

"TOXICITY OF ORGANOTIN CHEMICALS ADDED AS STABILIZERS AND THEIR USE
AS PESTICIDES"

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Introduction

Compounds which possess Sn-C bonds, the so-called organotin compounds, may be divided into the following 4 types: $R\text{SnX}_3$, $R_2\text{SnX}_2$, $R_3\text{SnX}$, and $R_4\text{Sn}$ (R= alkyl or aryl group). The toxicity of these compounds is in the order $R_3\text{SnX} > R_4\text{Sn} > R_2\text{SnX}_2 > R\text{SnX}_3$. $R_3\text{SnX}$ which has the highest biological activity is used as bactericide, fungicide, and algicide. This property will be discussed later on.

Compounds used as stabilizer for plastics, especially for polyvinyl chloride (PVC), are $R_2\text{SnX}_2$ and $R\text{SnX}_3$, the most commonly used substances being di-n-butyl- and di-n-octyl-tin compounds, X being a fatty acid, maleic acid, maleic semi-ester, mercaptan, mercaptocarboxylic acid, or its ester.

Lower alkyltin compounds are irritants and injure the skin. When administered by mouth to animals, the stomach is irritated, and after absorption through the stomach, the biliary system of the liver is damaged. In general, however, toxicity diminishes with increasing alkyl chain length, and di-n-octyl compounds have been accepted as stabilizer for PVC products used as wrappers and containers for food in the United States, West Germany, the Netherlands, and other countries. Methyl compounds have also been included recently in the accepted substances. Thus in the Netherlands the following have been accepted: dimethyltin-S,S-bis(isooctylmercaptoacetate), monomethyltin-S',S'',S''' -tris-(isooctylmercaptoacetate).

Among $R\text{SnX}_3$ compounds there is butylthiotin ($\text{C}_4\text{H}_9\text{SnS}_{1.5}$) which has been accepted in the United States, West Germany, and the Netherlands.

The toxicity of PVC stabilizers, their extraction and transfer from products, and regulations relating to them have been reviewed by one of us (Miyake) in Volumes I and II of "Effects of Plastic Additives on Health" edited by the Discussion Group

on Vinyl Chloride, Food, and Health, and therefore the discussion to follow will concern work done subsequent to the publication of the above review, since space does not permit inclusion of earlier materials.

1. Toxicity of Organotin Compounds

Di-n-butyltin chloride or $(C_4H_9)_2SnCl_2$ is used in largest amounts in the preparation of organotin compounds. It is also formed as a product of reaction between organotin stabilizer and HCl which is formed upon decomposition of PVC. There is, therefore, a real need for thoroughly studying its toxicity.

Gaunt et al¹⁾ in England have reported on the acute and subacute toxicity of this compound in the rat. At 24 hours after an oral administration of 50 mg/kg, there was edema and inflammation of the bile duct. This was in agreement with the findings of Barnes and Magee who have reported widely on the toxicity of organotin compounds.

Short term toxicity tests were also conducted, the animals being fed diets containing 0 (Control), 10, 20, 40, and 80 ppm of the compound for 90 days. During the feeding period, food consumption was measured and blood and urine were analyzed. At the end of the period all animals were autopsied and organ weights and pathological changes were recorded. It was found that at the high dose of 80 ppm there was a slight body weight loss (growth arrest) and decreased food intake, with mild anemia. The "no effect level" was 40 ppm, or 2 mg/kg/day in terms of daily intake.

The 100-fold safety level for man was calculated to be 0.02 mg/kg/day, or 1.2 mg/day for a 60 kg adult.

Mazur²⁾ in Poland reported on the oral toxicity in rats of dioctyltin bis(isooctylthioglycollate) (I) and the analogous derivative of dibenzyltin (II) used as wrappers and containers for food. Since the original paper has not been available, details cannot be given, but the following observations are said to have been made. In 1) a 3-month study in which (I) and (II) were administered by stomach tube at 1.0, 1.5, 2.0, 5.0, and 10.0% of LD_{50} suspended in edible oil and 2) an 18-month

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study in which (I) and (II) were added to feed at 0.02% or 0.018%, it was found that toxicity was proportional to the dose and timing of dosage, and that (I) was less toxic than (II).

Next we describe the works of Pelikan et al of Czechoslovakia.

In one study³⁾, acute toxicity of various dioctyltin compounds was tested in the mouse. Dosing was by stomach tube, and the LD₅₀ (mg/kg body weight) 48 hours after dosing was as follows:

Di-n-octyltin

Bis(butyl maleate)	3,750
Bis(2-ethylhexyl maleate)	2,700
Bis(2-ethylhexylmercaptoacetate)	2,010
Bis(butylmercaptoacetate)	1,140
Bis(dodecylmercaptide)	4,000

The clinical observations in the animals were also described briefly.

In the next study⁴⁾, the above authors tested the toxicity of various di- and mono-n-octyltin compounds in albino mice by establishing the LD₅₀ by mouth. In addition to results which duplicated the earlier study, they found that the LD₅₀ of mono-n-octyltin tris(2-ethylhexylmercaptoacetate) was 1,500 mg/kg.

For histologic study of toxicity of these compounds, the animals were given a dose of 4,000 mg/kg. Acute toxicity was observed. Upon autopsy at 24 hours, the outstanding pathologic change was fatty infiltration of the liver. In some, fatty infiltration was also seen in the renal tubular epithelia.

The same authors⁵⁾ also reported toxicity of various mono-n-butyltin compounds, namely the trichloride (I), tris(2-ethylhexylmercaptoacetate) (II), mono-n-butyltin (III), and mono-butylthiotin (IV) in albino mice.

In that study, 4,000 mg/kg of the above compounds were administered by stomach tube, and clinical inspection was made at 4, 12, and 24 hours. After 24 hours, all animals were autopsied, and gross and microscopic histology was carried out. All showed acute toxicity. Histologically there was marked change in the digestive organs in the group given (I), in which hemorrhage was observed in the mucosa and

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the submucosa. In mice given (II), (III), or (IV), there were fatty changes in the liver and the gall bladder, and irregular fatty change in the renal epithelia.

The above authors also determined the LD₅₀ (mg/kg body weight) by mouth at 48 hours, which were as follows:

(I)	1,400
(II)	1,520
(III)	76,000
(IV)	15,000-20,000

The values for (IV) were those found by Klimmer (Arzneimittelforschung 19, 934-939, 1967).

2. Transfer and Extraction of Stabilizer (Organotin Compounds)

The extent to which stabilizer added to PVC products, especially to wrappers and containers for food, is extracted and transferred to food is a problem as important as that of toxicity itself.

The FDA (Food and Drugs Administration) of the United States permits the addition of di-n-octyltin-S,S'-bis(isooctylmercaptoacetate) and its maleate polymer, singly or in combination, to specific wrappers and containers for food, provided the amount does not exceed 3 parts per 100 parts resin. It also stipulates that food in contact with the finished PVC product must not contain more than 1 ppm of either or both of the 2 above-named stabilizers.

Woggon et al⁶⁾ of East Germany have published many papers on the transfer and extraction of these materials. They added monobutylthiotin (I), monobutyltin trichloride (II), monobutyltin triacetate (III), monobutyltin tris(2-ethylhexylthioglycollate) (IV), dibenzyltin bis(2-ethylhexylthioglycollate) (V), or di-n-octyltin bis(2-ethylhexylthioglycollate) as stabilizer to hard PVC sheets, then allowed 200 cm² of the surface of these sheets to contact 200 ml of test solution, and measured the amount of transfer.

The amount of transfer of course varied with the type of stabilizer. The largest amount was transferred when (IV) was the additive, especially to water and 3% acetic acid. The least transfer was seen with (I) and (V). When different acid

residues were combined there was a difference in the amount of transfer, the difference being 10-fold in the case of sunflower oil, as shown in Table 1.

The above authors also used radioactive tracer for further observation. With di-n-octyltin bis(2-ethylhexylthioglycollate), approximately the same amount was transferred whether the label was on the ester or on octyltin (Table 2). The question then was whether the compound was transferred without decomposition or whether the decomposition products were transferred in approximately the same amounts.

Table 1. Transfer of Stabilizer in 10 Days of Standing at 45°C (ppm)

PVC and Additive	Parts	Double Distilled Water	3% Acetic Acid	15% Ethanol	50% Ethanol	n-Heptane	Sunflower Oil
PVC	100						
Stabilizer 1	1.5	< 0.15	0.4	0.2	1.5	0.45	1.5
Lubricant	1.0						
PVC	100						
Stabilizer 2	1.5	< 0.15	0.25	< 0.15	0.15	0.25	< 0.15
Lubricant SH	1.0						

Stabilizer 1: Di-n-octyltin bis(2-ethylhexylthioglycollate)

Stabilizer 2: Stabilizer 1 + di-n-octyltin bis(mono-2-ethylhexylmaleate)

Table 2. Transfer of Di-n-octyltin Bis(2-ethylhexylthioglycollate) from PVC to Sunflower Oil

Amount of Stabilizer	Storage Conditions	Stabilizer Transferred (ppm)	
		Label on Ester Group	Label on Octyl Group
2%	45°C for 10 days	0.25	0.39
1% ester	"	0.06	-
1% di-n-octyltin chloride	"	-	0.09
2%	20°C for 30 days	0.35	0.31
2%	" and 2 U-V irradiations*	0.16	0.14

*One surface of test sheet irradiated with unfiltered U-V light for 1 hour, before and after the test (Brenner S375, distance 30 cm).

Di-n-octyltin dichloride and thioglycollate ethylhexyl ester formed from di-n-octyltin compound added as stabilizer have a very different manner of transfer from that of the original stabilizer. Thus under identical conditions, there was

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about 0.3 ppm of stabilizer transferred, whereas only 0.09 ppm of the dichloride and 0.06 ppm of the ester were transferred. It may be deduced, therefore, that the alkyltin residue and acid residue which are decomposition of the stabilizer are firmly bonded to PVC and do not transfer readily.

When stored in the dark, maximum transfer was 0.47 ppm (not shown in the tables), but in daylight the amount was 0.31 ppm, and under U-V radiation it was only 0.14 ppm (see bottom line of Table 2). This is a phenomenon of considerable interest.

Figge⁸⁾ of Unilever Forschungsgesellschaft mbH (Hamburg, West Germany) has begun a 9-part report titled "Transfer of Additive from Plastic Film to Fatty Food" and has authored numerous papers on this subject. His work described in the present report is that in which transfer of di-n-octyltin dithioglycollic 2-ethylhexyl ester (trade name Irgastab 17 MOK), already frequently mentioned, from hard PVC to food was studied by radioactive tracer technique and fluorescent X-ray analysis. In other words, this was an increasingly micro-scale approach.

The procedure consisted of cutting out a 40x80 mm sample fragment from the PVC film, washing the 2 surfaces with 25 vol% Twinko solution, and measuring the radioactivity of the wash. The results are shown in the right hand column in Table 3. The values are not greatly different from the amounts transferred. In other words, the stabilizer present in the surface of the film is transferred to the fluid which comes into contact, but there is apparently no diffusion of the additive from the interior to the surface of the film. Even under identical conditions, there were 3- and 4-fold differences depending on the brand of resin.

A considerable amount of di-n-octyl($1-^{14}\text{C}$) tin residue was transferred from thioglycollic($2-^{14}\text{C}$) ester residue to edible oil. This is important when we consider the higher toxicity of thioglycollic ester ($\text{LD}_{50}=390$) compared to the original stabilizer ($\text{LD}_{50}=1,900-2,000$).

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Table 3. Radioactivity Washed Off the Surface of PVC Test Film and the Transfer of Radioactivity from Film to HB307, a Fat-Like Substance

Test Film	Transfer of Radioactivity		Surface Radioactivity of Film (%)
	At 40° and 65% RH for 10 days (%)	At 20°C and 65% RH for 30 days (%)	
Vinoflex-Sn- ¹⁴ C	0.053	0.059	0.066
Vinoflex-S- ¹⁴ C	0.034	0.037	0.041
Solvic-Sn- ¹⁴ C	0.144	0.151	0.176
Solvic-S- ¹⁴ C	0.098	0.115	0.123

HB-307: Synthetic triglyceride mixture, simulating pure salad oil and fat-containing food.

%: Calculated on the basis of original radioactivity of the test film

Vinoflex: Suspension-polymerized PVC, a product of BAS Co.

Solvic: Suspension-polymerized PVC, a product of Solvay-Werke Co.

Not only the resin brand but also the method of preparation of the film affects transfer to a marked extent (Table 4). In this study, ¹⁴C-labeled di-n-octyltin bis(2-ethylhexylthioglycollate) was added to octyltin residue and added to PVC which was made into a hard film(Solvic-Sn-¹⁴C) by extrusion. After 30 days at 20°C, 0.016% of the radioactivity was transferred to HB 307. In contrast, when the film was made by press, nearly 10 times as much radioactivity, i.e., 0.151% was transferred. This was explained as being due to the difference in mechanical and thermal load in the 2 processes of molding, resulting in chemical and physical differences and hence in different interactions with the oil.

Next, the state of bonding of Sn and S at the surface of PVC was studied by means of fluorescent X-ray analysis. Whether the material was kneaded or made into a film, the Sn-S bonding of the stabilizer was no longer present, the bonds being those of mercaptan, sulfide, sulfoxide, sulfone, and sulfonic acid, representing various stages of oxidation. There was strong bonding with the polymer and no divalent tin could be found.

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Table 4. Transfer of ^{14}C -Labeled Irgastab 17 MOK in Hard PVC to Edible Oil or Imitation-Oil HB 307

Name of Preparation	Method of Molding	Oily Material	Radioactivity Transferred (%) (After 60 Or 30 Days at 20°C/65% RH)	Additive in Oil (ppm)		
				Irga-stab	Di-n-octyl-tin dichloride	Thioglycollic 2-ethylhexyl ester
Solvic-Sn- ^{14}C	Extrusion	Olive oil	0.017	0.117	0.065	0.064
		Sunflower oil	0.021	0.144	0.080	0.078
		Biskin*	0.009	0.062	0.034	0.033
		SB margarine	0.007	0.048	0.027	0.026
		Butter	0.017	0.117	0.065	0.064
		Cocoanut oil	0.014	0.096	0.053	0.052
		HB 307	0.016	0.110	0.061	0.060
Solvic-S- ^{14}C	Kneading and Press	HB 307	0.151	0.996	0.551	0.542
		"	0.115	0.709	0.392	0.386
		"	0.059	0.338	0.187	0.184
Vinoflex-Sn- ^{14}C	Press	"	0.037	0.200	0.111	0.109
Vinoflex-S- ^{14}C						

*Biskin: Partially oxidized peanut oil

3. Decomposition of Organotin Compounds

It has already been mentioned that organotin compounds added to PVC reacts with HCl which has been produced as decomposition product of PVC, to become organotin chloride and acid residue, etc. In addition to this problem, there is the question of decomposition by U-V of bactericidal agricultural product such as tricyclohexyltin compounds, to constitute the so-called residual toxicity. Thus the behavior of organotin compounds relative to the environment cannot be ignored.

If alkyl (or aryl) groups in tin compounds are removed one by one to leave inorganic tin in the end, removal of several hundreds of ppm at once would cause acute toxicity, but otherwise there should be no damage (tin has been claimed recently to be one of the essential elements in the human body), and there should be no fear of toxicity resulting from the use of organotin compounds.

Akagi et al¹⁰⁾ of the National Health Institute have studied the decomposition of triphenyltin, dioctyltin, and butyltin compounds by U-V rays. From among the

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dialkyltin compounds used as stabilizers for PVC, they selected dioctyltin dichloride (DOTC) and dibutyltin dichloride (DBTC), and irradiated them in watchglasses with U-V light at a distance of 10 cm. Aliquots were removed at intervals and tin compounds were sought by TLC.

Table 5. Decomposition of DOTC by U-V Light

Com- pound \ Time (hr)	0	6	45	90	250	325	370
DOTC	++	++	++	++	+	±	-
MOTC	-	±	++	+	+	±	-
TC	-	+	++	++	++	++	++

Table 6. Decomposition of DBTC by U-V Light

Com- pound \ Time (hr)	0	6	12	24	45	90	135
DBTC	++	++	++	+	±	±	-
MBTC	-	±	+	+	+	±	-
TC	-	+	++	++	++	++	++

-: Undetectable. ±: barely detectable,
+: definitely detectable, ++: very clearly
detectable

MOTC: Mono-octyltin trichloride

MBTC: Mono-butyltin trichloride

TC: Tin tetrachloride

It may be seen from Tables 5 and 6 that in all instances there was partial decomposition within 6 hours and tin tetrachloride (TC) became detectable. In the case of DBTC, this compound became virtually undetectable in 45 hours, and in 90 hours virtually all of it was decomposed to TC. With DOTC, on the other hand, the time required to reach the stage of undetectability was over 300 hours, indicating the marked difference between the 2 compounds. In PVC film containing DBTC, decomposition also occurred within 6 hours, and virtually complete decomposition was reached after 45 hours. The film changed from colorless transparent state to one of greenish brown color, and flexibility was lost so that the film broke readily.

Price et al¹¹⁾ of Tin Research Institute of England carried out similar experiments on triphenyltin acetate which is an agricultural chemical, and obtained results indicating a similar trend for decomposition.

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The final resting place of plastic products is in most instances the municipal incinerator. Regarding incineration of PVC products there has been considerable study on gas generation but the behavior of additives which are used in small quantities has not been pursued to any extent. There is only one report, that of Fukaya and Kato¹²⁾ of Industrial Guidance Office, Aichi Prefecture, which stated that tin was volatilized from PVC (sheet) with added dibutyltin maleate, beginning at 150°C and completely ending at 250°C.

4. Biological Activity of Organotin and Its Utilization

The same chemical agent may show considerably different biological activity depending on the biological subject. In the present discussion, the main interest is on the production of industrial poison, so that the subjects are the lower organisms such as molds, bacteria, and algae. Against these organisms, the tertiary (R_3SnX) type to be described below are the most active. The tetra- and di- forms are intermediate in activity, while the mono- type is virtually inactive. The structure of R has the greatest effect on biological activity. Against the lower organisms, potency is highest in C_3 (Pr) and C_4 (Bu) compounds in which R is an alkyl group. When the number of carbons is above or below this range, activity diminishes rapidly. When R_3 is asymmetric, i.e., in the case of $(RR'R'')SnX$, activity is not related to the properties of the individual alkyl groups but is determined by the total number of carbons in the 3 alkyl groups, the highest activity being obtained with C_9-C_{12} compounds¹³. When the number of carbons is above or below this range, activity diminishes rapidly. Consequently dimethyloctyltin has the same activity as tripropyltin. When R is an iso- configuration, there is no real difference from the activity of the normal compound. When R is cyclized, activity is greater than in the alkyl compound of the same number of carbons¹⁴⁾. Triphenyltin follows tripropyltin and tributyltin in activity. Aryl compounds are more complicated, i.e., activity diminishes as the number of carbons increases. It has been reported¹⁵⁾ that when the hydrogen

in R is replaced by hydrophilic groups, for example, activity is reduced.

The X group is considered to be unrelated to biological activity, but it is profoundly related to solubility, volatility, and swelling, so that it has an important effect on the property of the product, which means that the effectiveness of the product as a drug is greatly affected.

The mechanism of toxicity of organotin, in the case of tertiary compounds, is through interference with oxidative phosphorylation. It is believed that the variation among the different organotins is due to their specific enzymatic activity and the difference in their capacity to permeate cells. In the case of the di- compounds, it is believed that the compound reacts with coenzyme having thiol group to interfere with synthesis of acetyl coenzyme A, and in the case of tetra- compounds it is thought that the compound is de-alkylated in the body to form the tertiary compound.

Since environmental pollution is always a problem, we shall touch upon the subject of toxicity for higher organisms. The effect on plants has been studied by agricultural chemists. Sensitivity has been found to vary greatly depending on the species. Among organotins, the lower alkyltins such as triethyl and tripropyl compounds have been found to be the most toxic, whereas aryltins such as triphenyltin were considerably milder in their toxicity. This toxicity in plants, or drug toxicity, has greatly limited the use of these compounds in agriculture. They have been used, on the other hand, as weed killers.

Toxicity in mammals has been found to be different from that in lower organisms. Triethyltin is the most toxic, and as R becomes larger, toxicity diminishes rapidly. Comparative toxicity of $R_3\text{SnOAc}$ compounds in the rat (LD_{50} by mouth) has been found to be as follows: methyl 9.1, ethyl 4.0, propyl 118.3, butyl 380.2, hexyl 1,000, and octyl $>1,000$ mg/kg¹⁶⁾. In a separate study¹⁷⁾, the LD_{50} by mouth in the rat of Ph_3SnOAc was found to be 429-491 mg/kg.

The fact that substances such as tributyltin and triphenyltin which are important industrial poisons have only moderate or low toxicity to mammals, and the fact that

non-toxic inorganic tin compounds or metallic tin are obtained upon decomposition make these compounds objects of expectation and development to replace mercury and lead systems which are toxic even in the metallic states.

We have discussed the toxicity of organotin, next we shall take up briefly the utilization of this toxic property.

4.1 Agricultural Bacteriocides

There are many bacterial diseases that attack farm products. Drugs which combat these diseases are called agricultural bacteriocides. For the simple destruction of the causative bacteria, tripropyltin and tributyltin are the most potent, but these agents are highly toxic to the crop, and therefore triphenyltin is the group that is used for the most part. The crop to be treated is also limited to vegetations which are resistant to organotins. The compound being used in the largest quantity today is triphenyltin acetate, followed by the hydroxide and the chloride. The use of suitable adjuvants is of course permissible, and the products are in the form of powder, hydrate, and emulsion. There are commercial products which are combinations of these agents with other bacteriocides, the purpose being to obtain synergistic effects. The diseases treated by these agents include sticky (sic) disease in potatoes, brown spots in sugar beets, and celery wilt. The effectiveness is said to be roughly 10 times that of copper or dithiocarbamate types of bactericides. The concentration used is about 0.3%. Residual toxicity has been studied in detail, and no problem has been found regarding toxicity to man and livestock¹⁹⁾. In addition to the above uses, these agents are employed also for treating coffee, peanuts, and pecans, as well as for disinfecting seeds and bulbs.

There is nevertheless some danger of drug toxicity, so that the compounds are not widely used as bacteriocides. There have been many recent patents which manipulate R and X for the purpose of reducing drug toxicity. Triphenyl has been replaced by a tricyclohexyl group in one of these studies, since the latter is less toxic to plants.

4.2 As Insecticides and Tick-killers

Various organotin compounds have been proposed as insecticides, and there have been a number of reports on their application, but since this area is dominated by organic chlorine and phosphorus compounds, organotins have not made much inroad. The principal agents in use have been derivatives of triphenyltin and tributyltin, although recently hexamethyl-ditin ($\text{Me}_3\text{Sn-SnMe}_3$) and tricyclohexyltin derivatives have been made.

Organotin compounds have attracted interest since antifeeding (insects avoid eating treated leaves and starve to death) and antifertility effects could be obtained at concentrations far below those required for killing insects.

Triphenyltin chlorides and hydroxides and tricyclohexyltin hydroxide have been marketed as anti-tick agents²⁰⁾. These are effective against red ticks (citrus fruits) and spider ticks (cotton, beans) which are resistant to malathion. They are also effective against the scorpion, attaining 100% killing in the form of a 0.5% powder within 24 hours.

4.3. As Mollusc Killers^{21,22)}

Tributyltin oxide is being used to eradicate fresh water snails such as the Katayama snail which are intermediate hosts for *Scistosoma*. Schistosomiasis is an endemic disease which, in developing countries, parallels malaria in causing economic damage. Eradication of this disease is one of the main projects for the United Nations. Both larvae and adults of these worms are killed by $(\text{Bu}_3\text{Sn})_2\text{O}$ at 0.015-0.03 ppm, but at high concentrations there is injury to fish and shrimp. The drug is therefore dissolved in elastomer and scattered in the form of pellets to permit slow solution.

4.4. As Vermicide (in Fowls)

Dibutyltin dilaurate is used to treat chickens infested with intestinal tapeworm. The tertiary compound is also effective but the di- form is used to avoid toxicity to the bird. The dose is 125 mg/kg body weight, and a single administration suffices.

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The drug is highly effective against both larva and adult, but it is not very effective against roundworms. Most of the administered organotin is directly excreted, and even the absorbed portion disappears completely in about 9 days. Egg laying is temporarily reduced, but no tin is detectable in the egg.

4.5. As Anti-rot Agent for Lumber, and as Agent Against Marine Parasites^{23,25,26)}

The use of organotin to prevent rotting of lumber is a relatively recent development following demonstration of its biological activity. The target includes bacteria, insects, and marine parasites (molluscs), and thus the appropriate organotin compounds are tripropyltin and tributyltin. Tripropyltin is effective against Gram negative bacteria also and has a wider bactericidal spectrum, but its ability to bind with wood is less than that of the butyl compounds, and toxicity to warm blooded animals is higher, so that tributyltin is used for the most part. The X group affects volatility and effluence, and many types have been suggested, but at the present time $(n\text{-Bu}_3\text{Sn})_2\text{O}$ is used most frequently. The drug is prepared as a 0.1-1% solution, and applied in a variety of ways, from painting on with a brush to injection under pressure. An interesting technique is to dissolve the drug in liquid butane and inject under pressure, recovering the solvent under vacuum. The procedure is used for lumber which has undergone mechanical processing. The solvent is organic but aqueous suspensions are also used. The latter include quaternary ammonium salts which act as surfactant as well as reinforcer of bactericidal activity. The usual injection dose is 0.2-0.5 kg/m^3 , which is lower than all other antirot agents, being about 1/10 the amount of pentachlorophenol (PCP) and about 1/20 that of creosote.

The features of organotin include the following: affinity for cellulose in lumber is very strong, so that immersion in running water for a long time does not result in washing out of the agent; resistance to photo-destruction is greater than that of PCP or organomercury²⁴⁾; it is colorless; it is highly toxic to bacteria which are the main cause of rotting, the activity being 10-30 times that of PCP; there is

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no adverse effect on nails and aluminum materials, which is a real advantage over mercury, copper, and zinc agents; it can be mixed with paint; and there is less odor than creosote. It is, however, less effective against termites, and should be used in mixture with agents such as Deildrin.

For use against marine parasites, the concentration should be increased to 0.5-2% and the volume of injection should also be increased. It is especially effective against sea lice and gull parasites.

According to findings in the United States and Great Britain, the material is safer for injection than creosote. There is little seepage, and since it binds strongly with cellulose, it does not float out on the surface. As for contact toxicity, tests made with cotton fabrics showed that there is no skin irritation if the amount of $(n\text{-Bu}_3\text{Sn})_2\text{O}$ adhering to the cloth is under 500 ppm.

4.6 Prevention of Slime Formation (in Paper Factories)²⁷⁾

Paper plants use large volumes of circulating water. The water is called white water and contains, in addition to cellulose, hydrocarbons, phosphates, and nitrogen compounds, which promote growth of microorganisms. Thus bacteria and yeasts proliferate, and their aggregation produces viscous slime which interferes with processing and causes deterioration of the product. To prevent this, mercury and chlorine agents are being used, but these are toxic or malodorous, so that $(\text{Bu}_3\text{Sn})_2\text{O}$ has been recommended to take their place. It is said that only a small amount of the tin compound suffices, for example 1.3 kg added to 60,000 tons of circulating water every 8 hours, and that organotin is transferred to paper and does not pollute the effluent.

4.7. As Mold Preventive in Paints²⁸⁾

Mildew often develops on painted surfaces, spoiling the appearance and destroying the coat. This is often seen with emulsion paints. To prevent this, mold preventive is added to paint at the time of manufacture, but since mercury and lead agents are highly toxic to man and animal, organotins have been recommended. Derivatives of

tributyltin and triphenyltin, led by $(n\text{-Bu}_3\text{Sn})_2\text{O}$, have been used. The amount in the case of emulsion paints is 0.05-0.1% for ordinary purposes, and 0.5-1% for places which tend to develop mildew, for example fermentation chambers.

4.8. As Preventive Against Contamination (Ship Bottom Paint)^{25),28-30)}

The poison for use on ship bottoms has been copper suboxide for the last 100 years, Mercury agents have been used in combination with the above. These preparations, however, are not completely satisfactory by any means, having numerous deficiencies, such as being ineffectual against seaweed, being subject to galvanic corrosion, and being limited in the range of color. There are additional demands including the desirability of lower toxicity to man and animal, and of extending the duration of effectiveness. When ships are docked, barnacles adhere to the vessels, and during sea voyages there is deposition of certain seaweeds. Since the development of container ships and rush (sic) ships and with advances in loading processes, anchorage time has been greatly shortened, and consequently damage caused by seaweeds has become more conspicuous. As result there is demand for improved decontaminant. History of the organotin type of ship bottom paint is still short and experience is limited, but this group of compounds have been found to be effective against seaweeds, free from electrical corrosion, and capable of mixing with paints of a wide range of coloration, thus overcoming many of the deficiencies of the copper type of compounds. Good performance is anticipated. Taking solubility and human toxicity into consideration, the suitable compounds turn out to be derivatives of tributyltin and triphenyltin. Various possibilities exist for the X group which has an effect on the rate of effluence to be discussed later. The anti-contamination effect is caused by the drug being dissolved out at the surface and acting on the organism attempting to attach to the vessel. The balance of the rate of effluence and toxicity (minimum concentration which prevents deposition of organism) becomes important. The rate of effluence is related to the physical properties of the anti-contaminant and the type and properties of the paint vehicle. In the case of $(\text{Bu}_3\text{Sn})_2\text{O}$, the optimum rate of effluence,

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taking toxicity into consideration, is believed to be about $1 \mu\text{g}/\text{cm}^2/\text{day}$. To obtain this rate, vinyl rosins are believed to be suitable. Thus it is not only the active poison but also the appropriate combination with paint that is important. At the present time, various derivatives of tributyltin and triphenyltin, led by $(\text{Bu}_3\text{Sn})_2\text{O}$, are being used, and various types of paints are also being studied. Among the unusual substances is one in which organotin is dissolved in an elastomer, and another in which organotin is copolymerized in a polymer and allowed to gradually release organotin side chain through hydrolysis by sea water. New patents are being reported one after another.

4.9. As Disinfectant³¹⁻³³⁾

Today when hospitals have become sources of infection, there are staphylococci called "hospital staph" which are resistant to antibiotics and disinfectants. They are extremely pathogenic, causing virulent suppurations characterized as carbuncles, which may be fatal through septicemia. Ordinary disinfectants are ineffectual and constant disinfection is necessary. It was discovered in the United States that organotins are effective against these staphylococci. These compounds have been prepared under a variety of trade names. They utilize the synergism between $(n\text{-Bu}_3\text{Sn})_2\text{O}$ and quaternary ammonium salts, and are used at concentrations of several hundred ppm. The effect is long-lasting. It is said that after being used to disinfect a hospital floor, the effect was maintained even after 8 weeks. In Germany, a similar product is sold under the name of Incidin. This is a combination of tributyltin benzoate $(\text{Bu}_3\text{SnOBz})$ and hexamethylenetetramine, formalin, and a small amount of SO_2 in an emulsion. This preparation also exhibits good synergism, and besides being effective against Gram positive bacteria such as staphylococci and molds, it is also active against Gram negative bacteria and viruses against which tributyltin alone is ineffectual.

These agents are not limited in their use to hospitals but are used in the household as general disinfectants for shoes, athletic tools, and damp walls. In

these instances they are used as concentrations around 200 ppm.

4.10. Others^{25,27)}

In addition to the above, tributyltin compounds are used to inhibit algal growth in industrial water, for example circulating water for cooling, and for inhibiting iron and sulfur bacteria. They are also used as disinfectants for fiber products such as underwear, tent, and awning, leather products such as furs and shoes³⁴⁾, and substances that are subject to mildew, for example wood, bamboo, and paper. The products used are those consisting of derivatives of tributyltin and triphenyltin in appropriate combination with other ingredients such as described above to broaden the bactericidal spectrum. The concentration used is usually around 0.02%, and the preparations are used by spraying or impregnating.

In a different route of application developed recently, tributyltin agents have been used to inhibit growth of moss and lichen on stone materials such as tombstones. The effect is reported to be long-lasting³⁰⁾.

Another use of a different sort is as rodent repellent (prevents gnawing)^{25,35)}. Here again tributyltin and triphenyltin are used. Hemp bags for storing grains may be impregnated with these agents, and electric cables may be sheathed with material containing these agents. To sustain the effect, effort is being made to devise a proper adhesive.

In general, selective poisons which are non-toxic to man and animal but toxic to microorganisms tend to vary greatly in their effect depending on the type of organism. Thus a given drug may be effective against mold A but not against mold B. It therefore becomes necessary to make careful studies of the target organism in selecting drugs and their combinations.

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