Organotin Compounds: Industrial Applications and Biological Investigation

by Warren T. Piver*

Industrial Uses of Organotin Compounds

According to Ross (1), there are three main areas in which organotin compounds have product and process utility: (1) heat stabilizers; (2) catalytic agents; (3) biocidal compounds. Organotin derivatives account for the fourth largest production of organometallics amounting to about 3-4 million pounds per year as compared with about 485 million pounds per year for organolead compounds. Originally, organotin compounds were developed as thermal stabilizers for chlorinated hydrocarbons which would be used in those applications for which there was a strong possibility of thermal degradation. However, as the chemistry of organotin compounds became better understood, their application expanded to catalytic and biologically active agents.

Heat Stabilizers

Organotin stabilizers prevent the thermal degradation of many chlorinated compounds such as certain types of transformer oils, PVC, poly(vinylidene chloride), chlorinated rubbers, paraffins, and modified plastics. The organotins have also been used to stabilize other nonhalogenated compounds of industrial and commercial importance such as some lubricating oils, hydrogen peroxide, cellulose acetate, polyamides (nylon), polycarbonates, polyethylene, and polypropylene.

Chlorinated Transformer Oils: The use of organotin compounds as stabilizers for chlorinated transformer oils dates back to 1932. At that time, the transformer insulation consisted of paper and mineral oil. Large temperature gradients across the oil generated by power fluctuations in the transformer, caused decomposition of the mineral oil to a sludge. This oxidative decomposition was prevented by the addition of tetraalkyl or tetraaryl tin. In 1957 General Electric developed replacements for mineral oils which were trichlorobenzene, pentachlorodiphenyl, and pentachlorodiphenyl oxide. The chlorinated aromatic transformer oils had more accurately defined heat transfer characteristics than did mineral oil. However, when arcing occurred in transformer operation, these compounds decomposed and liberated HCl which corroded the interior of the transformer. Tetraalkyl and tetraaryl tin compounds were added to react with the liberated HCl to form organotin chlorides (and alkanes or benzene). The motivation for using tetraorganotin compounds was the desirable volume to efficiency factor for corrosion prevention: one mole of organotin

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removed four moles of HCl. For example, tetraphenyltin stabilized chlorinated transformer oil as shown in eqs. (1) and (2).

Chlorinated aromatic transformer oil $\rightarrow_{\Delta} \text{HCl}$ (1)

$$(\text{C}_6\text{H}_5)_4\text{Sn} + \text{HCl} \rightarrow (\text{C}_6\text{H}_5)_3\text{SnCl} + \text{C}_6\text{H}_6 \quad (2)$$

**PVC Stabilizers:** By far the largest proportion of organotin stabilizer production is for the stabilization of PVC. PVC resin is a white powder produced by free-radical, ionic, and emulsion polymerization. In order to mold the resin into finished products, the resin is softened by heating. For unplasticized PVC, this softening temperature approaches the thermal decomposition temperature of the resin. PVC polymers are particularly susceptible to thermal degradation during processing and use. Thermal stabilizers are therefore an essential additive for both rigid and flexible PVC products.

PVC polymers are usually not linear molecules; therefore, several mechanisms are required to explain the thermal decomposition of PVC (1,2). For the general polymer structure, which may be linear or branched, degradation begins at a site on the molecule either containing or adjacent to a tertiary or allylic chlorine atom. These two kinds of sites can act as activating groups to initiate degradation. Once the first molecule of HCl is liberated, the reaction is propagated down the chain, forming eventually a long-chain, colored, conjugated polyene. Beginning with the linear molecular model of PVC, this degradation reaction is as shown in eq. (3), where X denotes the activating group.

$$\sim \text{CH}_2-\text{CHCl}-\text{CH}_2-\text{CHCl}-\text{CH}_2-\text{CHCl} - \text{X}$$

$$\Delta \rightarrow \text{HCl}$$

$$\sim \text{CH}_2-\text{CHCl}-\text{CH}_2-\text{CHCl}-\text{CH} = \text{CH} - \text{X}$$

$$\text{HCl}$$

$$\sim \text{CH} = \text{CH} - \text{CH} = \text{CH} = \text{CH} \sim$$

Also, for a linear molecule, an allylic chlorine is a weak point for degradative attack. An allylic chlorine is formed generally from disproportionation chain termination mechanisms. An example of this kind of structure is I:

$$\sim \text{CH}_2-\text{CHCl}-\text{CH}_2-\text{CH} = \text{CHCl} \sim$$

I

Branching creates a tertiary chlorine on the main chain which is vulnerable to degradative attack. An example of this type of structure is II:

$$\sim \text{CH}_2-\text{CHCl}-\text{CH}_2-\text{C} = \text{CH}_2-\text{CHCl} - \text{CH}_2$$

II

In both the allylic and branched PVC structures, heating results in the liberation of HCl, which initiates the reaction. The reaction is then propagated down the polymer chain producing colored conjugated polyenes.

The organotin stabilizers probably come closest to being the ideal compounds for preventing the thermal degradation of PVC. Particularly in unplasticized PVC products such as water and sewer pipe, organotin stabilizers make it possible to heat PVC resin to the high temperatures required for molding.

The concentration range of organotin compounds required to heat stabilize PVC during processing is between 0.5 to 3.0 parts per hundred parts of resin (phr). Organotin compounds are compatible with PVC resins and plasticizers and give clear products. The organotins also stabilize for long periods of time. This is important, since the scrap generated during processing can be recycled. The major drawback to the widespread use of organotin compounds is their cost which ranges from $1.50 to $2.50 per pound. Organotin stabilizers are four times as expensive as barium-cadmium compounds, and approximately six times more costly than lead stabilizers on a weight basis.
There are approximately 1000 patents for organotin stabilizer formulations, but only about 11 basic compounds are of commercial value. The dibutyl and dioctyltin derivatives are the most important. In general the dibutyl and dioctyl derivatives are synthesized by reacting the dibutyl or dioctyltin oxides with a fatty acid, anhydride, or mercaptide to form the respective stabilizer (and water). The main organotin stabilizers are given in Table 1, which has been compiled from Nass (2).

The most effective organotin stabilizers for PVC are the dibutyl derivatives. Their solubility in the resin and in almost all plasticizers imparts a clarity to the finished product which is unmatched by any other group of stabilizers currently in use. Most dibutyl derivatives are used in rigid PVC products such as pipes, bottles, insulation, siding, etc. Each particular dibutyl derivative has special properties for each method of processing. Therefore, the finished product usually contains a mixture of several stabilizers which was designed for a specific product, its processing scheme, and its environmental exposure. Because of this, the stabilizer manufacturer works very closely with the plastic manufacturer and custom blends his additives for the processing and end product use.

The dioctyltin derivatives were developed specifically for PVC items which come in contact with food. The FDA regulates these stabilizers in the CFR, Title 21, Part 121, Subpart F, 121.2602. The dioctyltin stabilizers must not be contaminated with the mono- and tri-n-octyltin derivatives and food in contact with these stabilized plastic containers shall contain no more than 1 ppm of the organotin stabilizer. The analytical procedure (3) prescribed by this regulation determines total tin content extracted by the foodstuff in contact with the dioctyltin stabilized container or wrapping.

Because of the complex nature of PVC molecules, there are four highly probable paths of thermal decomposition. It is for this reason that a blend of several stabilizers is required to accomplish the stabilization of PVC polymers. Corresponding to the four mechanisms of thermal decomposition, the four mechanisms of stabilization of PVC are as follows.

1. Scavenging of HCl to form dibutyl or dioctylmonochlorides and dichlorides:

$$\text{PVC} \xrightarrow{\Delta} \text{HCl}$$

$$\text{Bu}_2\text{Sn}(X)_2 + \text{HCl} \rightarrow \text{Bu}_2\text{SnXCl} + \text{XH}$$

where $X$ represents fatty acid, anhydride or mercaptide ligand.

2. Radical inhibition (chain transfer mechanism):

$$\text{R} - + \text{Bu}_2\text{Sn}(X)_2 \rightarrow \text{RX} + \text{Bu}_2\text{SnX}.$$ 

In this particular application, the mercaptide ligand is a very effective radical scavenger and inhibitor.

3. Carbalkoxylation:

$$\text{Bu}_2\text{SnX}_2 + (\text{-CH}_2 - \text{CHCl} - \text{C=CH}-) \rightarrow$$

$$\text{Bu}_2\text{SnCl}_2 + 2 (\text{-CH}_2 - \text{CHX} - \text{C=CH-})$$

4. Diels - Alder addition:

$$\begin{align*}
\text{Bu}_2\text{Sn} & \xrightarrow{\text{O}} \begin{array}{c}
\text{O} \\
\text{C} \end{array} \begin{array}{c}
\text{CH} & + \begin{array}{c}
\text{O} \\
\text{C} \end{array} \begin{array}{c}
\text{CH} & \text{-CH} = \text{CH-CH}2\text{-CHCl-} \end{array} \\
\text{CH} & \text{-CH} = \text{CH-CH}2\text{-CHCl-} \end{array} \\
\text{Bu}_2\text{Sn} & \xrightarrow{\text{O}} \begin{array}{c}
\text{O} \\
\text{C} \end{array} \begin{array}{c}
\text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH2} - \text{CHCl} - \\
\text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH2} - \text{CHCl} - \\
\text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH2} - \text{CHCl} - \\
\text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH} & \text{CH2} - \text{CHCl} - \\
\end{array}
\end{align*}$$
| Name and structure | Trade names | Suppliers | Description and uses |
|-------------------|-------------|-----------|----------------------|
| Dibutyltin dilaurate | Thermolite 12 | M & T Chemicals | Excellent lubricating properties for easy processing; usually combined with other stabilizers; for film and sheet |
| \( \text{C}_4\text{H}_9\text{SnOCC}_{11}\text{H}_{23} \) | Advastab DBTL, Niax D-22, Clear 1 | Adv.Div., Carbide Chem. Union Carbide Chem. | |
| Dibutyltin maleate | Thermolite 13 | M & T Chemicals | Good stabilizer; poor lubricating ability; for film and sheet |
| \( \left[\text{C}_4\text{H}_9\text{SnOOCCH} = \text{CHCOO}\right]_n \) | Advastab T-340 | Adv.Div., Carbide Chem. | |
| Dibutyltin laurate-maleate | Thermolite 17 | M & T Chemicals | Outstanding heat and light stability for film and sheet with good lubricating properties for processing |
| \( \left(\text{C}_4\text{H}_9\right)\text{Sn} - \text{OOCCH} \) | | | |
| \( \left(\text{C}_4\text{H}_9\right)\text{Sn} - \text{OOCCH} \) | | | |
| Dibutyltin bis (lauryl mercapto- | Thermolite 20 | M & T Chemicals | Good lubricating properties; used with dibutyl tin \( S,S\)-bis (isoctylthioglycolates) |
| \( \left(\text{C}_4\text{H}_9\right)\text{Sn} - (\text{SC}_{12}\text{H}_{25}) \) \( \text{C}_8 \) | Advastab TM-918, Mark A | Adv.Div., Carbide Chem. Argus | |
| Dibutyltin bis(monoalkyl | Thermolite 25, 26 | M & T Chemicals | Light and heat stability to tubing; and PVC and PVC copolymer sheet and film |
| \( \left(\text{C}_4\text{H}_9\right)\text{Sn} - \text{OOCCH} = \text{CHCOOR} \) \( \text{C}_8 \) | Advastab T-52N, T-150, Mark 275 | Adv. Div., Carbide Chem. Argus | |
| Dibutyltin \( S,S\)-bis (isoctyl thioglycolate) | Thermolite 31 | M & T Chemicals | Stabilizer for rigid PVC pipe; control of melt viscosity; permanence; good for pigmented rigid applications |
| \( \left(\text{C}_4\text{H}_9\right)\text{Sn} - (\text{SC}_8\text{H}_{17}) \) \( \text{C}_8 \) | Advastab TM-180, Mark 292, Synpron 1001 | Adv. Div., Carbide Chem. Argus Synthetic Prod. Co. | |
| Dibutyltin \( \beta \)-mercapto-propionate | Thermolite 35 | M & T Chemicals | Used for bottles, film and sheet |
| \( \left[\text{C}_4\text{H}_9\text{SnSCH}_2\text{CH}_2\text{COO} \right]_n \) | Advastab T-360, Mark 488 | Adv. Div., Carbide Chem. Argus | |
| Di-\( n \)-octyltin maleate | Thermolite 813 | M & T Chemicals | Used in bottles, film and sheet for food contact according to CFR, FDA, Title 21, Part 121, Subpart F, 121.2602. |
| \( \left[n - \text{C}_6\text{H}_{17} - \text{Sn} - \text{OOCCH} = \text{CHCHOO} - \right]_n \text{C}_6\text{H}_{17} \) | Mark OTS | Argus | |
| Di-\( n \)-octyltin \( S,S\)' | Thermolite 831 | M & T Chemicals | Maximum heat stability and processability. FDA sanctioned for bottles, films and sheets for food contact |
| \( \left(n - \text{C}_6\text{H}_{17} \right) - \text{Sn} - (\text{SC}_8\text{H}_{17}) \) | Advastab TM-188, Mark OTM | Adv. Div., Carbide Chem. Argus | |
| \( \left(n - \text{C}_6\text{H}_{17} \right) - \text{Sn} - \text{OOCCH}_2\text{S} \) \( \text{C}_8\text{H}_{17} \) | | | |
Table 1. Commercially important butyltin and n-octyltin stabilizers. (Continued)

| Name and structure | Trade names | Suppliers | Description and uses |
|--------------------|-------------|-----------|----------------------|
| Di-n-octyltin β-mercapto-1 propionate | Advastab T-270 | Adv. Div., Carbide Chem. | FDA sanctioned for bottles, films and sheets for food contact. |
| \(n\text{-C}_8\text{H}_{17}\) \(\text{SnSCH}_2\text{COO}\) \(\text{CH}_2\) \(\text{CH}_2\) \(\text{C}_8\text{H}_{17}\) | Mark 492 | Argus | |
| or \(\frac{\left[n\text{-C}_8\text{H}_{17}\right]}{n}\text{-SnSCH}_2\text{COO}\text{CH}_2\text{CH}_2\) \(\text{C}_8\text{H}_{17}\) | | | |
| Di-n-octyltin \(S,S'\)-bis (2-ethyl hexyl mercaptoacetate) | Mark OTM | Argus | |
| \(n\text{-C}_8\text{H}_{17}\) \(\text{Sn(S-CH}_2\text{COOCH}_2\text{CHC}_4\text{H}_9)_2}\) | | | |
| \(n\text{-C}_8\text{H}_{17}\) \(\text{C}_2\text{H}_5\) | | | |

Catalytic Agents

**Urethane Catalysts:** In the production of polyurethane foams, organotin catalysts allow the foam to be made directly from hexamethylene diisocyanate and 1,4-butanediol. The overall reaction mechanism is as shown in eq. (4).

\[
n[\text{O=C=N-(CH}_2\text{)}_6\text{N=C=O}] + n[\text{HO-(CH}_2\text{)}_4\text{-OH}] \rightarrow \text{Addition} \\
\begin{array}{c}
\text{O=C=N-(CH}_2\text{)}_6\text{N=C} \\
\| \\
\text{O}
\end{array}
\begin{array}{c}
\text{O-(CH}_2\text{)}_4\text{-OH}
\end{array} \rightarrow n
\]

\[
\begin{array}{c}
\text{C-NH-(CH}_2\text{)}_6\text{-NH-C-O-(CH}_2\text{)}_4\text{-O-}
\end{array}
\begin{array}{c}
\| \\
\| \\
\text{O} \quad \text{O} \quad \text{O}
\end{array} \rightarrow n \quad (4)
\]
There are three main steps to this mechanism. They are: chain extension [eq. (4a)], gas reaction [eq. (4b)], and crosslinking [eq. (4c)].

\[
\begin{array}{c}
\text{O=C=N-(CH}_2\text{)}_6\text{-N=C=O + HO-(CH}_2\text{)}_n\text{-OH} \\
\rightarrow \\
\text{O - C - N (CH}_2\text{)}_6\text{-N - C - O} \\
\mid \\
\text{O H H O} \\
\end{array}
\]  

\[\text{eq. (4a)}\]

\[
\begin{array}{c}
\text{R - N=C=O + H}_2\text{O} \rightarrow \text{R - N - C - OH} \rightarrow \text{R NH}_2 + \text{CO}_2 \\
\mid \\
\text{H O} \\
\end{array}
\]

\[\text{eq. (4b)}\]

\[
\begin{array}{c}
\text{R - N=C=O + R' - NH}_2 \rightarrow \text{R - N - C - N - R'} \\
\mid \\
\text{H O H} \\
\end{array}
\]

\[\text{eq. (4c)}\]

In urethane foam production, the rate of generation of \(\text{CO}_2\) is extremely important for the properties of the final product. On the other hand, the chain extension reaction has to proceed at a sufficient rate so that the gel will have sufficient strength to retain the \(\text{CO}_2\) gas bubbles which produce the foam. The organotins appear to be most effective in catalyzing the chain extension reaction so that the optimum rates of both the chain extension and gas formation reactions are achieved. The organotin catalysts most commonly used are dibutyltin dicarbonate, dibutyltin dilaurate, dibutyltin dichloride, dibutyltin dilaurylmercaptide, and dimethyltin dichloride. Several stannous compounds have been discovered to be particularly effective in flexible urethane foam applications. In particular, stannous octoate has been used very successfully in this application.

Other Applications: Dibutyltin dioctoate and dibutyltin dilaurate are commonly used to catalyze the room temperature curing of silicone rubbers used in making dental impressions and encapsulating electronic parts. The usual technique of curing silicone rubbers is with peroxide catalysts at elevated temperatures. Curing is a crosslinking reaction, and the influence of organotin catalysts on this reaction is shown in eq. (5).

\[
\begin{array}{c}
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \\
\mid \\
\text{Si - OH + RO - Si - OR + HO - Si - O} \\
\mid \\
\text{CH}_3 \quad \text{CH}_3 \quad \text{CH}_3 \\
\downarrow \\
\text{Bu}_2\text{Sn(OOCR)}_2 \\
\end{array}
\]

\[\text{eq. (5)}\]
Organotin compounds have distinct advantages as catalysts for esterification reactions. They are: (1) high catalytic efficiency; (2) low tendency to eliminate water from secondary alcohols to form olefins; (3) ability to produce colorless esters; (4) absence of acidic or basic residues in the esters; (5) ability to impart heat stabilization to condensation type polymers (i.e., polyesters); (6) ability to improve physical and electrical properties of the product.

Plasticizers, polyesters, lactones, pyrrolidones, and glycolic acid have been polymerized with organotin catalysts.

The catalytic activity of the organotin compounds has been attributed to low-energy 5d orbitals of the tin atom which can form hexa- and pentacoordinate bonds. In this type of bond, the tin coordinates with either an oxygen or nitrogen. This coordination bond causes polarization of the carbon atom bonded to an oxygen or nitrogen atom, and makes the carbon atom more susceptible to attack by an electrophilic reagent, such as an alcohol, as in the urethane and esterification reactions.

Biocidal Compounds

Organotin compounds, because they have been found to be effective in the control of many fungi and bacteria, have been used as preservatives for wood, textiles, cordage fibers, paper, leather, electrical and electronic equipment, and glass. Most biologically active organotin compounds are trialkyl or triaryltin compounds. Bis(tributyltin) oxide, TBTO (M & T Chemicals, Inc.), gives antibacterial, antifungal, and mothproofing properties to treated fabrics. In this application, the tin compounds must compete with such compounds as copper 8-quinoalinolate, copper and zinc naphthenates, zinc dimethyldithiocarbamate, pentachlorophenol, and quaternary ammonium compounds. Their main disadvantage is cost, but their major advantage is their lack of color and staining.

TBTO is extremely effective in controlling bacteria in hospitals, such as Staphylococcus aureus. TBTO has also been used to prevent odors in garbage pails, control athlete’s foot, control molds in bathrooms, control mildew on leather goods, textiles, and plastics, and mothproof stored garments.

Industrial applications of organotin biocides include their use for slime control in paper pulp mills and cooling towers. Their use in processes involving food-grade papers, however, has been curtailed. In the control of slime in cooling towers, the tin compounds must compete with less costly, highly effective, but hazardous compounds such as trichlorophenol and organomercurials.

TBTO and tributyltin linoleate are active ingredients in marine lumber preservation. Paint formulations containing TBTO have controlled marine fouling for as long as cuprous oxide paints. Concentrations between 10 and 20% weight TBTO usually gives enough protection for the entire boating season. In this application, the organotins compete with organomercurials and organolead antifouling paints.

Dibutyltin dilaurate is effective for the control of Raillietina cesticillus in chickens, and the control of other poultry tapeworms. Dialkyltin compounds have also been used in the control of other parasitic diseases of poultry, sheep, and swine.

Tributyltin chloride is an effective rodent repellent.

Triphenyltin acetate and triphenyltin chloride are effective mollusicides for the control of snails which serve as vectors for schistosome infections in man.

Tributyl- and isopropyltin compounds are effective fungicides. Triphenyltin acetate and hydroxide control the fungus causing late blight of potatoes, control sigatoka in bananas, and control 11 other fungal diseases of important crops.

As insecticides, organotin compounds have been very effective. Trialkyltin compounds such as triphenyltin acetate and hydroxide, tributyltin chloride, and dibutyltin dilaurate when applied to foliage generally repel insects.

Figure 1 gives an overview of organotin product use patterns. It is interesting to note that the dialkyltin derivatives are used as heat stabilizers and catalysts, and the trialkyl- and
Migration of Organotin Stabilizers from Plastic Devices and Biological Reactions to these Compounds

The ability of biological fluids to extract organotin heat stabilizers from plasticized PVC medical devices has been well documented (4-11). The migration of organotin stabilizers from PVC bottles into liquid foods has been studied by Carr (12), Woggon et al. (13-15), and Koch and Figge (16).

Guess and Haberman (4) have studied the biological reactions to PVC resins obtained from different manufacturers, and to a large variety of PVC additives which include the commercially important plasticizers and heat stabilizers. This is probably the most comprehensive toxicological evaluation of these compounds in the literature (and for this reason will be discussed in some detail). As a comparison, biological reactions to Teflon, nylon, polypropylene, polycarbonate, ABS, poly(phenylene oxide), cellulose triacetate, and polyethylene plastics were also reported. This class of plastics usually does not require plasticizers during processing, whereas PVC plastics do. However, all plastic formulations to some degree require stabilizers as essential additives to prevent degradation during product use.

Several biological tests were employed to evaluate the toxicity of the PVC plastic formulation, the PVC resin, and the additives. In one test, slivers of the plastic were implanted into rabbit tissue. After one week the rabbits were sacrificed. Tissues surrounding the implant were excised, transferred to buffered formalin, sectioned and stained with hematoxylin and eosin for histopathologic evaluation. Cell culture reactions for PVC resins and for the additive compounds were obtained for mouse fibroblasts (L-929) and 10-day chick embryo cells which were both allowed to form monolayers in petri dishes. The liquid nutrient medium was aspirated and replaced with a 1% agar suspension in nutrient media. After gelation the sample was placed on the agar overlay and cells were incubated for 24 hr. A toxic sample produced a zone of dead cells. Additional tissue culture tests

triaryltn derivatives are used mainly in biocidal applications.

Biological Investigations on Organotin Compounds

Figure 1. Organotin product distribution chart.
included human amnion and nasopharyngeal cancer cells. In general these tests were done with the undiluted chemical additives and the observations were for whether or not the additive enhanced cell growth or resulted in death of the cell culture. These biological tests were common to many of the toxicologic studies of plastic medical devices.

The results of these studies by Guess and Haberman (4) showed that the organotin stabilizers, not the primary plasticizers in which they were dissolved, were the primary cause of toxicity. This was an important observation because the stabilizer was soluble in the plasticizer, and the plasticizer was readily extracted by lipid materials. In both the mouse fibroblast and chick embryo tissue culture tests, the organotin stabilizers gave positive results. Cell necrosis was the observed result which was considered a positive test. The organotins tested included all of the commercially important dibutyl derivatives and one dioctyl derivatives which has not been approved by the FDA for food package use. The structures and use pattern for these compounds are shown in Table 1 and Figure 1.

Guess and Haberman (4) also studied the toxicologic reactions to unplasticized PVC resins. Samples of the compacted resin from three different manufacturers were evaluated by the rabbit implantation and cell culture methods described previously. Two different brands of PVC resin revealed an extreme degree of eosinophilia, while a third brand of PVC and the polyethylene control did not show this reaction. These results suggested that the two brands which produced the eosinophilic reaction must be contaminated with a leachable material which was extremely toxic. Alcohol extraction of these two resins yielded 3.5% leachable material. The purified PVC resin was then implanted and showed only the usual foreign body reaction. The composition of the alcohol extract was not determined, but when examined by the tissue culture tests also gave very toxic reactions.

Several possibilities as to the nature of these toxic substances in PVC resins depend on the production scheme involved. The two main schemes involve free-radical initiation with benzoyl peroxide in monomer solution or in an emulsion. Impurities may be in the vinyl monomer, free-radical initiator, or the solvents used. However, it seems possible, because of the amount of material extracted, that the alcohol-extractable material is un-reacted vinyl chloride monomer, which is very soluble in methanol and is also extremely toxic and even carcinogenic (17).

Cell culture and rabbit implantation tests for other commercial plastics which usually are unplasticized but contain stabilizers, either caused a very low degree of cell destruction in the tissue culture tests, or produced no destruction at all. Alcohol extracts of these plastics produced measurable quantities of material which gave positive toxic reactions for Teflon, polycarbonate, ABS, poly(phenylene oxide), and cellulose triacetate. The volume of the extract in all but the Teflon and polycarbonate samples again suggested that this was unreacted monomer or low molecular weight dimers and trimers. Another interesting aspect of this comprehensive study was that the toxic reaction for a particular plastic formulation diminished with the absence of plasticizer. This observation reinforced the earlier conclusion that the plasticizer was the vehicle for the transport of the more toxic stabilizer into lipid materials, i.e., the diffusion of the stabilizer into the lipid material was enhanced by the presence of the plasticizer. Those plastics which did not require plasticization appeared to produce less toxic reactions in biological applications than did plasticized plastics.

In a related study, Haberman et al. (5) studied the effects of commercially available PVC plastics and resins on human serum protein, antibodies, and developing chick embryos. In all, 56 heat stabilizers, 45 plasticizers, 5 PVC resins, and 120 finished plastics prepared from these components were tested. Of the organotin thermal stabilizers tested, only bisdibutyltin monolauryl maleate and dibutyltin di(lauryl mercaptide) had no effect on complement. Dibutyltin diisoctyl thioglycolate and monobutyltin carboxylate
improved the biological activity of the proteins in the blood serum tests. Other test results showed that bisdibutyltin monolauryl maleate caused no change in blood grouping antiserum, but did cause red blood cell agglutination. Dibutyltin diisooctyl maleate was destructive to antibodies and caused blood grouping reagents to lose their ability to selectively agglutinate human blood cells. This compound also caused human blood cells to lyse within 24 hr. Dibutyltin dilaurate, which affected the delicate serum protein complex of guinea pig complement, had no observed effect on human red blood cells and blood grouping antisera.

Guess and Stetson (6) found that intubation devices made from PVC demonstrated toxicity to cells in culture and to rabbit muscle tissue. The PVC device was plasticized with tributylacetyl citrate and used a mercapto ester of an organotin heat stabilizer. The toxicity was manifested as necrosis of cell cultures and rabbit muscle tissue.

Other reports dealing with toxicological reactions to medical devices were by Duke and Vane (18), PVC tubing used in extracorporeal circulation; Autian (7), evaluation of dental materials; Guess (8), plastic tracheal tubes; Stetson (19), biological reactions to prolonged tracheal intubation; O'Leary et al. (20), evaluation of organotin stabilizers for rigid PVC using differential thermal analysis; Guess et al. (11), characteristics of subtle toxicity of certain plastic components used in manufacturing PVC; Little and Parkhouse (21), tissue reactions to polymers; and Nimni (22), biological tests for medical grade plastics and the toxicity of organotin stabilizers.

The migration of stabilizers from PVC food containers into liquid foods has been studied by Woggon et al. (13-15), Carr (12), and Koch and Figge (16). Woggon et al. investigated the migration of di-n-octyltin bis(2-ethyl hexyl thioglycolate) (or isoocxyl thioglycolate) into sunflower oil. The concentration of the organotin stabilizer was less than 2 ppm after 6 months’ storage. The daily tolerance level set by the West German government for humans has been established at 0.0065 mg/kg. For the daily consumption of 50 g of sunflower oil, the migration of the diocytlytin stabilizer into the oil did not exceed the daily tolerance level. The oral LD₅₀ for di-n-octyltin bis(2-ethyl hexyl thioglycolate) was 2100 mg/kg in rats.

Carr (12), in a study with 10 liquid foods, attempted to distinguish between the tin content of these foods due to processing and absorption of tin from the environment, the so-called “natural tin,” and the tin which diffuses into the food from the food container. In this study food was analyzed for total tin before packaging in PVC containers and after storage in these containers for two months at 30°C. The tin was in the form of diocytlytin stabilizers which have been sanctioned for food packaging by the FDA. The results of this investigation are shown in Table 2.

It is interesting to note that the FDA regulations provide that the allowable levels of octyltin stabilizers in food shall not exceed 1 ppm. This regulation is given in CFR, Title 21, Subpart F, 121.2602, 1971. The organotin stabilizers identified in this regulation are di-n-octyltin S,S'-bis(isooctyl mercaptoacetate) and di-n-octyltin maleate polymer. The analytical technique prescribed for determining tin content is given by Farnsworth and Percola (3).

Koch and Figge (16) studied the migration of an organotin stabilizer from PVC beer bottles into beer. The organotin stabilizer was di-n-octyltin bis(2-ethyl hexyl thioglycolate), and its concentration in the PVC bottle was 1.13% by weight. Beer was stored in these bottles at 20°C for 8 weeks. At the end of this 8-week period, the concentration of the organotin stabilizer in the beer was 0.01 ppm.

Toxicity of Organotin Compounds

Trisubstituted Organotin Derivatives: Besides the toxicity evaluation of commercially important organotin stabilizers found in PVC medical devices, there have been many investigations concerned with the toxicity of all types of organotin compounds. The toxicity of alkyl- and arylltin derivatives has been recognized for a long time and is primarily due to the solubility of these organotin derivatives in body fluids. Many of the investi-
Table 2. Results of tin extraction tests compared with tin extractions of natural foods.\textsuperscript{a}

| Food product       | Natural tin, ppm\textsuperscript{b} | Tin content after aging in PVC bottle, ppm | Tin extracted from bottle, ppm | Organotin stabilizer extracted from PVC bottle, ppm\textsuperscript{c} |
|--------------------|--------------------------------------|-------------------------------------------|-------------------------------|--------------------------------------------------|
| Blended whiskey    | 0.01                                 | 0.02                                      | 0.01                          | 0.063                                             |
| Mineral water      | 0.76                                 | 0.088                                     | 0.01                          | 0.063                                             |
| Tomato juice       | 0.03                                 | 0.03                                      | 0.01                          | 0.063                                             |
| Peanut oil         | 0.05                                 | 0.06                                      | 0.01                          | 0.063                                             |
| Vegetable oil      | 0.08                                 | 0.09                                      | 0.01                          | 0.063                                             |
| Apple juice        | 0                                    | 0.02                                      | 0.02                          | 0.126                                             |
| Cherry soda        | 0                                    | 0.07                                      | 0.07                          | 0.443                                             |
| Beer               | 0                                    | 0.01                                      | 0.01                          | 0.063                                             |
| Milk\textsuperscript{d} | 0.2                                  | 0.04                                      | 0.02                          | 0.126                                             |
| Red wine           | 0                                    | 0                                         | 0                             | 0                                                 |

\textsuperscript{a}Data of Carr (12).

\textsuperscript{b}Natural tin defined as tin in food as a result of processing and absorption from environment.

\textsuperscript{c}Concentration of octyltin in ppm was obtained by multiplying the tin extracted from the bottle by 6.3. The organotin stabilizer was di-n-octyltin S,S'-bis(isooctyl mercaptoacetate), Argus Chemical, Mark OTM.

\textsuperscript{d}Milk sample in PVC bottle was aged for 2 weeks at 65°C.

 Investigations have been conducted in trialkyl-, triaryl-, and tetraalkyltin derivatives which find their main use in biocidal applications.

Renewed interest in the toxicology of organotin compounds occurred as a result of the Stalinon affair, which happened in France in 1954 and resulted in the death of about 100 people. Stalinon was a proprietary preparation sold in capsules throughout France for the treatment of furuncles and other staphylococcal skin infections, osteomyelitis, anthrax, and acne. The main active components of this preparation were diethyltin diiodide (15 mg/capsule) and Vitamin F (linoleic acid, 100 mg/capsule). The main impurities were monoethyltin and triethyltin iodides. The concentration of the triethyltin derivatives was found to be approximately 10% by weight of the diethyltin component. It was concluded that people so treated received a total dose of 3 g over a period of six to eight weeks. Triethyltin derivatives were found to be 10 times more toxic than diethyltin derivatives to rats when administered orally. The most constant complaints of patients were of severe, persistent headaches. Other common symptoms were vomiting, retention of urine, vertigo, abdominal pain, photophobia, loss of weight, psychic disturbances, and several cases of hypothermia (35°C). At autopsy, marked interstitial edema of the white matter of the brain was seen. There was no degeneration of the fat tissue of the nerve fiber which had been severed from its nutritive centers (Wallerian degeneration), and the only other lesion of possible significance was some endothelial proliferation in the smaller veins accompanied in some cases by thrombosis and small perivenous hemorrhages. Immediately following the Stalinon affair, there was a proliferation of articles concerned with the toxicology of trialkyltin derivatives and their influence on biochemical reactions.

Because the triethyltin derivative was identified as the toxic contaminant in Stalinon which resulted in neurological symptoms in many of the afflicted patients, the toxicity of this compound has been widely studied. In one of the earliest toxicity studies on organotin compounds following the Stalinon affair, Stoner et al. (23) studied the acute and chronic effects of a series of tetra-, tri-, di-, and monoalkyltin compounds and some inorganic tin salts in rats, rabbits, and guinea pigs. In acute studies with rabbits, triethyltin appeared to be the most active, producing muscular weakness followed by some recovery, but progressing in turn to muscular tremors, convulsions, and death. In other animal species the compounds used in these acute studies produced similar response...
patterns. The results of the acute studies are given in Table 3.

On discounting the unexpected acute oral toxicity for the rat for the trimethyl derivative on a comparative basis, the toxicity of trialkyltin derivatives decreases as the size and stability of the ligand increases. Generally, the toxicity of the dialkyl derivatives was less than the toxicity of the trialkyl and triaryl derivatives.

The chronic studies in this investigation by Stoner et al. (23) were conducted on rats, rabbits, and chickens, and the only organotin compound used was triethyltin hydroxide. In rats, the daily dose was 20 ppm, in rabbits 20 ppm and 40 ppm, and in domestic fowls 160 ppm of triethyltin hydroxide. The outstanding feature of chronic poisoning was muscular weakness. Although there was no evidence of concentration of tin in any organ, these alkyltin derivatives appeared to have their main effect on the central nervous system.

Further work by Magee et al. (24) made it clear that triethyltin derivatives exerted a powerful toxic action on the central nervous systems of rats. Both acute and chronic studies were performed; acute studies used triethyltin sulfate; chronic studies used triethyltin hydroxide. In the acute studies, a dose of 10 mg/kg body weight (approximately 2LD50 doses) was injected intraperitoneally and produced a generalized progressive weakness which ended in death after a maximum of 5 days. An intraperitoneal dose of diethyltin dichloride of 20 mg/kg of body weight did not produce the characteristic paresis, but still caused death within 24 hr. In chronic studies, the daily dose was 20 ppm of triethyltin hydroxide in rats. The only noteworthy lesion in these animals was an interstitial edema confined to the white matter of the brain. It seemed clear from these studies that the first reaction in the rat to poisoning was the accumulation of fluid in the white matter of the central nervous system. Furthermore, this accumulation of fluid persisted for as long as these organotin compounds were administered. When feeding of the triethyltin compound was stopped, the lesion was reversible. It was interesting to note that the symptoms exhibited by the animals used in this chronic study with triethyltin compounds were similar to the symptoms of the victims involved in the Stalinon affair.

**Table 3. Acute toxicities of organotin compounds.**

| Compound                  | Lethal dose, mg/kg body weight |
|---------------------------|-------------------------------|
|                           | Rabbit                        | Rat              | Guinea         |
|                           | Oral  | IP   | Oral  | IP             | pig, oral |
| Trimethyltin sulfate      | –     | –    | 30    | 16             | –         |
| Triethyltin sulfate       | 10    | 10   | 10    | 10(LD50 = 5.7) | 5–10      |
| Tri-n-propyltin acetate   | –     | –    | >40   | –              | –         |
| Triisopropyltin acetate   | –     | –    | 80    | –              | –         |
| Tri-n-butyltin acetate    | 60    | –    | 50–100| 10             | 20        |
| Tri-n-hexyltin acetate    | –     | –    | >100  | –              | –         |
| Triphenyltin acetate      | >40   | –    | >150  | –              | 10        |
| Diethylphenyltin acetate  | –     | –    | 50–100| –              | –         |
| Diethyltin dichloride     | –     | –    | >40   | 15             | –         |
| Diethyltin diiodide       | –     | –    | 100   | 26             | –         |
| Dibutyltin dichloride     | –     | –    | 100   | –              | –         |
| Dibutyltin dilaurate      | –     | –    | –     | 85             | –         |
| Monoethyltin trichloride  | –     | –    | –     | 200            | –         |

*Data of Stoner et al. (23).*
In the discussion of these results, Magee et al. (24) noted that the lesion produced by the triethyltin derivatives was very different from the lesions caused by alkyl derivatives of lead, antimony, bismuth, and mercury, which cause damage to the nerve cells. It was suggested that the explanation for the lesions produced by the triethyltin compounds must incorporate the general tissue effects of these compounds on the inhibition of oxidative phosphorylation. There was no explanation of why the brain tissue should be more sensitive to these compounds, but it was suggested that the transport of free fluid and overall metabolic processes should be studied in more detail in order to find out more about the exact biochemical changes in the central nervous system of rats as a result of triethyltin poisoning.

More recently, Pelikan and Cerny (25) studied the acute toxicity of tri-n-butyltin derivatives in white mice. The tributyltin derivatives were the acetate, benzoate, chloride, laurate, and oleate. These compounds were given per gavage in a single dose of each compound at 500 mg/kg body weight. After 8 hr autopsy findings showed signs of damage to the digestive tract, liver, and spleen. The histological findings included steatosis of the liver cells in all animals, but to varying degrees, traces of lipids were found in renal tubule cells of animals receiving the laurate and oleate compounds, and hemorrhages were found in the digestive tract and kidneys. The LD₅₀ results for these compounds in white mice are shown in Table 4.

A large amount of acute toxicity data has been obtained for trisubstituted organotin compounds; the results of these and several other important studies are summarized in Table 5.

Suzuki (28) performed acute and chronic studies with triethyltin sulfate on newborn rats. In the acute studies, 5 mg/kg body weight of the triethyltin sulfate was injected daily intraperitoneally. The rats in this study died after 3 days. The brains of the test animals showed diffuse hemorrhagic encephalopathy. In the chronic studies, 5 mg/l. in drinking water was taken each day. The test animals showed no clinical symptoms of cerebral involvement, but severe, diffuse status spongiosus was evident throughout the white matter of the central nervous system.

Pelikan (29) studied the effects of bis-(tri-n-butyltin) oxide, an important preservative for wood, textile paper, leather, and glass, on the eyes of rabbits. Both male and female albino rabbits, ratio 1:1, were used in this study, and were divided into four groups. The actual concentrations of the organotin compound administered to each group were: 6.1 mg/kg; 4.6 mg/kg; 0.61 mg/kg; and 0.46 mg/kg. A single dose of 0.03 ml per rabbit was administered to the conjunctival sac of the left eye. The largest concentration approximated the highest accidentally adminis-

| Compound                  | LD₅₀, mg/kg | Animal used   | Reference |
|---------------------------|------------|---------------|-----------|
| Triethyltin chloride      | 5 (IP)     | Female rats   | (26)      |
| Tributyltin oxide         | 7 (IP)     | Female rats   | (26)      |
| Trioctyltin dilaurate     | >800 (IP)  | Female rats   | (26)      |
| Tributyltin acetate       | 133 (oral)| Male rats     | (27)      |
| Tributyltin salicylate    | 137 (oral)| Male rats     | (27)      |
| Bis(triethyltin) oxide    | 122 (oral)| Male rats     | (27)      |
| Tri-n-octyltin chloride   | >10,000 (oral) | Male rats | (27)      |

*Data of Pelikan and Cerny (25).*
tered dose. The lower two concentrations produced very profound changes in the rabbits' eyes. Within 3 hr after administration, erythema and mild edema of the eyelids was observed. In addition, there were numerous large necrotic areas, petechial hemorrhages, early chemosis of the bulbar and palpebral conjunctivae, and distinct pericorneal injection and dullness of the shine of the cornea with decreased transparency. These effects persisted so that 2-5 days after administration of the organotin compound, eschars and ulcerations, some 10-15 mm in size, formed on the eyelids partly covered with pus. Between these eschars were numerous papules, pustules, hemorrhages, and small necroses. In the rabbits given the larger concentrations, these effects were more pronounced and produced in two of the animals a clinical situation which showed marked deterioration after 3-4 days. These two animals (after 3-4 days) showed extreme weakness, kept their eyes closed, and let their heads hang down. On day 11 and 12 the rabbits died. (Microscopic examinations of tissue in and around the eye were performed, and results are given in the paper.) This commercially important biocidal agent, when administered in low concentration doses, has a very pronounced and irreversible effect on normal eye functions in rabbits.

Di- and Monosubstituted Organotin Derivatives: From this work on the triethyltin derivatives, interest in other organotin compounds of commercially importance was generated. Barnes and Magee (30) studied the toxicity of the salts of dibutyltin hydroxide because these stabilizers were used for plastics which were made into flexible tubing for blood-transfusion sets and the transport of liquids such as beer and milk. In acute studies with rats a single oral dose of dibutyltin dichloride of 50 mg/kg body weight produced bile-duct lesions. It was shown that the flow of bile was a prerequisite for the development of bile duct lesion. It was, therefore, conceivable that the dibutyltin salt was present in the bile in sufficient concentration to produce injury. As a result of this initial damage, bile escaped into the adjoining parts of the pancreas and a yellow-stained edema developed locally. Liver damage was also noted in the rats.

Chronic toxicity studies on di-n-butyltin dichloride in rats were conducted by Gaunt et al. (31). The compound was fed to rats for 90 days at dietary levels of 0 (control), 10, 20, 40, and 80 ppm. At 80 ppm, there was a slight reduction of growth and food intake, and instances of mild anemia. The no-effect level in rats was established at 40 ppm for 90 days. This level corresponded to an intake of approximately 2 mg/kg-day. Di-n-butyltin dichloride is the final product of the stabilization reaction of PVC resins, and is a catalyst for the formation of polyurethane foam. Other important acute toxicity studies with di- and monosubstituted organotin derivatives are summarized in Table 6.

Biochemical Studies on Organotin Compounds

Tri-substituted Organotin Derivatives: Most of the biochemical research on organotin compounds has been confined to triethyltin compounds and how they inhibit oxidative phosphorylation. Oxidative phosphorylation is a complex heterogeneous, catalytic, electro-chemical process occurring on the mitochondrial membrane. Although the exact mechanism of conversion of ADP to ATP has not been determined completely, studies by Aldridge and Street (35,36) indicate that part of this process involves binding of the reactants to sites on the mitochondrial membrane. Mechanisms for catalytic reactions involve adsorption-desorption steps and therefore the determination of an equilibrium constant which can be related thermodynamically to the binding energy involved in adsorption-desorption processes. The exact nature of the equilibrium constant is a function of the number of binding sites involved in the reaction mechanisms.

Triethyltin derivatives and trimethyltin derivatives have been shown by Aldridge and Street (35,36) to have very high affinity constants (~10^5 M^-1) for the binding to rat liver mitochondria. It was shown for rat liver mitochondria that the presence of these compounds could inhibit oxidative phosphory-
Two the showed inhibiting pounds, it was concluded that the order of effectiveness in inhibiting coupled respiration was tributyltin > tripropyltin > triphenyltin > trimethyltin. It was concluded that with two exceptions, all the effects of trialkyltin compounds on mitochondria could be explained on the basis of two separate effects. These were the oligomycinlike inhibition of coupled phosphorylation exhibited in all media and the anion-hydroxide exchange across lipid membranes. In the latter effect, it was shown that media containing certain anions could produce uncoupling, swelling, and the lowering of intramitochondrial substrate and phosphate concentrations together with structural damage following gross swelling. The two exceptions are the detergentlike action at high concentrations of chlorides of trialkyltin compounds and the potent inhibition of electron transfer found at high trialkyltin concentrations with iodide and thiocyanate anions.

Radioactive triethyltin ($^{113}$Sn) chloride was used by Rose and Lock (38) to identify the molecular groups of guinea-pig liver mito-

Table 6. Acute toxicity data for disubstituted organotin compounds.

| Compound                                  | LD$_{50}$, mg/kg | Animal used | Reference |
|-------------------------------------------|------------------|-------------|-----------|
| Dibutyltin oxide                          | 520 (oral, oil solution) | Male rats   | (27)      |
| Dibutyltin oxide                          | 39.9 (IP)        | Female rats | (26)      |
| Dibutyltin dichloride                     | 35 (oral)        | White mice  | (31)      |
| Dibutyltin dichloride                     | 112 (oral)       | White mice  | (31)      |
| Dibutyltin di-2-ethylhexyl thioglycolate  | 510 (oral, oil solution) | Male rats   | (27)      |
| Dibutyltin di(monobutyl) maleate          | 120 (oral, oil solution) | Male rats   | (27)      |
| Dibutyltin di(monononyl) maleate          | 100 (oral, oil solution) | Male rats   | (27)      |
| Dibutyltin dilaurate                      | 175 (oral, oil solution) | Male rats   | (27)      |
| Di-n-octyltin thioglycolate               | 945 (oral)       | Male rats   | (27)      |
| Di-n-octyltin $\beta$-mercaptopropionate  | 1,850/2,050 (oral) | Male rats   | (27)      |
| Di-n-octyltin 1,4-butanediol bismercaptoacetate | 2,950 (oral) | Male rats   | (27)      |
| Di-n-octyltin ethyleneglycol dithioglycolate | 880 (oral)   | Male rats   | (27)      |
| Di-n-octyltin maleate                     | 1,265 (oral)     | Male rats   | (27)      |
| Di-n-octyltin di-(1,2-propyleneglycol maleate) | 4775 (oral)/30 (IP) | Male rats   | (27)      |
| Di-n-octyltin di-(monobutyl maleate)      | 2030/2750 (oral) | Male rats   | (27)      |
| Di-n-octyltin bis(2-ethylhexylmaleate)    | 2760/3500 (oral) | Male rats   | (27)      |
| Di-n-octyltin dilaurate                   | 6450 (oral), 95 (IP) | Male rats   | (27)      |
| Di-n-octyltin bis(lauryl thioglycolate)   | 3700 (IP)        | Male rats   | (27)      |
| Di-n-octyltin oxide                       | 2500 (IP)        | Male rats   | (27)      |
| Di-n-octyltin acetate                     | >800 (IP)        | Female rats | (26)      |
| Di-n-octyltin bis(2-ethylhexyl mercaptoacetate) | 2010 (stomach tube) | White mice  | (33, 34) |
| Di-n-octyltin bis(dodecyl mercaptide)     | 4000 (stomach tube) | White mice  | (33, 34) |
| Di-n-octyltin bis(butylmercaptoacetate)   | 1140 (stomach tube) | White mice  | (33, 34) |
| Mono-n-octyltin tris(2-ethylhexyl mercaptoacetate) | 1500 (stomach tube) | White mice  | (33, 34) |
| Mono-n-octyltin trichloride               | 10000 (oral)     | Male rats   | (27)      |

lation by binding with high affinity to sites on the mitochondria which would be normally used for phosphorylating oxidation. This is comparable to catalyst poisoning experienced in industrial catalytic processes. The concentration of triethyltin required to effectively inhibit oxidative phosphorylation is 0.3 $\mu$M.

In related studies on the inhibition of oxidative phosphorylation by trialkyltin compounds, Stockdale, Dawson, and Selwyn (37) showed that the order of effectiveness in inhibiting coupled respiration was tributyltin > tripropyltin > triphenyltin > trimethyltin. It was concluded that with two exceptions, all the effects of trialkyltin compounds on mitochondria could be explained on the basis of two separate effects. These were the oligo-
chondrial protein involved in binding triethyltin compounds. It was shown that the binding sites consisted of a pair of histidine residues. The type of coordination binding proposed involved the formation of a system of linear polymers with trialkyltin binding the imidazole portion of histidine. This kind of trigonal bipyramidal coordination complex is shown as:

\[
\begin{align*}
N & \quad \text{R} \quad \text{Sn} \quad \text{R} \quad N \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{CH-NH}_2 & \quad \text{CH-NH}_2 \\
\text{COOH} & \quad \text{COOH}
\end{align*}
\]

In studies by Coleman and Palmer (39) it was shown that pH influences the inhibition of oxidative phosphorylation and electron transport by triethyltin sulfate. With rat liver mitochondria, in an assay medium containing Cl\(^-\) at an alkaline pH, above 7.1, triethyltin inhibited both the ADP stimulated rate of oxygen uptake and the dinitrophenol-induced ATPase, but had no effect on the dinitrophenol-stimulated rate of oxygen uptake. If the pH was reduced to below 6.9, the pattern of inhibition changed and both the ADP and dinitrophenol-stimulated rates of oxygen uptake were inhibited by triethyltin. In the absence of Cl\(^-\) in the medium, trialkyltin inhibited both the ADP-stimulated rate of oxygen uptake and dinitrophenol-induced ATPase, and had no effect on the dinitrophenol-stimulated rate of oxygen uptake at either pH 7.4 or 6.6. In either the presence or absence of Cl\(^-\) the ability of triethyltin to inhibit ATP synthesis appeared to markedly decrease as the pH was lowered from 7.4 to 6.6.

\textit{In vivo} studies were conducted by Cremer (40) on the selective inhibition of glucose oxidation by triethyltin sulfate in rat brain. \(^{14}\text{C}\) tracers were used to study the metabolism of glucose and acetate after intraperitoneal injection of triethyltin sulfate, 10 mg/kg body weight. It was shown that incorporation of \(^{14}\text{C}\) from glucose into glutamate, glutamine, \(\alpha\)-aminobutyrate and aspartate was greatly decreased. The incorporation of \(^{14}\text{C}\) from acetate into these amino acids was unaffected. The experimental data indicated that the main action of triethyltin was to decrease the rate at which pyruvate was oxidized. Glycolysis was not inhibited. Changes in glucose metabolism in the brain were shown not to be directly due to hypothermia.

In a related study, Joo et al. (41) demonstrated that triethyltin poisoning in rats resulted in increased permeability of the blood-brain barrier. It was shown that the pattern of soluble brain protein underwent marked changes due to increased permeability of the barrier on the one hand, and/or to metabolic disturbances of the brain substance on the other.

\textit{Disubstituted Organotin Derivatives}: Unpublished results obtained by personal communication with Aldridge stated that action of the whole series of homologs from dimethyl to diocetyl on mitochondrial fractions of rat liver had been examined. Most of these compounds inhibited mitochondrial respiration by preventing the oxidation of \(\alpha\)-keto acids. Dihexyltin was an active homolog, but the diocetyl tin derivative appeared to be inactive.

\textbf{Conclusions}

In this review, an attempt has been made to bring together from technological and biological literature information about organotin compounds. There were several reasons for a review article on this particular group of chemicals. Because of the unique chemistry of these compounds, they have been developed as important thermal stabilizers for plastics, as catalysts, and as biocides. Important questions asked at this point were whether or not these chemicals in their product and process use patterns constituted either an immediate or potential health
hazard to living organisms. In order to begin answering these questions, current information was gathered on the toxicity of these substances and about the methods of transport of these compounds through the environment. With this background information, rational discussions about the potential of these substances as environmental health hazards, and about the types of additional information required to evaluate this potential completely can continue in a non-crisis atmosphere.

Renewed biological interest in these compounds was a result of the disastrous poisoning of over 100 Frenchmen in 1954 by a triethyltin contaminant in the drug called Stalion. The toxicity of these compounds was shown to be associated with their organic ligands which increased their solubility in biological fluids.

Acute toxicity studies in rats showed that trialkyltin and triaryltin compounds were very toxic, with toxicity diminishing as the size and stability of the organic ligand increased. Chronic toxicity studies in rats showed that these compounds affected the function of the central nervous system, but that these lesions were reversible when administration of these compounds ceased. It was also shown in in vitro studies that these compounds bind to mitochondria and inhibit oxidative phosphorylation. Trialkyltin and triaryltin derivatives are commercially important biocides.

Acute and chronic toxicity studies in rats with dialkyltin and diarylthtin compounds, commercially important as thermal stabilizers and catalysts, showed them to be less toxic than the trialkly- and triaryltin derivatives. The toxicity of these compounds again diminished as the size and stability of the organic ligand increased. However, it was shown in in vitro studies that these compounds did have the ability to inhibit mitochondrial respiration by preventing the oxidation of α-keto acids.

The transport mechanisms for these compounds into biological systems have profound implications for environmental health. Two methods of introduction of dialkyl- and diarylthtin derivatives into man are migration from plasticized plastic containers into liquid foods and migration from plasticized plastic medical devices into biological fluids. Tissue culture tests with dialkyl- and diarylthtin thermal stabilizers showed them to be more toxic than the plasticizers in which they were dissolved. It was also shown that the presence of the plasticizer enhanced the diffusion of the more toxic stabilizers into biological fluids. The FDA has specified that only dioctyltin derivatives can be used to stabilize plastic food containers. These compounds are not the most effective stabilizers, but they are much less toxic than the dibutyltin derivatives. Medical devices use the more effective dibutyltin stabilizers. Although this group of products does not represent a significant percentage of plasticized plastic products, the use of dibutyltin stabilizers in these devices, offers a direct route of entry for the more toxic group of compounds into biological fluids.

With the increasing information on the number of methods by which chemicals can be transported throughout the environment, it is possible to apply these methods to the prediction of environmental distribution of organotin compounds. The combined organic—inorganic nature of these substances allows them to be soluble in a very broad range of fluids, so that liquid transport mechanisms by many types of fluids are possible. On examining the use patterns for these compounds, the dialkyl- and diarylthtin derivatives are widely used in a variety of commercially important plastic products, because of their effectiveness in preventing thermal degradation of the polymer chains of these plastics. Marketing of plastics is a high volume business because they are generally inexpensive and can be fabricated into products which can compete favorably with established market items. Plastics are also considered to be disposable. The percentage of solid waste as a result of the disposability of plastics is increasing yearly, from the present 3% to approximately 5% by 1980. The methods of solid waste disposal—landfilling, composting, and incineration—could offer
an increased number of mechanisms for concentration through the food chain, and an increased number of possibilities for entry into man's systems.

The solution to these problems would be an example of responsible consideration of the total life cycle of a product for the consumer market. Several possible suggestions are therefore given as a beginning. The use of unplasticized plastic food containers and medical devices would decrease the diffusivity of organotin stabilizers in liquid foods and biological fluids from approximately $10^{-8}$ cm$^2$/sec to approximately $10^{-12}$ cm$^2$/sec. Recognition of what additives were present in plastic products would result in better waste management procedures and would result in the design of waste disposal equipment for more efficient reclamation of these trace materials. The economic incentive would certainly be there since the organotin compounds have a market value of approximately $2.00/lb. Recognit of the health hazards of the more toxic trialkyl and triaryl biocides should result in their curtailment or use in closed systems, which would prevent entry of these compounds into the environment.

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