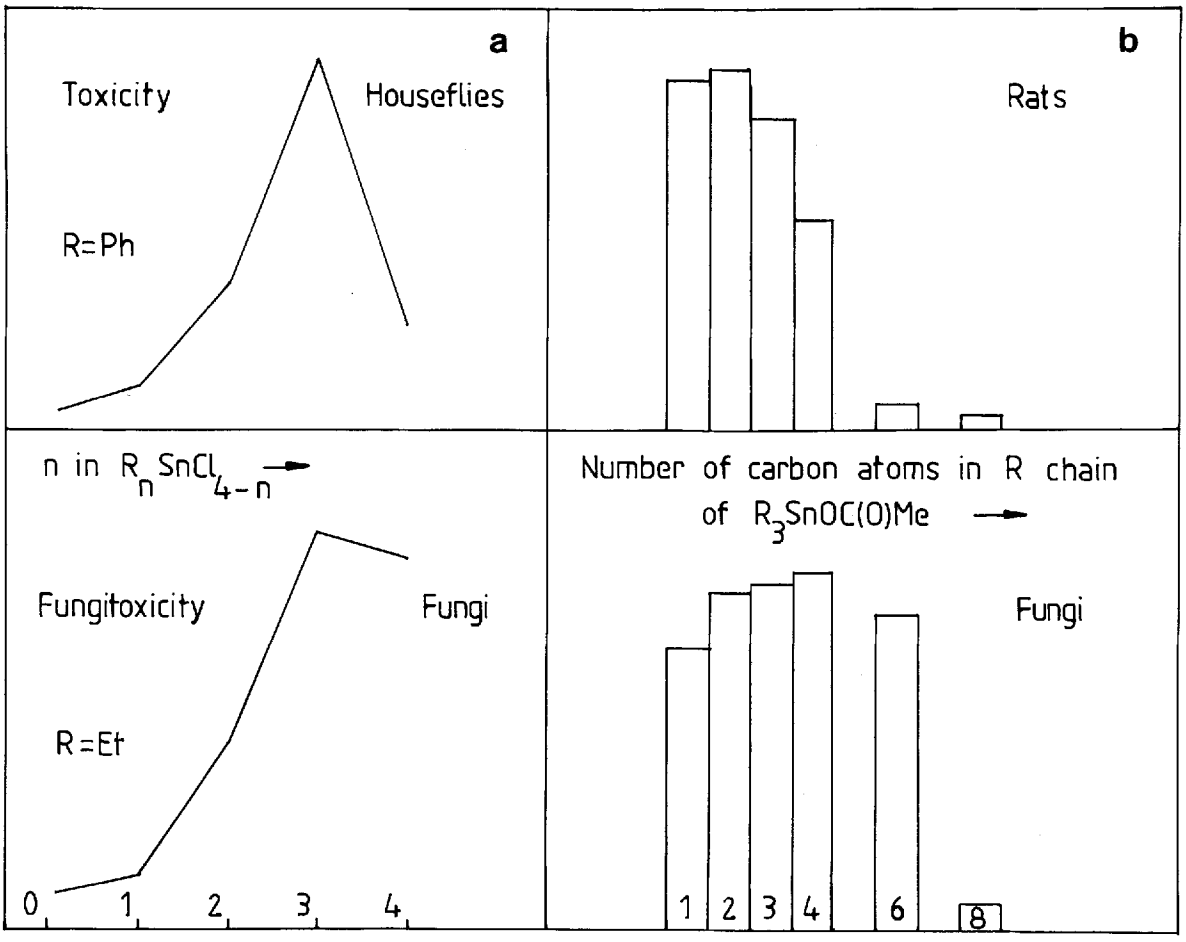


**Figure 1** Variation of the toxicity of organotin compounds, $R_nSnX_{4-n}$, with (a) the number of organic groups bound to tin for $Et_nSnCl_{4-n}$ and $Ph_nSnCl_{4-n}$ compounds, and (b) the nature of the organic group bound to tin for $R_3SnOC(O)Me$ derivatives. (Taken from Ref. 17.)

### Number of organic groups

The maximum toxicity appears when the number of organic group is one less than the periodic group number 4; that is triorganotin compounds are more toxic. For example, Laughlin et al.[21] have confirmed this for the mud crab *Rhithropanopeus harrisii.*

### Method of administration

Organotin compounds that are injected into the body are more toxic than the same compound ingested orally.[15]

| Compound | $LD_{50}$ | Method |
|---|---|---|
| $Bu_3SnCl$ | $129\ mg\ kg^{-1}$ | oral |
| | $2.24\ mg\ kg^{-1}$ | i.p. |
| | $0.0026\ mg\ l\ h^{-1}$ | vapour/dust |
| $Me_2SnCl_2$ | $237\ mg\ kg^{-1}$ | oral |
| | $1.91\ mg\ l\ h^{-1}$ | vapour |

### Frequency of doses

Most organisms show tolerance, in various degrees, towards toxic organotin compounds administered in repeated sublethal quantities over a period of time. However, many compounds are cumulative poisons and repeated doses, even at very low levels, can eventually become fatal. Mushak et al.[18] have studied the accumulation of total tin in rats from degradation of organotin compounds. Di-*n*-butyltin sulphide and laurate have been reported[22] to be cumulative poisons in mice and rats. Accumulation of $^{14}C$-bis(tri-*n*-butyltin)oxide by *R. harrisii* has been determined.[23]

### Nature of inorganic group

Variation of inorganic group, X, within any particular series is usually found to have no significant effect on the toxicity, e.g.,

| Compound | X | $LD_{50}\ (mg\ kg^{-1})$ |
|---|---|---|
| $Ph_3SnX$ | F | 160 |
| | Cl | 135 |
| | OH | 171 |

### Organisms tested

Fetuses and neonatals show greater sensitivity than developing infants, which in turn show greater sensitivity than adults. In order of decreasing sensitivity in mammals generally[1]:

fetuses < neonatals < infants < male adults < female adults.

Mazaev[24] has developed the mathematical equations for calculating $LD_{50}$ values and chronic threshold doses for organotin compounds to species at various stages in their life cycle.

## Sublethal dosage effects

A variety of biochemical and physiological alterations occur at higher dose levels (lower than lethal dose). $Me_3SnCl$, when administered i.p. in mice, caused body tremors and brain damage.[25] $Et_3SnCl$ caused muscular weakness in hind limbs in mice when administered intravenously.[26] Seinen et al.[27] studied the atrophy of thymus in rats caused by $Me_2SnCl_2$, $Pr_2SnCl_2$, $Bu_2SnCl_2$ and $Ph_2SnCl_2$. $Bu_2SnCl_2$ caused skin necrosis in rats when given cutaneously.[28] Yermakoff et al.[29] observed the biliary damage in rats 4 days after administration (gavage) of $Bu_2SnCl_2$. Lymphocyte toxicity was observed in rats when $Bu_2SnCl_2$ was given in drinking water.[30] Henninghausen et al.[31] reported the toxic effects of $Bu_2SnCl_2$ on thymus and bile ducts when given intravenously. Behavioural effects of both acute and subacute trialkyltin exposure have been examined in rats.[32-34] Subacute exposure to triethyltin resulted in performance decrease in motor activity, open field behaviour, acoustic startle response and binding foot response.[35] Rastogi et al.[36] studied the effects of triethyltin sulphate in rats performing under a multiple fixed ratio.

Effects of $Me_3SnCl$ on dopaminergic and seratonergic function in the central nervous system in male rats were studied.[37] Long-term effects of TBTO, TBTF on the Baltic amphipod, *Gammarus oceanicus* were studied by Laughlin.[38] $Me_3SnCl$ was observed to reduce appetitive acquisition and resistance to extinction as compared to controls.[39] Penninks et al.[40] have discussed the mechanism of dialkyltin induced immunopathology. Studies on a series of trialkyl- and phenyltin chlorides to evaluate their toxic effects on brain, lymphoid organs, thymus and spleen have been reported.[41] Pattern reversal, visual evoked potentials and flash evoked potentials were recorded in adult rats after exposure to $Et_3SnBr$.[42] Functional significance of TBTO induced thymus atrophy, lymphocyte depletion in spleen and lymph-nodes and

lymphopenia were evaluated.[43-45] Learning deficiencies[46] have been observed in rat litters on exposure to $Me_2SnCl_2$; learning deficits and alterations in locomotor activity were also observed during the pre- and post-weaning periods by i.p. administration of triethyltin.[47]

Inbred rats fed diets containing $Oct_2SnCl_2$ demonstrated a progressive reduction in thymus weight.[48] Doses of $Me_3SnCl$ resulted in temporary body weight reduction, elevated water intake and persistent increase in open field activity.[49] Gordon et al.[50] reported that thermoregulatory control is especially susceptible to triethyltin. Trimethyltin inhibits uptake of neurotransmitters into mouse forebrain synaptosomes.[51] Effects of postnatal trimethyltin or triethyltin on CNS catecholamine, $\gamma$-aminobutyric acid and acetylcholine systems in rats were studied.[52] Locomotor activity was studied in male rats after intragastric gavage doses of trimethyltin.[53] $Oct_2SnCl_2$ causes morphologic changes in spleen, thymus and immune reaction of rats.[54] Trimethyltin causes a rapid kidney disfunction in rats by cytotoxic action on the cells of the proximal tubular epithelium.[55]

Inhalation of thermolyzed TBTO vapour caused pulmonary toxicity in mice and guinea pigs.[56] Pre- and post-weaning indexes of neurotoxicity in rats caused by triethyltin have been reported.[57,58] Brown et al.[59] have studied the neurotoxicity of $Me_3SnCl$ in hamsters, gerbils and marmosets. Hioe et al.[60] reported that treatment with $Me_3SnCl$ induced atrophy of thymus, spleen and lymph nodes. Wenger et al.[61,62] have studied the behavioural effects of $Me_3SnCl$ on two strains of mice. Metabolism of butyltin compounds in isolated viable rat hepatocytes was studied[63] and tributyltin showed the most potent cytotoxicity. Comparative developmental toxicity of triethyltin using split litter and whole litter dosing has been reported.[64]

Dermal irritation was observed in rabbits exposed to antifouling paints containing $Bu_3SnCl$.[65] Specific and non-specific symptoms of intoxication of CNS including cycles of depression and destructive rage were observed in workers exposed to $Me_3SnCl$ spillage.[66]

All these effects are dose dependent and become increasingly severe as the concentration increases. These effects are often reversible: e.g., subcutaneous administration of $Et_3SnX$ (X = F, Cl, Br, I) to Fischer-344 rats caused a variety of neurotoxic effects, which ceased within 2 weeks after administration.[67]

### Fetal and neonatal toxicity

Kurzel et al.[68] reported that many pollutants containing organotin compounds when ingested by expectant mothers can have deleterious effects on the offspring. The compound, $[Oct_2SnCH_2COO(CH_2)_2OCOCH_2S]$ and its dibenzyltin analog, increased fetal toxicity in Wister rats.[69] Dyer et al.[70] reported that rats exposed to triethyltin halides as neonates showed altered brain electrophysiology as adults. Noland et al.[71] reported the gastrointestinal absorption of $Me_2SnCl_2$ and its transplacental transfer and accumulation in blood and brain of embryo. Danil'chenko[72] has studied the effects of organotin compounds on fish embryos. $Me_3SnOH$, $Et_3SnOH$ and $(Pr_3Sn)_2O$ show toxicity on the development rate and growth of mud crab larvae.[73] Combined effects of decreased salinity and $Et_3SnCl$ on the development of the marine form of three spined stickleback *Casterosteus aculeatus* have been studied.[74]

Chang[75] reported the induction of hippocampal lesions in neonatal rat brains by $Me_3SnCl$ and Reuhl et al.[76] studied the intoxicating effects on developing mouse brain. The uptake, distribution and elimination of tin were determined in neonatal rat brain following i.p. administration of $Et_3SnBr$.[77] Myelin deficits produced by early postnatal exposure to triethyltin are persistant.[78] Immediate and long-term alterations in maximal electroshock seizure responsiveness in rats neonatally exposed to $Et_3SnBr$ have been reported.[79]

## MECHANISMS OF TOXICITY

A number of mechanisms have been proposed to explain the toxicological properties of organotin compounds. However, none of them is able to explain the toxicities of all types of compounds. Some of the important ones are discussed below.

### Inactivation of enzymes

The majority of organotin compounds are toxic because they combine with an enzyme, and thereby inactivate it. Usually, the metal forms a bond with the active site that is too strong to be readily broken, thus preventing the enzyme from reacting with its substrates.

Lipoic acid exemplifies one type of enzyme that frequently becomes inactivated by complexation with organotin compounds.[80] In vivo it becomes

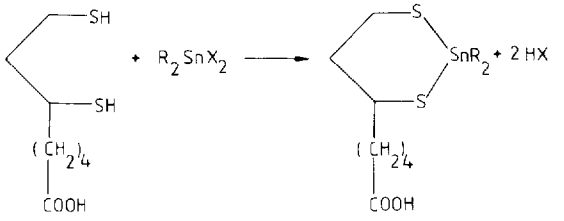


**Figure 2** Thiol group coordination to diorganotin compounds.

part of the enzyme dihydrolipoamide acetyl transferase and participates in the Kreb's cycle of glucose metabolism by converting pyruvic acid to acetyl coenzyme A. During this process the disulphide linkage of lipoic acid is broken to form two thiol groups. In the presence of certain diorganotin compounds, these thiol groups bind to the metal to form a stable chelate (Fig. 2) which destroys enzyme activity. This mechanism derives support from the fact that $Me_2SnCl_2$ is more toxic than $Me_2Sn(SCH_2COOOct)_2$ for rats, since the former reacts readily with —SH groups due to the absence of Sn—S bonds.[81]

Trialkyltin compounds have been reported to inhibit electron transport phosphorylation in mitochondria, chloroplasts and bacteria. The inhibitory site is on the membrane bound components of the coupling ATPases, and the action of $R_3SnX$ compounds is the inhibition of proton flow through these components.[82,83] The mechanism can be represented as in Fig. 3.

Rosenberg et al.[84] demonstrated that various organotin compounds lowered cytochrome P-450 mixed oxidase activity in rats.

Organotin compounds react with several other enzymes, e.g. $Et_3SnBr$ with membrane adenosyl triphosphate[85] and basal adenylate cyclase,[86] $Bu_3SnX$ with glucose-6-phosphate dehydrogenase[87] and $Ph_3SnCl$ with cytochrome oxidase.[88] Casida and co-workers[89] have recently shown that organotin biocides interact with cytochrome P-450 dependent mono oxygenases in rat liver, giving rise to hydroxylated metabolites. Others have also studied the interaction of organotin compounds with P-450 dependent enzyme systems.[90,91] Differential inhibition of $F_0F_1$-ATPase-catalyzed reactions in bovine-heart submitochondrial particles by triorganotin compounds was reported by Emanuel et al.[92] Saito et al.[93] have reported the inhibition of enzymic glutathione (GSH) conjugation in the activation and detoxication of 3-hydroxyamino-1-methyl-5H-pyrido [4,3-b] indole (H-OH-Trp-P-2) by organotin compounds. $Ph_3SnCl$ inhibits ATP synthesis and hydrolysis without uncoupling.[99] $Bu_3SnCl$ is a potent inhibitor of a $Mg^{2+}$-ATPase found in prolactin secretory granules.[95] Binding of $Et_3SnBr$ to yeast hexokinase B results in a rapid change in the reactivity of the SH groups of the molecule.[96] $Ph_3SnF$ inhibits rabbit platelet collagen induced aggregation, ATP secretion and blockade of arachidonic acid mobilization from membrane phospholipids.[97]

## Effects on the nervous system

Certain organotin compounds are toxic because they cause edema in the brain and CNS. Many of them weaken or destroy myelin and proteins,

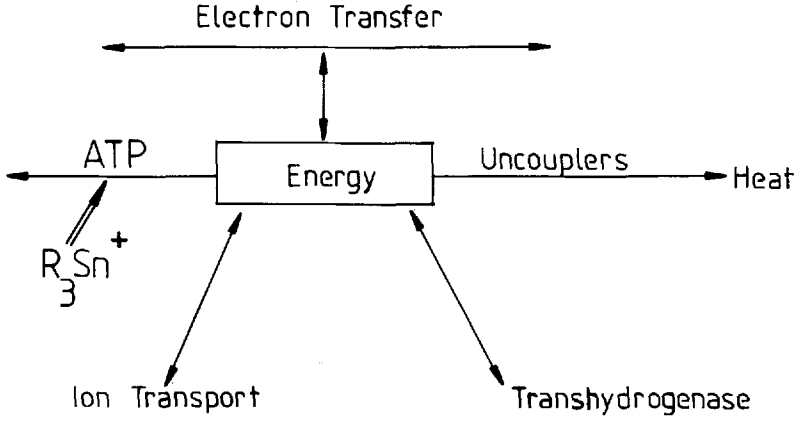


**Figure 3** Reprinted with permission from Chapter 15, "Triorgano tin compounds as ionophores and inhibitors of ion translocating ATPases," by M.J. Selwyn in *Organotin compounds: New chemistry and applications* (ed. J.J. Zuckerman), Advances in Chemistry Ser. 157, 1976. Copyright (1976) American Chemical Society.

which coat nervous fibres. Chin et al.[98] reported that triethyltin compounds create edema in the tissues of CNS. Similar observations on triethyltin compounds were also made by Amochaev et al.[99] Intravenous injections of triethyltin compounds in rats caused the appearance of vacuoles in myelin.[100,101] Smith[102] reported that $(Et_3Sn)SO_4$ sharply lowered myelin content in spinal cord and brain when given in drinking water, and increased cerebral water and glucose levels when given i.p.[103] The rats developed intramyelinic edema of major CNS white matter tracts when fed daily on $Et_3SnBr$.[104] Developing rats receiving triethyltin compounds showed decreased forebrain weight and myelin yield.[105] A preparation of triethyltin has been reported[106] to generate cerebral inflammation and edema. A trimethyltin compound has been shown to cause intracellular changes in neurons.[107] The relationship between the cellular response of a neuron to trimethyltin and its morphological subspecialization was studied by light microscopy.[108] NMR studies have been reported to follow cerebral edema caused by $Et_3SnCl$ in male rats.[109] Golden hamsters were studied for vascular permeability changes taking place during the formation of triethyltin induced brain edema.[110] Large intraneuronal vacuoles were formed as a result of extensive intraneuronal endema caused by $Me_3SnCl$.[111] Trimethyltin induced changes of neurotransmitter levels and brain receptor binding in the mouse have been studied.[112]

## Blocking of binding sites

Active sites for biochemicals (present in organisms) may be blocked by binding to an organotin compound. Binding of some organotin compounds to the cysteine and histidine residues of protein through pentacoordination of tin atoms (Fig. 4) has been suggested.[113] Taketa et al.[114] reported that triethyltin compounds bind to cat haemoglobin through thiol groups of residue Cys-13 and His-20 of the α-chain. Organotin compounds damage the cholchicine binding properties of rat brain tubulin.[115]

## Physiological disorders

Organotin compounds cause a number of physiological disorders. $Ph_3SnF$ has been reported to induce hyperglycemia and hyperglyceremia in rabbit plasma.[116,117] $Me_3SnCl$ and $Et_3SnCl$

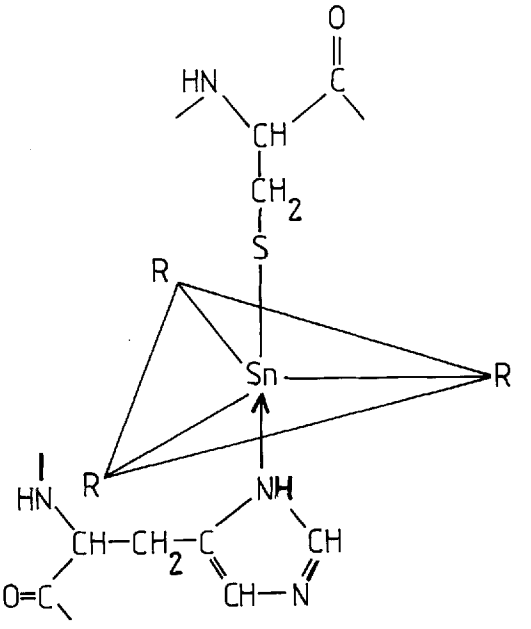


**Figure 4** Cysteine and histidine residue complexation to triorganotin moiety.

altered evoked visual potentials in rats.[118,119] Byington et al.[120] have reported that organotin compounds show hemolytic activity in rats. Di-*n*-butyltin dilaureate affected the biotransformation of heme by rat hepatocytes.[121] Some triethyltin compounds have been reported to interfere with $Ca^{2+}$ conduction in biological systems.[122] Di-*n*-butyltin compounds caused immunosuppression in animals.[123] Certain organotin compounds, upon oral administration, inhibited gastric emptying, thereby causing fluid distension.[124] Triethyltin compounds decreased resting membrane potentials in rats.[125,126]

Johnson et al.[127] reported that $(Bu_3Sn)_2O$, $Cy_3SnOH$ and $Bu_3SnCl$ interfere with ATPase mediated systems and that the shape of red platelets was changed. Dwivedi et al.[128] studied the effects of $(Oct_2SnO)_n$, $Cy_3SnOH$ and $(Bu_3Sn)_2O$ on enzymic activities in liver and kidney and measured biogenic amine levels in rat brain. Kao et al.[129] reported that mouse skin culture showed inhibition of [$^3$H] thymidine in DNA and [$^{14}$C] leucine in protein by exposure to $Bu_3SnCl$. Organotin compounds produce a prolonged induction response of heme oxygenase in liver but not in kidney.[130] Arakawa et al.[131] discovered that $Bu_2SnCl_2$ and $Ph_3SnCl$ suppressed significantly not only the chemotactic response of neutrophils to stimulation by *f* Met-

Leu-Phe but also phospholipase activity in situ. Low doses of dibutyltin difluoroacetate, $(Bu_3Sn)_2O$ and monobutyltin laureate inhibit serum glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase activity, but however, stimulate cholinesterase activity.[132]

Triphenyltin has been reported to provoke an 'all or none' $K^+$ loss pattern from cells.[133] Oral administration of $(Bu_3Sn)_2O$ produced a substantial elevation in heme oxygenase activity in rat's small intestine.[134] Tonoplast-bound $H^+$-translocating ATPase from *Hevea latex* was found to be sensitive to $Me_3SnCl$.[135]

## APPLICATIONS

Organotin compounds find applications in many areas. The important ones can be summarized as:

### Studies related to biochemistry

Organotin compounds have been frequently used in biochemical and biological investigations. The capacity of organotin compounds to deactivate enzymes makes these compounds very useful for investigating the nature of enzyme active sites. Byington et al.[136] have studied the inhibitory effects of organotin compounds on enzyme ligandin. Kanetoshi et al.[137] reported the inhibiting activity of the series $(C_4H_9)_nSnX_{4-n}$ on yeast glucose-6-phosphate dehydrogenase. $Cy_3Sn$ compounds cause a significant and prolonged induction of haemoxygenase and a sustained decrease in haemoprotein contents in liver.[138] Putinsev et al.[139] have studied the effect of $Me_3SnCl$ on alkaline phosphatase (AP) and alanine aminotransferase (ALAT) activities and cholesterol content in the blood serum of carp. Exposure of intact human red cell suspensions to $Et_3SnBr$ inhibited hexokinase activity.[140]

Apps et al.[141] assayed highly purified resealed bovine chromaffin-granule ghosts for ATPase and ATP-driven $H^+$-translocation and 5-hydrotryptamine [5-HT, serotonin] activities. Respiration and ATP dependent transhydrogenation of $NADP^+$ by $NAD^+$ in everted membrane vesicles from *E. coli* is inhibited by $Bu_3SnCl$.[142] $Ph_3SnCl$ inhibits cytochrome oxidase electron transport activity in the liposomes and in the mitochondrial membranes.[143] A number of organotin compounds were tested for their ability to inhibit the uptake of $^3H$ labeled GABA into mouse forebrain synaptosomes in vitro.[144] A tributyltin compound inhibits release of secretory granule growth hormone and prolactin.[145] Oral administration of $(Bu_3Sn)_2O$ produced a substantial elevation in heme oxygenase activity. Tributyltin compounds inhibited the entry of a strain of poliovirus 1 (Brunede) into cervical carcinoma $HeLaS_3$ cells.[146]

Effect of triethyltin on the transport of Taurine, Glutamate, Lysine, $Na^+$, $K^+$ and $Cl^-$ by rat glioma LRM-55 cells was studied.[147] The effect of $Me_3SnCl$ on membrane potentials in vacuoles isolated from storage roots of red beet has been observed.[148] $Et_3SnBr$ was used as inhibitor for discrimination and identification of the major basic isozymes of glutathione transferase in rat liver cytosol ($L_2$, BL, $B_2$, $A_2$, AC and $C_2$).[149] However, it activates the *cAMP*-dependent protein kinases of human cell membranes and of bovine brain.[150]

Organotin compounds bind to biologically important biomolecules other than enzymes and as such help in finding the binding sites. Chloromethyl di-*n*-butyltin chloride binds to beef mitochondrial adenosinetriphosphate sites.[151] $Ph_3SnCl$ binds to high affinity binding sites in rat liver mitochondria.[152] $Bu_3SnX$ compounds have been reported to inhibit $Ca^{2+}$ transport in rats,[153] whereas $Et_3SnCl$ is supposed to inhibit denovoglycogen synthesis in carp.[154]

Organotin compounds bind to membranes. Cellular membranes have electrochemical potentials across them, arising in part from concentration gradients of $Na^+$, $K^+$ and $Cl^-$ ions. $Ph_3SnCl$ binds to high affinity binding sites in rat *Nitella syncarpa*.[155] $Pr_3SnCl$[156] and $Ph_3SnCl$[157] mediate $Cl^-/OH^-$ ion exchange across membranes. Interference with $Cl^-/OH^-$ exchange may be the reason that $(Et_3Sn)_2SO_4$ inhibits ADP stimulated $O_2$ evolution by pea chloroplasts.[158] Binding of triethyltin compounds to high affinity sites on yeast mitochondrial membranes is the likely cause of the inhibition of oxidative phosphorylation.[159] $Bu_3SnCl$ enhances ion exchange diffusion across membranes.[160]

The treatment of mouse spinal cord cultures with 1 $\mu$mol dm$^{-3}$ $(Et_3Sn)_2SO_4$ caused marked degeneration.[161] $Et_3SnCl$ interacted with rat phrenic nerve tissue and inhibited rat brain cortex oxidation of glucose.[162] $Bu_3SnCl$ inhibited $Ca^{2+}$ transport in mitochondria.[163] $Ph_3SnCl$ induced chloride–hydroxide exhange in beef mitochondria.[164] $Ph_3SnCl$ inhibited oxidative phosphorylation in barnacle muscle mitochondria[165]

and $(Et_3Sn)_2SO_4$ has a similar effect on *Tetrahymena pyridormis* mitochondria.[166] Di-*n*-butyl and tri-*n*-butyltin compounds attacked the terminal step of the rat liver mitochondrial respiration chain.[167] Methyl di-*n*-butyltin chloride inhibited oxidation by potato and mung bean mitochondria[168] and stimulated $K^+$ flux in rat liver mitochondria.[169]

## Studies related to agriculture

About a third of the world's food production is lost due to pests and fungal diseases, despite great progress having been made in agriculture. Organometallic compounds have played a vital role in control of pests. Though the use of organotin compounds is relatively new compared to organomercury and arsenic compounds, they are the predominant organometals currently used.

One of the first organotin compounds to be used commercially was $Ph_3SnOAc$ which is used against *Cercospora beticola* in sugar beets and *Phytophthora infestans* in potatoes.[170] Kumar Das et al.[171] described the use of addition compounds of $Ph_3SnCl$ with dimethyl sulfoxide and quinoline-N-oxide for tomatoes, celery and sugar beet. Various di- and triorganotin acetates have been used against *Aspergillus niger* and *Botrytis allii*.[172] Di- and triorganotin halide or pseudohalide adducts with pyridine-2-carboxylic acid, 2-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine and 3-[2-(1,10-phenanthrolyl)]-5,6-diphenyl-1,2,4-triazine protected coffee plants from *Colletotrichum coffeanum*, *Pseudomonas syringae* and *Hemeleia vastatrix*.[173] $Ph_2SnCl_2$ complexes with 2,2′-bipyridine or 1,10-phenanthroline were used against *Colletotrichum falcatum*.[174] Wenschuh et al.[175] have used some organotin compounds to treat *Phytophthora infestans* on tomatoes, whereas similar compounds have been used against *Alternaria radicina*, *Alternaria dauci* on carrots[176] and European canker (*Nectria galligena*) on apples.[177]

Kanetoshi et al.[178] have studied the environmental and biological effects of organotin pesticides on orchard trees. Dibutyl bis(4-benzoyl-3-methyl-1-phenyl-2-pyrazoline-5-onato)tin is toxic (affecting the CNS) to *Trogoderma granarium* and *T. castaneum*, which are stored product pests.[179] Tolerance for the pesticide chemical [hexakis(2-methyl-2-phenylpropyl)distannoxane] in or on raw agricultural commodities has been studied.[180] Parkin et al.[181] have reported organotin complexes of sucrose as pesticides.

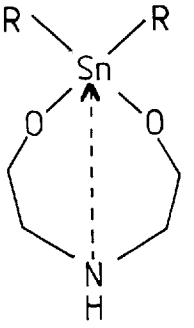


**Figure 5** Cyclic coordination in fungicidal diorganotin compounds.

Tricyclohexyltin hydroxide, halides, acetate and other derivatives have been used as pesticides for controlling arachnids. Bis[tris(2-methyl-2-phenyl propyl)tin] oxide is used as an acaricide for protecting fruits and citrus crops.[182] 1-Tricyclohexylstannyl-1,2,4-triazole is the latest organotin insecticide[183] to come to the market for use against red spider and spider mites in fruit, grapes and vegetable crops. Singh et al.[184] studied the effects of triorganotin diethyldithiocarbamates against fungus-caused red spot on sugar cane and root rot on sugar beet. Hill et al.[185] have reported the use of tributyltin ethanesulphonate against *Poria placenta*, *Gloeophyllum trabeum*, *Coriolus versicolor* and *Coriophora puteana*. Cyclic organotin compounds (Fig. 5) have been reported to show good fungicidal activity in lab experiments.[186]

Reports on the fungicidal activity of organotin derivatives of chlorooxazolylamines against *Piricularia oryzae* are available.[187] Bock[188] has reviewed the applications of triphenyltin compounds in agriculture and their environmental behaviour. Trialkyl and aryltin compounds of phosphordithioate, phosphate, phosphinate and phosphorodiamidate have been screened to show strong antifungal activity.[189] Kouri et al.[190] studied the antimicrobial activity of tripropyltin and tributyltin iso-carboxylates. Di-*n*-butyl bis(diethyldithiocarbamate)stannane,[191] tri-2-norbornyltin compounds,[192] tricyclopentyltin fluoride[193] and monophenyltin triformate[194] have been reported to possess insecticidal and fungicidal properties.

The series of organotins $Bu_3SnCH_2R$ (where R is a quaternized amino group) showed herbicidal properties.[195] Pyridine adducts of tetraorganotin compounds[196] and of diorgano stanncycloalkanes[197] have been used as herbicides. $Bu_3SnF$ controlled weeds which damage corn or rice.[198]

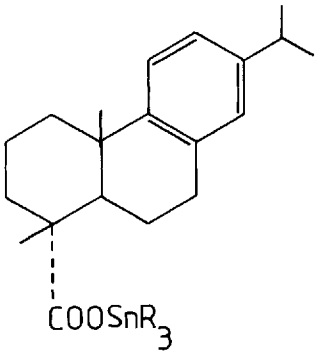


**Figure 6** Structure of compounds investigated by M.T.C. Inc, Harima Inc (Japan) for biocietal activity.[203]

Tri-*n*-butyltin acrylate increased pea seed germination.[199] Saxena et al.[200] have reported the fungicidal activity of di- and tributyltin compounds of semicarbazones and thiosemicarbazones. Asymmetric diphenyltin compounds have been patented as fungicides against *Plasmopara viticola* in grape crops.[201] Tolerance of *Cercospora beticola* isolates towards triphenyltin acetate was studied by Cerato et al.[202]

Compounds of the structure shown in Fig. 6 have been reported to possess insecticidal, miticidal and fungicidal activities.[303] Mishcenko et al.[204] have studied the fungal resistance of organotin derivatives of copolymers of maleic anhydride with methacrylate. Resistance to organotin compounds of *P. aeruginosa* and *E. coli* carrying antibiotic resistance plasmids has been studied.[205] Acaricidal and fungicidal activities of triorganotin complexes, e.g. tris(2-methyl-2-phenylpropyl)-tin-3-hydroxyflavone, tricyclohexyltin-3-hydroxyflavone, tricyclohexyltin-1,3-diphenylpropane-1,3-dione, triphenyltin quinoline-8-ol and triphenyltin-3-hydroxyflavone etc. against *Plasmopara viticola* and *Phytophthora infestans* have been reported.[206] The influence of fungicidal $Me_3SnCl$ upon metabolism and $K_2H^{32}PO_4$ uptake in *Lymnaea stagnalis* has been studied.[207] Fungicidal activity has been reported for monobutyltin- and monophenyltin triformates in a patent.[208]

Organotin compounds have long found applications for wood preservation and tributyltin compounds are the most important of them. However, this topic will not be dealt with in detail here since excellent reviews are available on the subject.[209,210] Some of the more important aspects are briefly discussed here.

The toxic limits of 26 tributyltin compounds, $Bn_3SnX$ (X = anionic radical) were reported for *Coniophora puteana* and *Coriolus versicolor*.[211] The preservative activity of these compounds was found to be independent of the nature of X group. Cox has extensively studied the effect of solvent systems on fungal activity. Enhanced fungicidal activity of $(Bu_3Sn)_2O$ against *C. puteana* in pine wood was reported using 5% water in 1,4-dioxane.[212] Hill et al.[213] evaluated the fungicidal activity of aqueous solution of tributyltin ethanesulfonate against *Poria placenta*, *Gloeophyllum trabeum*, *C. versicolor* and *C. puteana* using leached and unleached wood blocks and attempted to investigate the chemical nature of organotin preservative in timber. Tributyltin dithiocarbamates of the type $RR'NCS_2SnBu_3$ (R = Me, Et; R′ = H, Me, Et) have been reported to suppress growth of fungi on agar and protect samples of wood against fungal decay.[214]

## Studies related to biocidal applications

There are a number of studies on organotin compounds where their biocidal properties are opening new frontiers of research.

Leishmaniasis, a group of skin infections commonly found in tropical regions, is caused by the genus *Leishmania*. Trials have been described[215] with a number of experimental drugs in which di-*n*-octyltin maleate is amongst the most promising of the compounds tested. Saxena et al.[216] tested the organotin compounds with Schiff bases as amoebicidal agents. Eleven compounds were tested against *Entamoeba histolytica* in vitro and a tributyltin compound (Fig. 7) was reported to have greater activity than that of the drug emetine. Tributyltin esters of hydroxy aryl(alkyl) carboxylic acids were screened for their biocidal properties.[217] Duncan[218] has reviewed the molluscicidal activity of a number of trialkyl- and triaryltin compounds. Molluscicidal time-concentration relationships have been worked out

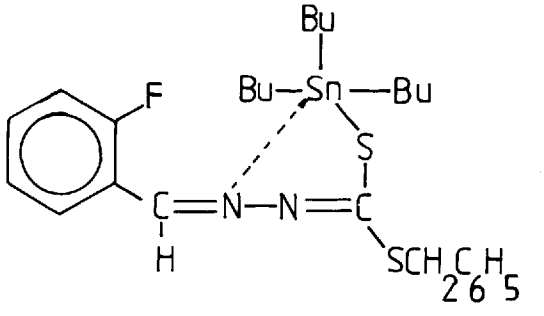


**Figure 7** Organotin compound active as an amoebicidal agent.[216]

for a number of organotin compounds to gauge their most effective application in the field. Buzinova et al.[219] have studied the toxicological behaviour of trimethyltin chloride on molluscs and reported decrease in dry material content and increase in mineral content. Cardarelli[220] has recently reviewed the slow-release molluscicides.

Mosquitos are still a serious problem in many parts of the world. Controlled-release organotins have been evaluated as potential mosquito larvicides.[221] Six per cent $(Bu_3Sn)_2O$, 20% $Bu_3SnF$ in natural rubber and 30% $Bu_3SnF$ in ethylene–propylene copolymer were evaluated against larvae of *Cx. pipiens* and *Cx. quinquafasciatus*. *Aedes aegyptii* larvae has been used as a test organism for the bioassay of $Bu_3SnF$.[222] The effects of triorganotin chloride adducts with $Ph_3PO$ or PyO, diethyltin diacetate and tributyltin sucrose phthalate on the mosquito *Aedes aegyptii* (L) have been studied.[223]

Sato[224] has reported the preparation of various ointments based on organotin compounds for treatment of fungal skin infections. Some phenyltin derivatives of imino diacetate are used as dentrificial agents.[225] Various di-*n*-butyltin dicarboxylate preparations are used to eliminate round worms, cecal worms and tape worms for poultry.[226] Organotin compounds have come into increasing use as antifeedants and have been successfully used against various insects.[227–230] Organotin biocides are used to protect certain textile fabrics (wool) against insect attack and also against microorganisms causing fabric rot.[231]

Pelikan et al.[232] have studied the toxic effects of tributyltin compounds on the testis of albino rats whereas, Ladd[233] reported on the toxicity and reproductive inhibition of triphenyltin compounds on houseflies, red ballworms and Japanese beetles. Saxena et al.[234] have recently reported that intratesticular administration of di-*n*-butyltin (*o*-hydroxyacetophenone S-methyl dithiocarbazate (Fig. 8) produced marked degenerative changes in the testis of albino rats. A possible mechanism has been discussed to explain the atrophy of the seminiferous tubules with consequent arrest of spermatogenesis. The dibutyltin compound exerts its main pharmacological action on the spermatocytes and spermatids and produces a specific type of damage to germinal epithelium. The marked inhibition of spermatogenesis is patchy. It was suggested that the compound undergoes controlled hydrolysis in the body.

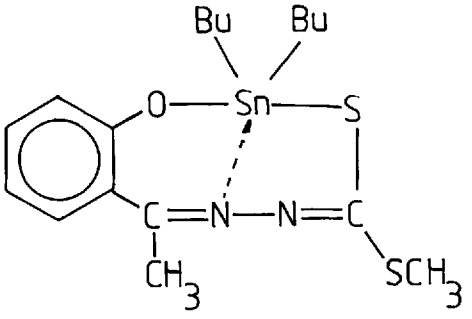


**Figure 8** Di-*n*-butyltin (*o*-hydroxyacetophenone-S-methyldithiocarbazate).

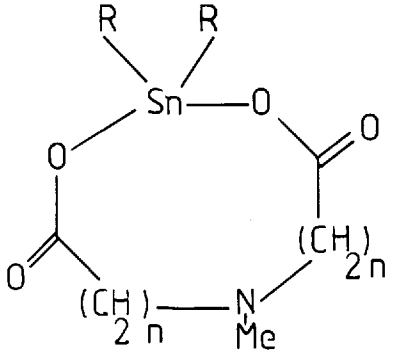


**Figure 9** Diorganotin compounds of *N*-methyliminodiacetate ligands.

Organotin compounds have been widely used against microorganisms. Van der Kerk[235] reported the first detailed study on the inhibitory effects of organotin compounds on various bacterial strains. They also proposed that the active species is the $R_3Sn^+$ ion (in the $R_3SnX$ series) and that X has little effect. Similar results were obtained by Srivastava et al.[236] on the bactericidal activity of triphenyltin isoselenocytes. Tzschach et al.[237] reported that some organotin compounds (R = Cy or Et; $n = 1$ or 2) of *N*-methyl iminodiacetate (Fig. 9) inhibited the growth of *E. coli* and *Staphylococcus aureus*. $[Bu_2Sn(OC_5H_4NO)_2]$ has been reported[238] to be a bactericide against *S. aureus*, *Bacillus subtilis* and *Candida albicans*. Diorganotin compounds $R^1R^2Sn(XCR^3R^4CH_2)_2NR^5$ ($R^1$ and $R^2 = C_{1-10}$ alkyl or alkenyl or aryl; $R^3$ and $R^4$ = H, $C_{1-10}$ alkyl or $R^3R^4 = O$; $R^5$ = H, $C_{1-10}$ alkyl or alkenyl or aryl; X = O or S) are bactericides against *B. subtilis*, *B. mesentericus* and *Chaetomium globosum*.[239] Sixteen organotin compounds, $R_3SnC{=}CR'$ (R = Me, Et, Bu; R' = SEt, $CH_2OMe$, $CH_2NEt_2$, piperidinomethyl, morpholinomethyl,

$CH_2Cl$ and $SnEt_3$), were tested for bactericidal activity against *S. aureus* and *Stachybotrys atra.*[240]

Srivastava et al.[241] reported that the bactericidal activity of 18 new triorganotin compounds $(R_3Sn)_nX$[R = Bu, Ph; X = selenate, tellurate, phosphate, arsenate, citrate, salicylate, tartarate, maleate or borate; $n = 2$ or 3] against *S. aureus*, *Salmonell. typhi*, *E. coli* and *B. subtilis* is independent of the nature of the electronegative group, Yamada et al.[242] have studied the effect of tripropyltin chloride on the transport system in *E. coli.* Kourai et al.[243] reported that [3-(tripropylstannyl)propyl] trimethyl ammonium iodide inhibited respiration of *E. coli* and cell wall synthesis in *B. subtilis.*

Saxena et al.[244] reported the bactericidal activity of a series of di- and tri-*n*-butyltin compounds with Schiff bases of *o*-aminothiophenol and fluoroaniline against *S. aureus*, *B. subtilis* and *E. coli.* $(Et_3Sn)_2SO_4$ has been reported to inhibit mitochondrial ATPase of the kinetoplastid protozoa *Crithidia fasculata.*[245] $Ph_3SnCl$ inhibits the uptake of methyl glucose by *Setaria cervi.*[246] Attramadel et al.[247] have reported the antibacterial effects of tin compounds on oral microflora. Various organotin compounds having 2-alkylindole group were found to be active against *B. subtilis*, *B. punilus* and *S. aureus.*[248]

Various studies have been carried out on organotin compounds as chemosterilants,[249,250] in the control of biological growth on stone and masonry structures[251] and as antifouling paint additives.[252]

One of the most controversial uses of organotin compounds (due to environmental aspects) is their use as antifouling paints. $(Bu_3Sn)_2O$ was one of the first organotins to be used as an antifouling coating.[253] Antifouling paints used nowadays contain organotin compounds attached directly to a polymer backbone, slow release from which gives long protective action. A composition from a 40% solution of 14:26 Memethacrylate-tributyltin methacrylate copolymer in toluene (55 parts), $Cu_2O$(35), hydroquinone (0.01), $TiO_2$(5), bentonite (1) and xylene (4 parts) gave a coating showing no marine fouling for 12 months.[254] A composition of 50% solid 2:3 Memethacrylate-tributyltin methacrylate copolymer solution in xylene (30 parts) $Cu_2O$(30), $Ph_3SnOH$(5) and 25:75 isobutyl ethene-vinylchloride polymer (2 parts) tricresylphosphate(3), red Fe oxide(5), talc(10) and xylene (15 parts), was used as antifouling coating.[255] $Bu_3Sn$ methacrylate (350 parts) Memethacrylate (150 parts) $Bz_2O_2$ 2.5 g in 500 g xylene gave a polymer on heating which was mixed with 10% tributylphosphate to give an antifouling paint.[256] A PVC board was coated with a composition containing a 50% solution of 45:30:25 (monosomer feed ratio) Memethacrylate-N-methyl-N-vinylacetamide-octylacrylate copolymer in xylene(30), $Ph_3SnCl$(12) and xylene (10 parts), dried and immersed for 16 months in sea water without adhesion of organisms over that period of time.[257]

## Studies related to anticarcinogenesis

One of the major developments in the field of bioorganotin chemistry in the eighties is the finding that organotin compounds can play an important role in anticarcinogenesis. Though organotin compounds have been extensively studied as fungicides, bactericides and acaricides, little information is available on the organotin compounds as anticancer agents.

Brown,[258] in her doctoral work concluded that a hydrolysable organotin compound, triphenyltin acetate, significantly retarded tumor growth, whereas the nonhydrolysable $Ph_3SnCl$ was inactive. Ozaki et al.[259] showed in a patent that dialkyltin fluorouridines are anticarcinogenic and will cause shrinkage of solid tumor upon direct injection. Bulten et al.[260] reported on the antitumor activity of $(ClMe_2Sn)_2O$, $(Et_2SnO)_n$, $Ph_2Sn(OH)Cl$ and 14 other structural analogs. In 1980, Crowe et al.[261] reported on the antitumor activity of a series of diorganotin dihalide and pseudohalide complexes, $R_2SnX_2.2L$ (where R = Me, Et, Pr, Bu or Ph; X = F, Cl, Br, I, NCS; L = bipyridyl, phenanthroline, 2-aminomethylpyridine, dimethylsulphoxide, pyridine etc.), which were modelled on the active platinum complexes. They proposed that (a) the mode of action may involve the initial transportation of the complex $R_2SnX_2.2L$ into the tumorigenic cells followed by reaction of $R_2SnX_2$ (or one of its hydrolysable products), and that (b) a moderately stable complex is required for activity.

Barbieri et al.[262] reported on the antitumor activity of $R_2Sn(Adenine)_2$ (Fig. 10) and $R_2Sn(Glycylglycine)_2$ complexes and suggested transportation of the complex species into the tumor cells, followed by attack of hydrolysed $R_2Sn$ moieties.

Saxena et al.[263] screened a number of di-*n*-

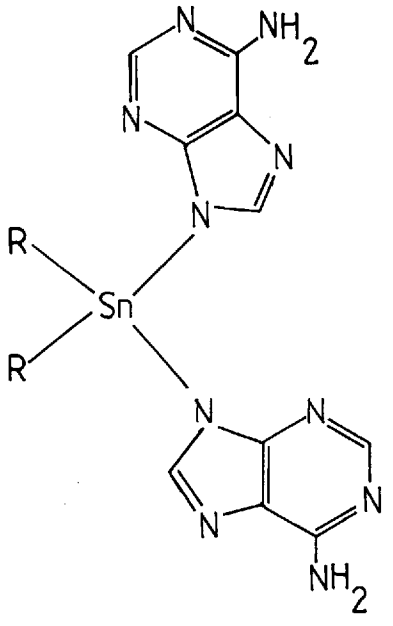

**Figure 10** Dialkyltin(adenine)$_2$ complex.

butyltin complexes of Schiff bases derived from S-substituted dithiocarbazate and fluoroaniline for their antitumor activity in the P388 Lymphocyte Leukaemia system. Takahashi et al.[264] reported on the effects of timing a single intragastric application of $Bu_2SnCl_2$ on N-nitrosobis(2-oxopropyl) amine (BOP) induced pancreatic carcinomas in female Syrian golden hamsters. Haiduc et al.[265] reported on the activity of 16 organotin compounds of the type $[R_2P(S)S]_2SnMe_2$ in vitro towards P388 Lymphocyte Leukaemia in mice. Clercq et al.[266] screened six organotin compounds of the type $[CF_3(CF_2)_5CH_2CH_2]_2SnX_2$ and $[CF_3(CF_2)_5CH_2CH_2]_2SnX_2$.*o*-phenanthroline towards murine P388 Lymphocyte Leukaemia tumor.

Crowe et al.[267] tried to correlate X-ray crystallographic data on organotin compounds with their antitumor activities. They suggested that more stable complexes have lower activities, implying that a predissociation of the bidentate ligand may be a crucial step in the formation of a tin–DNA complex. The results of screening on 115 diorganotin halide and pseudohalide complexes in the P388 Lymphocyte Leukaemia system were published by Crowe et al.[268] and suggested that (1) diethyl and/or diphenyltin complexes usually possess highest activity, and that (2) the mode of action for the formation of metal-base crosslinks for organotin compounds is different from platinum complexes.

A new impetus to the field of organotin compounds in anticarcinogenesis was given by Cardarelli in 1983. A number of organotin compounds, i.e., $Bu_3SnF$, dibutyltin dichloride.2,2'-bipyridyl, 1,10-phenanthroline dibutyltin complex and dibutyltin derivative of histidine were given to cancerous mice in drinking water and tumor growth rates were significantly reduced. $Bu_3SnF$ applied dermally was ineffective.[269,270] Cardarelli et al.[271] hypothesised that soluble organotin compounds of varying types introduced in the body are concentrated in the thymus gland. The tin in the thymus is then processed into one or more biochemicals that act as anticarcinogens and/or antioncogens. These tin steroids (Fig. 11), and probably -peptides, produced by the thymus are multifunctional, acting as hormones in the suppression of oncogenesis.[272]

Gielen et al.[273] reported screening data for a number of organotin complexes of the type $[(Ph_2SnBr)_2CH_2]$ and $[(PhSnBr_2)_2CH_2]$ against P388 Lymphocyte Leukaemia in mice. Vandendris et al.[274] reported the high activity of two diethyltin derivatives of substituted benzimidazole and phenanthroline against renal adenocarcinoma. Meinema et al.[275] screened a number

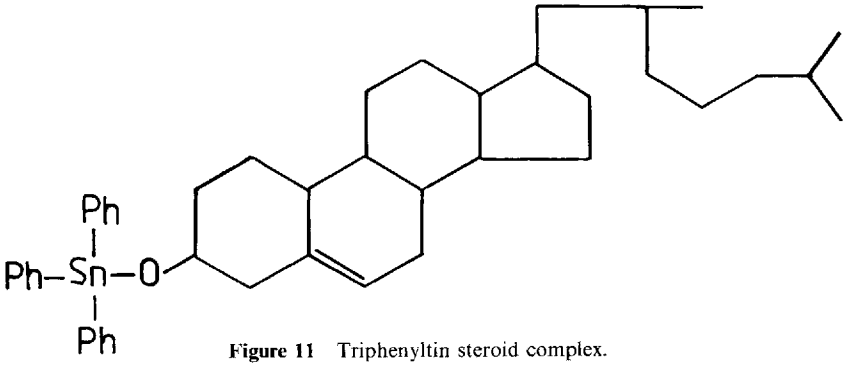

**Figure 11** Triphenyltin steroid complex.

of complexes of the type $RR'Sn(CH_2COOMe)_2$ [where R = Me, Et, Ph, Bu] and RR'SnO against P388 Lymphocyte Leukaemia in mice. Complexes of $Ph_2SnCl_2$ with 1,2-ethylene bis(diphenyl phosphine oxide) and 1,4-butylene bis(diphenyl phosphine oxide) were found to be active against P388 Lymphocyte Leukaemia.[276]

Yamamoto et al.[277] have studied the comparative antitumor activities of a number of organometallic complexes of alkylidenetriphenylphosphorane in L-1210 Leukaemia in mice. Barbieri[278] has reviewed the correlation of structures in diorganotin compounds with their antitumor activities. Huber et al.[279] reported the antitumor activity of 20 compounds of di- and triorganotin of the type $R_2SnL$ ($H_2L$ = L-cysteinate or DL-penicillamine; R = Me, Bu, Ph), $Me_2Sn$ complexes of N-benzoylglycinate and substituted glycinates, $[R_2Sn(SCH_2CH_2SO_3)_2]^{2-}$ and $Bu_2SnPut_2$ or $(Ph_3Sn)_3Put_2$ (HPut = purine-6-thiol).

They interpreted their results on the basis of structure–activity relationships and concluded that the antileukaemia activity of these compounds was due to $R_2Sn$ moieties possibly released into the cells. Ruisi et al.[280] have recently reported hydrolytic decomposition of $Me_2Sn$ glycylglycinate (which shows significant activity),[262] and found that dissociated species in water retain the tin–peptide nitrogen bond whereas in organic solutions peptide and amino nitrogen atoms and carboxyl oxygen are linked to tin.

The diverse studies discussed above clearly show that organotin compounds have a vast potential for exploitation in biology and medicine.

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