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Toxicity and Health Effects of Selected Organotin Compounds: A Review

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The toxicity of selected tin compounds is reviewed. Over the years, a variety of uses has been found for organic and inorganic tin compounds, as fungicides, as stablizers in plastics, moluscicides, and miticides; they have also been suggested as insect chemosterilants and for other industrial uses. Many of these products are unpalatable when mixed into diets and have been suggested as rodent repellents. Inhaling tin as dust or fumes may cause a benign pneumoconiosis in exposed workers. The organotin compounds can be divided into alkyltin and aryltin compounds. The trimethyl and triethyltin compounds are well absorbed from the gastrointestinal tract and are the most toxic in this group. Triethyltin particularly produces status spongiosus of the white matter of the central nervous system. Most of the other alkyl and aryl tin compounds are poorly absorbed from the gastrointestinal tract, and are less toxic when given orally than when given parentally. Only one compound, tricyclohexyltin hydroxide, is now registered by the Environmental Protection Agency as a miticide. This product produces skin irritation in rabbits. Studies should be conducted to determine whether it causes contact dermatitis in humans.

Introduction

The purpose of this short review is to present the characteristic and unique toxic effects of selected organotin compounds. Inorganic tin compounds will be briefly mentioned since one of the metabolites of aryl tin compounds is inorganic tin.

Little was known about the toxicity of organic and inorganic tin compounds (Table 1) until the beginning of the 19th century. Orfila (*1*) described the toxicity of tin chloride and tin oxide. The intravenous administration of tin chloride to a dog caused muscle weakness, loss of sense of pain, depression, immobility, and death within 12 hr. Orfila (*1*) also described tin chloride poisoning in humans which occurred because tin chloride was accidentally substituted for flour.

When White (*2*) tried to prepare triethyltin salts, he inhaled some of the fumes and developed a severe headache, nausea, generalized weakness and diarrhea, and albuminuria. Harnack (*3*) observed similar symptoms of toxicity. The toxicity of tin was studied because tin was used as a lining for food cans and because canned food might be contaminated by tin (*4*). By present standards, most of these early studies were not performed well, and not much useful information can be gained from them. Inhalation of metal fumes, and this includes tin oxide fumes, may cause metal fume fever with fever, chills, vomiting, myalgia, tracheobronchitis, and often fatal pneumonia (*5*). Inhalation of tin, either as dust or fumes leads to a benign pneumoconiosis in humans. This condition is asyptomatic and apparently does not interfere with respiratory function (*6–11*). The changes in the lung consist of nodular densities which were discovered primarily in x-raying workers in tin foundries during health check-ups. Arena (*5*) points out that patients with this condition may have shortness of breath and a slight cough.

Organotin Compounds

The alkyl organotin compounds (Table 1) were developed in the present century, and some have a fungicidal effect (*12*) and are used as fungicides in paints, food crops, and other products. Alkyltin

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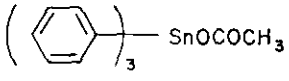
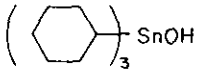
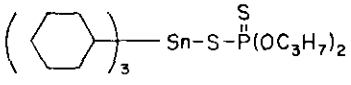
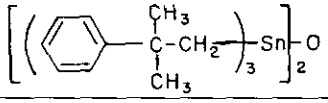
Table 1. Selected list of tin compounds.

Compound	Formula
Inorganic tin compounds	
Metallic tin	Sn
Tin salts	
Stannic chloride	$SnCl_4$
Stannous chloride	$SnCl_2 \cdot 2H_2O$
Organic tin compounds	
Alkyltin compounds	
Trimethyltin acetate	$(CH_3)_3SnO—CO—CH_3$
Triethyltin acetate	$(C_2H_5)_3SnO—CO—CH_3$
Tri-*n*-propyltin acetate	$(C_3H_7)_3SnO—CO—CH_3$
Triisopropyltin acetate	$(C_3H_7)_3SnO—CO—CH_3$
Tri-*n*-butyltin acetate	$(C_4H_9)_3SnO—CO—CH_3$
Tri-*n*-hexyltin acetate	$(C_6H_{13})_3SnO—COCH_3$
Tri-*n*-octyltin acetate	$(C_8H_{17})_3SnO—CO—CH_3$
Tetraethyltin	$(C_2H_5)_4Sn$
Diethyltin dichloride	$(C_2H_5)_2SnCl_2$
Aryl tin compounds	
Triphenyltin acetate (Breslan)	
Tricyclohexylhydroxytin (tricyclohexyltin hydroxide)	
Tricyclohexyl (diisopropoxyphosphinothioyl)thio stannane	
S-Tricyclohexyltin *O,O*-diisopropyl phosphorodithioate	
Hexakis (β,β-dimethylphenethyl) distannoxane (Vendex)	

compounds have also been used as stabilizers in certain plastics from which tubings or films for wrapping food are made (*13*) and have found a number of other industrial uses (*14*). Of the aryltin compounds, the triphenyltin compounds were suggested in the 1960's as chemosterilants for insects (*15-16*). Triphenyltin has also been tested as a molluscicide (*17*), and more recently the tricyclohexyltin compounds have been used as miticides (*18, 19*)

The acute oral and interperitoneal toxic doses of a number of these organotin compounds are listed in Table 2. The material is usually much more toxic when it is given interperitoneally than when it is given orally. Triethyl- and trimethyltin are exceptions to this rule. This difference in toxicity results from the fact that except for the dimethyl-, trimethyl- and triethyltin compounds, the organotin compounds are not very well absorbed from the gastrointestinal tract. In general, the rabbit and the guinea pig seem to be more sensitive to organotin compounds than the rat (*20*).

A number of alkyltin compounds have been more extensively investigated because of their specific toxic effects.

Diethyltin dichloride was found to be a general irritant with the ability to produce nasal irritation and headaches. It also has an emetic action on the gut (*24*).

The triethyltin compounds produce a very specific edema of the white matter of the central nervous system in a number of species, including man. This lesion was first described by Magee et al. (*25*) in the rat. These authors produced brain lesions by exposing rats to a dietary level of 20 ppm for about 2 weeks. The animals developed difficulty

Table 2. Acute oral and intraperitoneal toxicity of selected tin compounds in mammals.

Tin compound	Animal species (and sex)	LD_{50} or lethal dose, mg/kg body weight		Source
		Oral	IP	
Stannous sodium tartrate	Dog		8 × 6.74[a]	Ungar and Bodlander (*21*)
Trimethyltin	Rat	30	16	Stoner et al. (*20*)
Triethyltin	Rabbit	10	10	
Triethyltin	Rat	10	10	
Tri-*n*-butyltin	Rat	50-100	10	
Triphenyltin acetate	Rat (f)	491	11.9	Stoner (*22*)
Triphenyltin acetate	Guinea pig (m)	23.5	3.74	
Triphenyltin acetate	Rat	136	13.2	Klimmer (*23*)
Triphenyltin hydroxide	Rat (f)	360		Gaines and Kimbrough (*16*)
Tricyclohexyltin hydroxide	Rat	540	13	Dow Chemical Co. (*19*)
Tricyclohexyltin hydroxide	Sheep	150[a]		Johnson et al. (*18*)

[a]Lethal dose.

in moving their hind limbs. Finally, the rats moved about the cages with their forelimbs, dragging their motionless hind limbs. When exposure was stopped, the animals gradually recovered, and the brain lesions disappeared. This brain lesion is identical to the one produced with hexachlorophene (*26*). Electron microscopic examination of this lesion reveals that it consists of a split within the myelin sheath. The myelin sheaths are dilated and filled with fluid. The increase in the amount of water in the brain is accompained by an increase in sodium and chloride (*27*). In France, in the 1950's a poisoning outbreak occurred with a product called Stalinon, which was sold in capsules throughout France for the treatment of staphylococcal skin infections, osteomyelitis, anthrax, and acne. This preparation was said to contain diethyltin diodide, 15 mg per capsule, and linoleic acid, 100 mg per capsule. The Stalinon capsules contained impurities of monoethyltin and triethyltin. The triethyltin contributed up to 10% of the theoretical amount of diethyltin. The triethyltin was shown to produce the symptoms of toxicity. The estimated toxic dose for an adult was about 70 mg of triethyltin taken over 8 days (*28*). Symptoms of poisoning appeared in the victims after a latent period of about 4 days. The most constant symptom was severe persistent headache and, in addition, vomiting, retention of urine, vertigo, abdominal pain, and visual disturbances, particularly photophobia, and rapid loss of weight. Hyperthermia, signs of meningism, transient pareses, and sometimes permanent paralysis and papilloedema, were observed. The cerebral spinal fluid was usually normal in composition, but the pressure was raised. The more severely affected patients had convulsions. In all patients recovery was slow and in many instances, incomplete (*28,29*).

Although the cerebral edema produced by triethyltin can be induced in many species, a liver lesion which is primarily produced by dibutyltin seems to be more species-specific. The lesion of the bile duct is produced in rats and mice by dibutyltin salts and, to a lesser extent, by other analogs (diethyl to di-*n*-hexyl). It consists of an inflammatory reaction in the wall of the bile duct just before it enters the duodenum. The lining of the duct may perforate. The perforation leads to pancreatitis or peritonitis (*30*). Apparently it only occurs in species where the bile duct and pancreatic duct have a common course. In humans, the bile duct and the pancreatic duct are separate, even though they are in close proximity to each other.

The aryltin compounds are less soluble and less toxic than the alkyl tin compounds (Table 2). Triphenyltin, tricyclohexyltin, and hexakis(β,β-dimethylphenethyl)distannoxane are representatives of this group (see Table 1) and have been suggested for a number of uses. We conducted a feeding and reproduction study in rats with triphenyltin hydroxide (*16*). Only the male rats were fed the tin compound. As is true for most of the tin compounds, when triphenyltin hydroxide was mixed at high concentrations in the rat diet, the rats were repelled. This resulted in reduced food consumption and a number of rats died of starvation. Lower dietary levels of 100 and 200 ppm in the beginning of the study, reduced food consumption, but later the rats adapted to these concentrations. Early in the study, male rats had reduced fertility but the fertility later improved. The effect on fertility was explained by the partial starvation from which these rats suffered early in the study. A dietary level of 50 ppm did not affect the rats even when the triphenyltin hydroxide was fed for 276 days. Rats treated with an acute toxic

oral dose of triphenyltin hydroxide showed symptoms of sluggishness, unsteadiness, moderate diarrhea, anorexia and wheezing. Hartel (*31*) studied the toxicity of triphenyltin acetate, and no effect was produced in the rats in feeding studies that lasted for 170 days with dietary levels of 5, 25, and 50 ppm.

Tricyclohexyltin hydroxide (Plictran) has been registered in the United States as an acaricide. A tolerance of 0.2 ppm for meat fat and the meat byproducts of cattle has been set and 0.05 ppm for milk fat. The tolerance level on apples is 2.0 ppm. The Food and Agricultural Organization of the World Health Organization reviewed the available toxicity studies of this compound in 1970, and most of the information given in its report was a summary of unpublished material (*19*). This compound is apparently also very poorly absorbed from the gastrointestinal tract. After a single dose of radiolabeled material was given to rats, the entire dose was recovered within the excreta over a 10-day period after dosing, and 75–80% was excreted in the first 4 days. Most of the material was recovered in the feces, very little being found in urine. In studies with beagle dogs, dietary levels of 12 mg/kg per day reduced food consumption drastically, and some of the dogs died of starvation. Ingestion of 6 mg/kg-day for 2 yr resulted in a reduction in the final body weight, but no pathological changes were observed in the organs. At a 3 mg/kg-day dietary level, findings were normal after the material had been fed for 2 yr. The dogs that were fed 3 and 6 mg/kg-day showed brown discoloration of the serosal surface of the small intestine. This effect was not noted in dogs fed a daily dietary level of 0.75 mg/kg. Application of tricyclohexyltin hydroxide into the conjunctival sac of the rabbit eye caused irritational corneal injury which subsided in 1 week, and skin application of 0, 1.2, 2, 12, or 60 mg/kg bodyweight daily for 5 days a week for 3 weeks resulted in severe injury of the skin at all dosage levels of the test material. No systemic symptoms of toxicity were observed in these rabbits. Because of the unpalatability of the tricyclohexyltin hydroxide, the compound was administered to rats by gavage. A direct toxic effect was prodcued with doses of 25 mg/kg bodyweight. Lower doses had no effect. At the 25 mg/kg bodyweight level, severe diarrhea and weight loss were noted as well as morphological effects, namely, gastroenteritis, intrahepatic and extrahepatic cholangitis, degenerative changes in the adrenal glands, and a toxic nephrosis.

Toxicity studies with tricyclohexyltin hydroxide in livestock resulted in the death of sheep when an intrarumenal dose of 150 mg/kg was given. The repeated dermal applications of 0.5% to 1% suspensions resulted in some toxic effects, whereas lower concentrations were tolerated without any ill effect (*18*).

Barnes and Stoner (*28*) reviewed the specific pharmacological effects of alkyltin compounds in some detail, and a few of their findings will be noted. Some of these compounds apparently affect the cardiovascular and respiratory system. In cats, for instance, the intravenous administration of large doses of triethyltin sulfate may produce a fall in blood pressure (*20*). Lower doses, on the other hand, increased the blood pressure, and in rabbits the administration of triethyltin increased the respiratory rate. An acute toxic dose of an alkyltin compound caused a drop in the rectal temperature of both the rat and the rabbit (*20*).

Metabolism and Biochemical Effects of Organotin Compounds

Tetralkyltin compounds are very rapidly converted to the trialkyltin compounds in animals. The trialkyltin compounds are not degraded further (*32, 33*). The trialkyltin compounds are the pharmacologically active compounds. The most important site for the conversion of tetraethyltin is the liver. *In vitro* studies showed that the microsomal enzyme fraction and the soluble fraction of the liver cells participated in this conversion. Although tetraethyltin is fairly rapidly converted in mammals to triethyltin, the triethyltin is not further converted. This latter compound is apparently very stable (*32, 33*). The effect of different tin compounds on enzyme systems has not been extensively studied. Moore and Brody (*34*) and Aldridge and Cremer (*35*) found that triethyltin uncouples oxidative phosphorylation *in vitro*. Triphenyltin compounds have a similar effect (*36*). Moore and Brody (*34*) also established that triethyltin inhibited adenosine triphosphatases activated by magnesium and 2,4-dinitrophenol.

Only very little of the tricyclohexyltin hydroxide is absorbed, and in feeding studies only trace amounts of the parent compound were distributed to the tissues. For instance, in rats, fed 3 mg/kg body weight daily the levels in all organs were less than 1 ppm. Dicyclohexyltin oxide, trace amounts of cyclohexylstannoic acid, and inorganic tin were identified as metabolites in rats and dogs. Upon continuous exposure, a steady state in tissue is apparently reached in 40-60 days, and the tin compound is eliminated very slowly from the tissues upon cessation of feeding. The major quantity of tin

following cessation of exposure was eliminated in 20 days; trace levels were still noted, however, after 115 days (*19*).

Tricyclohexyltin hydroxide, when irradiated with a sunlamp, also breaks down to dicyclohexyltin oxide and cyclohexylstannoic acid; this is similar to its metabolism in mammals, with further degradation to inorganic tin (*37*). When apples were treated with tricyclohexyltin hydroxide, most of the residues that were recovered consisted of the parent compound (*37*). However, trace amounts of tin were also detected. Tin can be determined by wet oxidation of the sample, separation of the tin, and measurement by the colorimetric toluene-3,4-dithiol method (*38*).

Conclusions

This very brief review shows that although some of the symptoms produced by many of the tin compounds are similar: the trimethyl-, triethyl-, and butly- tin compounds are highly toxic, both in animals and man. The methyl- and ethyltin compounds, in particular, are highly soluble and are therefore well absorbed.

Inorganic tin compounds and the cyclic organic tin compounds are rather insoluble and are therefore very poorly absorbed. Because they are poorly absorbed, they are on the average only moderately toxic and at low dosage levels do not produce such undesirable side effects as edema or status spongiosus of the white matter of the central nervous system, as the triethyltin compounds do, or the degenerative changes of the bile ducts that have been observed in rats, mainly with the dibutyltin compounds. Tricyclohexyltin hydroxide does, however, cause intrahepatic and extrahepatic cholangitis in rats at high dietary levels. This effect on the liver may represent a species-specific lesion and needs to be further elucidated. Because tricyclohexyltin hydroxide produces skin irritation in rabbits, studies should be conducted to determine whether it causes contact dermatitis in man.

Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or by the U.S. Department of Health, Education, and Welfare.

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